



NDA 50-757/S-011

**PRIOR APPROVAL SUPPLEMENT**

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 January 31, 2005, received February 1, 2005, submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for PREVPAC® (lansoprazole/amoxicillin/clarithromycin).

This supplemental new drug application provides for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

1. The TRIMOX® (amoxicillin, USP) subsection of the **DESCRIPTION** section was revised to read:

Amoxicillin, USP, (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate is a semi-synthetic penicillin 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-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. Amoxicillin capsules are intended for oral administration.

2. The Amoxicillin: subsection of the **CLINICAL PHARMACOLOGY** section was revised to read:

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.

3. The **REFERENCES** subsection under *Susceptibility Test for Helicobacter Pylori* in the **Microbiology** section was relocated to the **REFERENCES** subsection following the **How Supplied** Section:

Reference

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

4. The first paragraph under the **CLINICAL STUDIES** section was revised to read:

The triple therapy regimen (PREVACID 30 mg ~~BD~~ b.i.d. plus amoxicillin 1 g ~~BD~~ b.i.d. plus clarithromycin 500 mg ~~BD~~ b.i.d.) produced statistically significant higher eradication rates than PREVACID plus amoxicillin, PREVACID plus clarithromycin, and amoxicillin plus clarithromycin dual therapies.

5. The formatting in the Amoxicillin subsection of the **WARNINGS** section was revised to make the existing information more prominent as follows. No new information was added.

- a. The first paragraph was changed to all capital letters:

~~Serious and occasionally fatal hypersensitivity (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 likely to occur in individuals with a history of penicillin hypersensitivity and/or a history to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and appropriate therapy instituted.~~

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (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 LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED

- b. The second paragraph was bolded:

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

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

6. The subsection Amoxicillin and/or Clarithromycin: in the Amoxicillin: subsection of the **WARNINGS** section was revised to read:

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 ~~of the drug~~ alone.

7. The **PRECAUTIONS** section was revised as follows:

- a. The Amoxicillin: subsection under **Drug Interactions** was revised as follows:

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

Chloramphenicol, ~~erythromycins~~ macrolides, sulfonamides, and tetracyclines may interfere with bactericidal effects of penicillin.

2. The following was added as a subsection:

**Drug/Laboratory Test Interactions**

High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

- b. The following was added to the **Nursing Mothers** section:

Caution should be exercised when amoxicillin is administered to a nursing woman.

7. The following changes were made to the Amoxicillin subsection of the **ADVERSE**

**REACTIONS** section:

- a. To the *Gastrointestinal* subsection:

Nausea, vomiting, diarrhea, and hemorrhagic/pseudomembranous colitis

- b. To the *Hypersensitivity Reactions* subsection:

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.

- c. To the *Liver* subsection:

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.

- d. A *Renal* subsection was added as follows:

Renal - Crystalluria has also been reported (See OVERDOSAGE)

- e. To the *Hemic and Lymphatic Systems* subsection

Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins.

- f. A *Miscellaneous* subsection was added as follows:

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

8. The following was added to the Amoxicillin subsection of the **OVERDOSAGE** section:

A prospective study of 51 patients at a poison control center suggested that overdoses of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdose with amoxicillin.

Crytalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdose in adult and pediatric patients. In case of overdose,

adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

9. The following was modified in the **HOW SUPPLIED** section:

~~Storage: Protect from light and moisture.~~

Store at a controlled room temperature between 200C and 250C (680F and 770F).

Protect from light and moisture.

10. The **REFERENCES** section was modified as follows:

- a. Reference 1. was relocated from the *Susceptibility Test for Helicobacter Pylori* subsection in the **Microbiology** section.
- b. Reference 2. was a new addition.

#### **REFERENCES**

1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Testing, Tampa, FL, January 11-13, 1998
2. Swanson Bierman B, Dean BS, Lopez G, Krenzelok P. The effects of penicillin and cephalosporin ingestions in children less than six years of age. Vet Hum Toxicol. 1988;30:66-67.

11. The revision number was updated from previous package insert

~~03-5322-R6 Rev. October, 2003~~

TAPDN253-V1 Rev. Month Year

©1997 ~~2003~~ Year TAP Pharmaceutical Products Inc.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text (enclosed).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL 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, but no 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, designate this submission “FPL for approved supplement NDA 50-757/S-011.” Approval of this submission by FDA is not required before the labeling is used.

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

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 Kristen Miller, Pharm.D., Regulatory Project Manager, 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

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Renata Albrecht  
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