



NDA 50-757/S-016

Takeda Global Research & Development Center, Inc.
Attention: Leslie Abelson
Manager Regulatory Affairs
675 N Field Drive
Lake Forest, Illinois 60045

Dear Ms. Abelson:

Please refer to your supplemental new drug application dated October 1, 2008, received October 2, 2008, submitted under section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act for PREVPAC[®] (lansoprazole/amoxicillin/clarithromycin).

We also acknowledge receipt of your submission dated March 18, 2009.

This supplemental application, proposes revisions to the **DESCRIPTION, CLINICAL PHARMACOLOGY/Special Populations, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, PRECAUTIONS/Information for Patients, PRECAUTIONS/Drug Interactions, ADVERSE REACTIONS** and **HOW SUPPLIED** sections of the package insert as described below, and provides for numerous editorial changes not reflected in this letter.

We have 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 submitted on March 19, 2009.

The revisions to the package insert are as follow (additions are noted with underline and deletions noted with ~~strikethrough~~):

1. In the **DESCRIPTION** section, the first paragraph, first sentence is revised as follows:

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

2. In the **DESCRIPTION** section, the PREVACID (LANSOPRAZOLE) Delayed-Release Capsules subsection, the order of the inactive ingredients is rearranged as follows:

~~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.~~ Sugar sphere, sucrose, methacrylic acid copolymer, low substituted hydroxypropyl cellulose, starch, magnesium carbonate, talc, polyethylene glycol, titanium dioxide, polysorbate 80, hydroxypropyl cellulose, colloidal silicon dioxide.

3. The **CONTRAINDICATIONS** section is revised as follows:

Prevpac is contraindicated in patients with known hypersensitivity to any component of the formulation of Prevacid, ~~any macrolide antibiotic, or any penicillin.~~

A history of allergic reaction to any of the penicillins is a contraindication.

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

Concomitant administration of Prevpac and any of the following drugs is contraindicated: cisapride, pimozone, astemizole, terfenadine, ergotamine or dihydroergotamine. (see **Drug Interactions**). There have been post-marketing reports of drug interactions when clarithromycin and /or erythromycin are coadministered with cisapride, pimozone, 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.~~

4. In the **WARNINGS** section, the last paragraph of the section in the last approved package insert is repositioned to become the 4th paragraph.

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.

5. In the **PRECAUTIONS** section, the third paragraph becomes the first paragraph as follows:

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

6. In the **PRECAUTIONS** section the third paragraph is added as follows:

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving clarithromycin therapy.

7. In the **PRECAUTIONS** section, the last paragraph is revised as follows:

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

8. In the **PRECAUTIONS/Information for Patients** section, the second paragraph is revised as follows:

~~Biaxin~~ PREVPAC may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.
9. In the **PRECAUTIONS/Information for Patients** section, the fourth paragraph is added as follows:

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.
10. In the **PRECAUTIONS** section, a new subsection titled **Laboratory Tests/Amoxicillin** is created as follows:

Laboratory Tests
Amoxicillin
As with any potent drug, periodic assessment of renal, hepatic and hematopoietic function should be made during prolonged therapy.
11. In the **PRECAUTIONS/Drug Interactions** subsection, the first paragraph is added as follows:

No drug interaction studies have been conducted specifically with PREVPAC. The following drug interactions are for the individual drug components, PREVACID (lansoprazole), amoxicillin, and clarithromycin. Therefore, the decision to adjust dosage should depend on the clinician's assessment of among other things, the cumulative or net effect of the drug components of PREVPAC.
12. In the **PRECAUTIONS/Drug Interactions/Clarithromycin** subsection, a fourth, fifth, sixth and seventh paragraph is added as follows:

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations. When 500 mg of clarithromycin were administered twice daily, steady-state zidovudine AUC was reduced by a mean of 12% (n = 4). Individual values ranged from a decrease of 34% to an increase of 14%. Based on limited data in 24 patients, when clarithromycin tablets were administered two to four hours prior to oral zidovudine, the steady-state zidovudine C_{max} was increased by approximately 2-fold, whereas the AUC was unaffected.

Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state clarithromycin C_{min} and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

Concomitant administration of clarithromycin and ritonavir (n = 22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin. Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. However, for patients with renal impairment and receiving ritonavir, the dose of clarithromycin should be reduced. Please refer to the clarithromycin package insert for complete information.

13. In the **PRECAUTIONS/Drug Interaction/Clarithromycin** subsection, the last paragraph is deleted from the section as follows:

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

14. In the **PRECAUTIONS/Drug Interaction/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the fifth paragraph is revised as follows:

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate. Amoxicillin and potassium clavulanate was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin and potassium clavulanate was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin and potassium clavulanate was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg per kg (approximately 3 times the human dose in mg per m²).

15. In the **PRECAUTIONS/Use in Geriatric Patients** subsection, three new paragraphs are added as follows:

Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering PREVPAC to this patient population.
An analysis of clinical studies of amoxicillin was conducted to determine whether subjects aged 65 and over respond differently from younger subjects. Of the 1,811 subjects treated with capsules of amoxicillin, 85% were less than 60 years old, 15% were \geq 61 years old and 7% were \geq 71 years old. This analysis and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment (see **WARNINGS** and **PRECAUTIONS**).

16. In the **ADVERSE REACTIONS/Incidence in Clinical Trials** subsection, the fifth paragraph is modified to add additional adverse experiences as follows:

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~~ gastrointestinal 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* – avitaminosis, gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss; *Musculoskeletal System* - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, ptosis, synovitis; *Nervous System* – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, dementia, 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, lung fibrosis, 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, amblyopia, blepharitis, blurred vision, cataract, conjunctivitis, deafness, dry eyes, ear/eye disorder, eye pain, glaucoma, otitis media, parosmia, photophobia, retinal degeneration/disorder, 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 retention, urinary tract infection, urinary urgency, urination impaired, vaginitis.

17. In the **HOW SUPPLIED** section the first sentence is revised as follows:

Prevpac is supplied as an individual daily administration ~~pack~~ card, each containing:

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling text for the package insert and patient package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, “**SPL for approved supplements NDA 50-757/S-016**”.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

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
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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 June Germain, Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

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

Enclosure: package insert

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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