DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-757/S-006, S-008

TAP Pharmaceutical Products, Inc.
Attention: Douglas Donovan
Assistant Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Mr. Donovan:

Please refer to your supplemental new drug application dated November 5, 2001 and November 4, 2002, received November 6, 2001 and November 5, 2002, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevpac® (lansoprazole 30-mg capsules, amoxicillin 500-mg capsules, and clarithromycin 500-mg tablets, USP).

These supplemental new drug applications provide for the following changes to the Prevpac® package insert. Added text is noted by double underline and deleted text is noted by ~~strikethrough~~:

1. "USP" was added to clarithromycin to read as follows:

> (lansoprazole 30-mg capsules, amoxicillin 500-mg capsules, and clarithromycin 500-mg tablets, USP)

2. DESCRIPTION

- The description of Trimox® was revised as follows:

> The ~~maroon and light pink~~ flesh body/maroon cap capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin.

- The description of Biaxin® was revised as follows:

> Each yellow oval film-coated immediate-release tablet contains 500 mg of clarithromycin and the following inactive ingredients: ~~cellulosic polymers~~ hydroxypropyl methylcellulose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, ~~FD&C Blue No. 1,~~ magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, ~~silicon dioxide~~, sorbic acid, sorbitan monooleate, ~~stearic acid, talc,~~ titanium dioxide, and vanillin.

3. CLINICAL PHARMACOLOGY

- In the PREVACID subsection the following subheadings were added in order to organize the text (which remained unchanged): **Special Populations** /***Geriatric, Renal Insufficiency, Hepatic Insufficiency, Race.***

- The **Amoxicillin** subsection was revised to read:

Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is ~~well~~ rapidly absorbed ~~from the gastrointestinal tract and may be given with no regard to food~~ after oral administration. It diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein-bound. In blood serum, amoxicillin is approximately 20% protein-bound as compared to 60% for penicillin G.

Orally administered doses of 500-mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 5.5 mcg/mL to 7.5 ~~ug/mL~~ mcg/mL.

Detectable serum levels are observed up to ~~eight~~ 8 hours after an orally administered dose of amoxicillin. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

- The first two paragraphs of the **Clarithromycin** subsection were revised to read:

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, ~~F~~food slightly delays ~~both~~ the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of ~~and the~~ formation of the antimicrobially active metabolite, 14-OH clarithromycin~~.~~ or its peak plasma concentration but does slightly increase the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, ~~clarithromycin~~ BIAXIN tablets may be given without regard to food.

In ~~fasting~~ nonfasting healthy human subjects (males and females), peak ~~serum~~ plasma concentrations were attained within ~~two~~ 2 to 3 hours after oral dosing. Steady-state peak ~~serum~~ plasma clarithromycin concentrations were attained ~~in~~ within two to three days and were approximately ~~2 to~~ 3 to 4 µg/mL with a 500-mg dose aministered every 8 to 12 hours. The elimination half-life of clarithromycin was 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended dose of 500 mg administered every 8 to 12 hours. With a 500-mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin~~, the principle metabolite~~ is up to 1 µg/mL, and its elimination half-life is about 7 to 9 hours. The steady-state concentration of this metabolite is generally attained within ~~2 to~~ 3 to 4 days.

- Omeprazole was deleted from the **Antisecretory activity** subsection which now reads as follows:

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

Mean Antisecretory Effects after Single and Multiple Daily Dosing

		PREVACID				~~*Omepra zole*~~	
	Baseline	15 mg		30 mg		~~20 mg~~	
Parameter	Value	Day 1	Day 5	Day 1	Day 5	~~Day 1~~	~~Day 5~~

Mean 24-Hour pH	2.1	2.7+	4.0+	3.6*	4.9*	~~2.5~~	~~4.2+~~
Mean Nighttime pH	1.9	2.4	3.0+	2.6	3.8*	~~2.2~~	~~3.0+~~
% Time Gastric pH>3	18	33+	59+	51*	72*	~~30+~~	~~61+~~
% Time Gastric pH>4	12	22+	49+	41*	66*	~~19~~	~~51+~~

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

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

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.

4. CLINICAL STUDIES

•The following sentence that appears after the **Eradication Rates-Triple Therapy** table was revised to read:

Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and H. pylori infection at baseline defined as at least two of three positive endoscopic tests from CLOtest® ~~(Delta West Ltd., Bentley, Australia.),~~ histology and/or culture.

5. CONTRAINDICATIONS

•The following sentence was added to the end of this section:

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

6. WARNINGS

•The **Amoxicillin** subsection was revised to read:

Serious and occasionally fatal hypersensitivity ~~(anaphylactoid~~ anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more ~~apt~~ likely 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~~s~~. Before initiating therapy with ~~any penicillin~~ amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, ~~and~~ or other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and ~~the~~ appropriate therapy instituted.

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

•The first sentence in the **Amoxicillin and/or Clarithromycin** subsection was revised to read:

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening.

7. PRECAUTIONS

•The second paragraph was revised to read:

The possibility of superinfections with mycotic ~~organisms~~ or bacterial pathogens should be kept in mind during therapy. ~~In such cases~~ If superinfections occur, ~~discontinue~~ PREVPAC should be discontinued and ~~substitute~~ appropriate ~~treatment~~ therapy instituted.

•The ***Information for Patients*** subsection was revised to read:

Each dose of PREVPAC contains four pills: one pink and black capsule (PREVACID), two flesh body/maroon cap ~~maroon and light pink~~ capsules (amoxicillin) and one yellow tablet (clarithromycin). Each dose should be taken twice per day before eating. Patients should be instructed to swallow each pill whole.

Biaxin may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

•The first two paragraphs of the **Drug Interactions, PREVACID** subsection were revised to read:

PREVACID is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that PREVACID 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 ~~or terfenadine~~ in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When PREVACID 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 PREVACID 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 PREVACID, 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.

•A new **Amoxicillin** subsection was added to **Drug Interactions** to read:

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin may result in increased and prolonged blood levels.

Chloramphenicol, erythromycins, sulfonamides, and tetracyclines may interfere with bactericidal effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

• The **Drug Interactions, Clarithromycin** subsection was revised to read (first four paragraphs remain unchanged):

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin levels concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin or erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

The following CYP3A based drug interactions have been observed with erythromycin products and/or with clarithromycin in post-marketing experience:

Antiarrhythmics: There have been post-marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should also be monitored.

*Ergotamine/dihydroergotamin*e: Concurrent use of erythromycin or clarithromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dyesthesia.

Triazolobenziodidiazepines (such as triazolam and alprazolam) and related benzodiazepines (such as midazolam): Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. There have been post-marketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

*HMG-CoA Reductase Inhibitor*s: As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin; reduction of sildenafil dosage should be considered. (See Viagra package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, and bromocriptine.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated (see C**ONTRAINDICATION**S.)

In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

For information on interactions between clarithromycin in combination with other drugs which may be administered to HIV-infected patients, see the BIAXIN package insert, Drug Interactions, under the **PRECAUTIONS** section.

~~The following drug interactions, other than increased serum concentrations of carbamazepine and active acid metabolite of terfenadine, have not been reported in clinical trials with clarithromycin; however, they have been observed with erythromycin products and/or with clarithromycin in postmarketing experience.~~

~~Concurrent use of erythromycin or clarithromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.~~

~~Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam. There have been postmarketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.~~

~~There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P_{450}, concomitant administration of clarithromycin with astemizole is not recommended.~~

~~As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin), through inhibition of cytochrome P450 metabolism of these drugs.~~
~~Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.~~

~~The use of erythromycin and clarithromycin in patients concurrently taking drugs metabolized by the cytochrome P_{450} system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin and/or clarithromycin with carbamazepine, cyclosporine, tacrolimus, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, cisapride, pimozide, rifabutin, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P_{450} system should be monitored closely in patients concurrently receiving these drugs.~~

• The **Carcinogenesis, Mutagenesis, Inpairment of Fertility, Amoxicillin** subsection was revised to read:

Long-term studies in animals have not been performed ~~with Amoxacillin~~ to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted.

• The **Nursing Mothers** subsection was revised to read:

~~Amoxicillin is excreted in human milk in very small amounts. Because of the potential for serious adverse reactions in nursing infants from PREVPAC, a decision should be made whether to discontinue nursing or to discontinue the drug therapy, taking into account the importance of the therapy to the mother.~~

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. It is not known whether clarithromycin is excreted in human milk. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk.

Due to the potential for serious adverse reactions in nursing infants from PREVPAC, and the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue PREVPAC, taking into account the importance of the therapy to the mother.

•The subheading "**Geriatric Use**" was changed to "**Use in Geriatric Patients**".

8. ADVERSE REACTIONS

•This section was revised as follows (the first two paragraphs and the "**Adverse Reactions Most Frequently Reported in Clinical Trials**" table remained unchanged):

PREVACID:

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

Worldwide, over ~~6100~~ 10,000 patients have been treated with lansoprazole in Phase ~~II-III~~ 2-3 clinical trials involving various dosages and duration of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term trials.

Incidence in Clinical Trials

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

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

Body System/Adverse Event	*PREVACID* ~~(N=1457)~~ ~~%~~	*Placebo* ~~(N=467)~~ ~~%~~
Body as a Whole		
Abdominal Pain	~~1.8~~	~~1.3~~
Digestive System		

Diarrhea	~~3.6~~	~~2.6~~
Nausea	~~1.4~~	~~1.3~~

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

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

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

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

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

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

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 labilitiy, hallucinations, hemiplegia, hostility aggravated, hyperkinesias, 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, albuminuria, 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

Ongoing 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, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Special Senses* – speech disorder; *Urogenital System* – urinary retention.

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 albuminurai, glycosuria, and hematuria were also reported.

Additional isolated laboratory abnormalities were reported. Additional isolated laboratory abnormalities were reported.

In the placebo-controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% ~~(1/250)~~ (4/978) placebo patients and ~~0.3% (2/795)~~ (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.

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.

~~Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea~~ The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal - Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. ~~(These reactions are usually associated with oral dosage forms.)~~

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (See **WARNINGS**.)

Hypersensitivity Reactions - ~~Skin~~ Erythematous maculopapular rashes, ~~and urticaria have been reported frequently. A few cases of exfoliative dermatitis and erythema multiforme~~ Stevens-Johnson Syndrome, toxic epidermal necrolysis, and urticaria have been reported. ~~Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.~~ ~~**Note**:~~ **NOTE:** ~~Urticaria, other skin rashes, and serum sickness like~~ These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ~~penicillin~~ amoxacillin should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to ~~penicillin~~ amoxacillin therapy. ~~Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.~~

Liver - A moderate rise in ~~serum glutamic oxaloacetic transaminase~~ AST (SGOT) has been noted, ~~particularly in infants,~~ but the significance of this finding is unknown.

Hemic and Lymphatic Systems - Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the 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.

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 and 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, 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.
~~Rarely, erythromycin and~~ As with other macrolides, clarithromycin ~~have~~ has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes ~~in individuals with prolonged QT_C intervals~~.

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

9. OVERDOSAGE

•The **Amoxicillin** subsection was revised to read:

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function

because of decreased renal clearance of amoxicillin. Amoxicillin can be removed from circulation by hemodialysis.

•A **Clarithromycin** subsection was added to read:

Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

10. HOW SUPPLIED

•The **Trimox** subsection was revised to read:

–four ~~maroon and light pink~~ flesh body/maroon cap amoxicillin 500-mg capsules, USP, printed with "BRISTOL 7279" ~~imprinted on the capsules.~~ in black ink on both body and cap.

•The **Biaxin** subsection was revised to read:

–two yellow oval film-coated clarithromycin 500-mg tablets, USP, debossed with the Abbott logo ~~and " KL" imprinted in blue~~ on one side and "KL" on the other side of the tablets.

•The storage statement was revised to read:

Storage: Protect from light and moisture.
Store at a controlled room temperature between ~~59° F and 86° F (15° C and 30° C).~~ 20°C and 25°C (68°F and 77°F).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revision noted below. Accordingly, these supplemental applications are approved effective on the date of this letter.

As Robin Anderson of this Division discussed with you, there is a typographical error in the **CLINICAL PHARMACOLOGY** section, PREVACID subsection. This subsection should be revised as follows:

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. ~~b) (b)~~ 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-dose oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert submitted November 4, 2002) and include the minor editorial revision indicated.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you

may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-757/S-006, S-008." Approval of this submission by FDA is not required before the labeling is used.

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

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
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

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