



NDA 50-757/S-014

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 November 21, 2006, received December 2, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREVPAC<sup>®</sup> (lansoprazole/amoxicillin/ clarithromycin).

We acknowledge receipt of your submission dated March 16, 2007.

This "Changes Being Effected" supplemental new drug application provides for the following changes to the PREVPAC<sup>®</sup> package insert (deletions are indicated by ~~strike through~~ and additions are indicated by underline):

1. In the **PRECAUTIONS/Drug Interactions/PREVACID** subsection, the following revisions were made:

PREVACID causes long-lasting inhibition of gastric acid secretion. PREVACID substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, PREVACID, or other proton pump inhibitors, should not be co-administered with atazanavir.

It is theoretically possible that PREVACID may also interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

PREVACID is metabolized through the cytochrome P<sub>450</sub> 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<sub>450</sub> system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P<sub>450</sub> 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.

PREVACID has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining PREVACID 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID Delayed-Release Capsules; this did not interfere with its effect.

~~PREVACID causes a profound and long lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that PREVACID may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin, esters, iron salts, digoxin).~~

2. In the **ADVERSE REACTIONS/Postmarketing** subsection, “myositis” and “interstitial nephritis” were added.

*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.*

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 dated March 16, 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

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