DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-757/S-015

TAP Pharmaceutical Products Inc.
Attention: John R. Lieberman, Ph.D.
Regulatory Advisor
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Lieberman:

Please refer to your supplemental new drug application dated April 27, 2007, received April 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREVPAC® (lansoprazole/amoxicillin/ clarithromycin).

This Prior Approval supplemental new drug application provides for the following changes to the PREVPAC® package insert (deletions are indicated by ~~strikethrough~~ and additions are indicated by underline):

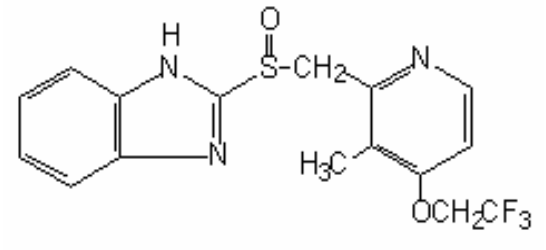
1. The following modifications were made throughout the label in accordance with recommendations of the Institute for Safe Medication Practices. These changes are numerous and not all of them will be reflected in this letter.

   - The symbol ">" was removed and replaced with the words "greater than".
   - Table numbers were added.
   - The abbreviation "qd" was changed to "daily".

2. The following changes were made in the **DESCRIPTION** section:

   PREVPAC consists of a daily administration pack containing two PREVACID 30-mg capsules, four amoxicillin 500-mg capsules, USP, and two clarithromycin 500-mg tablets, USP, for oral administration.

   PREVACID® (lansoprazole) Delayed-Release Capsules
   The active ingredient in PREVACID capsules is lansoprazole, 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~~PREVACID has the following structure:

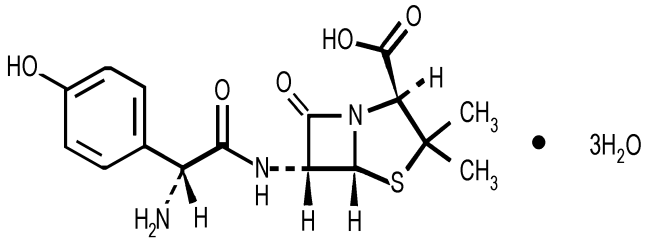


Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very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

Each delayed-release capsule contains enteric-coated granules consisting of 30 mg of lansoprazole ~~(30 mg),~~ (active ingredient) and the following inactive ingredients: 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, and FD&C Red No. 40 (inactive ingredients).

Amoxicillin Capsules, USP

Amoxicillin~~,~~ is a semisynthetic antibiotic, an analogue of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is (2S, 5R, 6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0] heptane-2-carboxylic acid trihydrate. Its empirical formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ with a molecular weight of 419.45. ~~It~~ Amoxicillin has the following ~~chemical~~ structure:



Amoxicillin capsules are intended for oral administration. The yellow opaque capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin.
Inactive ingredients: Capsule shells - yellow ferric oxide, titanium dioxide, gelatin, black ferric oxide; Capsule contents – cellulose microcrystalline and magnesium stearate.

BIAXIN® Filmtab® (clarithromycin tablets, USP)

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. ~~The structural formula is~~ Clarithromycin has the following structure:

3. The following changes were made in the **CLINICAL PHARMACOLOGY** section:

Pharmacokinetics
Pharmacokinetics when all three of the PREVPAC components (PREVACID capsules, amoxicillin capsules, clarithromycin tablets) were coadministered has not been studied. Studies have shown no clinically significant interactions of PREVACID and amoxicillin or PREVACID and clarithromycin when administered together. There is no information about the gastric mucosal concentrations of PREVACID, amoxicillin and clarithromycin after administration of these agents concomitantly. The systemic pharmacokinetic information presented below is based on studies in which each product was administered alone.

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

Absorption

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

Distribution

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

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H^+,K^+)-ATPase enzyme system] at the secretory surface of the gastric ~~within the~~ parietal cell. The two active species ~~canaliculus, but~~ are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the ~~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 PREVACID, 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 lansoprazole metabolites ~~of lansoprazole~~.

Special Populations

Geriatric Use

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.

Gender

In a study comparing 12 male and 6 female human subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results (see **PRECAUTIONS**, PREVACID **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). The AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment~~;~~, and the C_{max} and T_{max} (time to reach the maximum concentration) were not different than the C_{max} and T_{max} from subjects with normal renal function~~healthy kidneys~~.

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of ~~the drug~~ lansoprazole was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in the 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 pharmacokinetic parameters of PREVACID from twelve U.S. Phase I studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of PREVACID in Asian subjects were ~~are~~ approximately twice that seen in pooled U.S. data; however, the inter-individual variability was ~~is~~ high. The C_{max} values were ~~are~~ comparable.

4. The following changes were made in the **MICROBIOLOGY/*Antisecretory activity*** subsection:

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 ~~>~~ greater than 3 and ~~>~~ greater than 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~~ The intragastric pH results of a five-day, pharmacodynamic, crossover study of ~~that included~~ 15 mg and 30 mg of once daily lansoprazole are presented in Table 2.~~15 and 30 mg for five days, the following effects on intragastRIC PH WERE NOTED:~~

Table 2: Mean Antisecretory Effects after Single and Multiple Daily PREVACID 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 ~~>~~ greater than 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 30 mg of lansoprazole ~~30 mg~~ and 2-3 hours with 15 mg of lansoprazole ~~15 mg~~. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole ~~30 mg~~ and within 1-2 hours post-dosing with 15 mg of 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.~~daily, b.i.d. and t.i.d.

Table 3: Mean Antisecretory Effects After 5 Days of b.i.d. and t.i.d. Dosing

	PREVACID			
Parameter	30 mg daily ~~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.~~daily

The inhibition of gastric acid secretion as measured by intragastric pH ~~returns~~ gradually returned to normal over two to four days after multiple doses. There ~~is~~ was no indication of rebound gastric acidity.($p<0.05$) versus PREVACID 30 mg ~~q.d.~~daily, 15 mg b.i.d. and 30 mg b.i.d.

5. The following changes were made in the **CONTRAINDICATIONS** section:

CONTRAINDICATIONS
PREVPAC is contraindicated in patients with known hypersensitivity to any component of the formulation of PREVACID, any macrolide antibiotic, or any penicillin.

Concomitant administration of PREVPAC ~~with~~ and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, ergotamine or dihydroergotamine ~~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.

For information about contraindications of other drugs that may be used in combination with amoxicillin or clarithromycin, refer to the **CONTRAINDICATIONS** section of their package inserts.

~~(~~Please refer to full prescribing information for amoxicillin and clarithromycin before prescribing~~).~~

6. The following changes were made in the **WARNINGS/**Amoxicillin and/or Clarithromycin subsection:

Amoxicillin and/or 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, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation 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.~~

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

For information about warnings of other drugs that may be used in combination with amoxicillin or clarithromycin, refer to the **WARNINGS** section of their package inserts.

7. The following statement was added as the fifth paragraph in the **PRECAUTIONS** section:

For information about precautions of other drugs that may be used in combination with amoxicillin or clarithromycin, refer to the **PRECAUTIONS** section of their package inserts.

8. The following changes were made in the last paragraph of the **PRECAUTIONS/Drug Interactions/**PREVACID subsection:

~~Delayed-Release Capsules; this did not interfere with its effect~~ and there was no evidence of a change in the efficacy of PREVACID.

9. The following changes were made in the **PRECAUTIONS/Drug Interactions/Carcinogenesis, Mutagenesis, Impairment of Fertility/**PREVACID subsection:

Carcinogenesis, Mutagenesis, Impairment of Fertility
PREVACID:
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with ~~orally with~~ oral lansoprazole 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 (BSA)] 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 BSA~~body surface area~~) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. In addition, in a one-year toxicity study, ~~T~~testicular interstitial cell adenoma ~~also~~ occurred in 1 of 30 rats treated with 50 mg/kg/day of lansoprazole (13 times the recommended human dose based on BSA~~body surface area~~) ~~in a 1-year toxicity study~~.

In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole ~~orally with~~ doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on BSA ~~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 BSA ~~body surface area~~) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on BSA ~~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 BSA ~~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 BSA ~~body surface area~~) was found to have no effect on fertility and reproductive performance of male and female rats.

10. The following changes were made in the **ADVERSE REACTIONS** section:

PREVACID:
The following adverse reactions from the labeling for PREVACID ~~lansoprazole~~ are provided for information.

Worldwide, over 10,000 patients have been treated with PREVACID~~lansoprazole~~ in Phase 2~~-3~~ or Phase 3 clinical trials involving various dosages and durations of treatment. In general, PREVACID~~lansoprazole~~ treatment has been well-tolerated in both short-term and long-term trials.

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

Table 6
Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, PLACEBO-CONTROLLED PREVACID 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 of PREVACID, but higher in the patients who received ~~lansoprazole~~ 60 mg of PREVACID (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

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

Additional adverse experiences occurring in ~~<~~less than 1% of patients or subjects who received PREVACID 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~~ PREVACID has been marketed. The majority of these cases are foreign-sourced and a relationship to ~~lansoprazole~~ PREVACID 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 – anaphylactic/anaphylactoid reactions; *Digestive System* – hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopen0ia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System* – myositis; *Skin and Appendages* – severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, (some-fatal); *Special Senses* – speech disorder; *Urogenital System* – interstitial nephritis, urinary retention.

Laboratory Values

The following changes in laboratory parameters ~~for lansoprazole~~ in patients who received PREVACID 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, who received placebo and PREVACID, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these ~~lansoprazole~~ patients who received PREVACID reported jaundice at any time during the study.

Amoxicillin:
The following adverse reactions from the labeling for amoxicillin are provided for information.

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal - Nausea, vomiting, diarrhea, and hemorrhagic/pseudomembranous colitis.
Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (~~See~~see **WARNINGS**).

Hypersensitivity Reactions – Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson Syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported.
Note: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver - A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Renal – Crystalluria has also been reported (see **OVERDOSAGE**).

Hemic and Lymphatic Systems - Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System – Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Miscellaneous - Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Clarithromycin:
The following adverse reactions from the labeling for clarithromycin are provided for information.

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side effects.

The most frequently reported events in adults were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

Postmarketing Experience:
Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, manic behavior, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during postmarketing surveillance. Events usually resolve with discontinuation of the drug.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

There have been reports of interstitial nephritis coincident with clarithromycin use.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients~~.~~ (~~See~~ see **WARNINGS and PRECAUTIONS**).

Changes in Laboratory Values: Changes in laboratory values with possible clinical significance were as follows: *Hepatic* - elevated SGPT (ALT) ~~<~~less than 1%, SGOT (AST) ~~<~~ less than 1%, GGT ~~<~~ less than 1%, alkaline phosphatase ~~<~~ less than 1%, LDH ~~<~~ less than 1%, total bilirubin ~~<~~ less than 1%; *Hematologic* - decreased WBC ~~<~~ less than 1%, elevated prothrombin time 1%; *Renal* - elevated BUN 4%, elevated serum creatinine ~~<~~ less than 1%. GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

11. The following changes were made in the **OVERDOSAGE** section:

OVERDOSAGE
In case of an overdose, patients should contact a physician, poison control center, or emergency room. There is neither a pharmacologic basis nor data suggesting an increased toxicity of the combination compared to individual components.

PREVACID~~Lansoprazole~~:

~~Oral doses up to 5000 mg/kg in rats (approximately 1300 times the 30 mg human dose based on body surface area) and mice (about 675.7 times the 30 mg human dose based on body surface area) did not produce deaths or any clinical signs.~~

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

Oral PREVACID doses up to 5000 mg/kg in rats (approximately 1300 times the 30 mg human dose based on BSA) and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text dated April 27, 2007.

If you have any questions, please call Christine Lincoln, RN, M.S., MBA, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Renata Albrecht

10/30/2007 03:17:14 PM