



NDA 50-757/S-012

NDA 50-757/S-013

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 new drug application (NDA) for PREVPAC® (lansoprazole/amoxicillin/clarithromycin).

A. Approval of Prior Approval Labeling Supplement

Please also refer to your supplemental new drug application dated July 18, 2006 (S-012), received July 19, 2006 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREVPAC® (lansoprazole/amoxicillin/clarithromycin).

This supplemental new drug application provides for modification of the **ADVERSE REACTIONS/Postmarketing/Body as a Whole** subsection wording from “anaphylactoid-like reaction” to “anaphylactic/anaphylactoid reactions” to clarify the text.

B. Approval of “Changes Being Effected” Labeling Supplement

Please also refer to your supplemental new drug application dated July 21, 2006 (S-013), received July 24, 2006 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREVPAC® (lansoprazole/amoxicillin/clarithromycin).

This “Changes Being Effected” supplemental new drug application provides for the following changes to the PREVPAC® package insert, which correspond to revisions in the approved package insert for Biaxin (clarithromycin), one of the components of PREVPAC® (deletions are indicated by ~~strikethrough~~ and additions are indicated by double underline):

1. In the second paragraph of the **CONTRAINDICATIONS** section:

Concomitant administration of PREVPAC with cisapride, pimozone, astemizole, ~~or~~ 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.

2. In the **WARNINGS/Clarithromycin**: subsection, insert the following after the **bolded** paragraph.

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 **PRECAUTIONS**).

3. In the **PRECAUTIONS/Drug Interactions/Clarithromycin**: subsection:

- a. Insert the following after the fifth paragraph:

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity. (See **WARNINGS**).

- b. Modify the text as follows:

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

Ergotamine/dihydroergotamine: Post-marketing reports indicate that coadministration of ~~Concurrent use of erythromycin or clarithromycin and~~ with ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by ~~severe peripheral~~ vasospasm and ~~dyesthesia~~ ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

4. In the **ADVERSE REACTIONS/Clarithromycin/Postmarketing Experience**: subsection, add the following text after the last paragraph:

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 **WARNINGS and PRECAUTIONS**).

We completed our review of these supplemental applications (S-012 and S-013). These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

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

NDA 50-757/ S-012

NDA 50-757/ S-013

Page 3

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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions “**FPL for approved NDA 50-757/S-012 and S-013.**” Approval of these submissions by FDA is not required before the labeling is used.

Submit revised 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 in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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, please call Kristen Miller, Pharm.D., Regulatory 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 of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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

Renata Albrecht
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