CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 050757

Trade Name: PREVPAC

Generic Name: LANSOPRAZOLE/ CLARITHROMYCIN/ AMOXICILLIN

Sponsor: TAP HOLDINGS, INC

Approval Date: 12/02/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 050757

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Pharmacology Review(s)				X
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Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 050757

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-757

TAP Holdings, Inc.
Attention: Linda J. Peters, M.S.
Bannockburn Lake Office Plaza
22355 Waukegan Road
Deerfield, IL 60015

DEC 02 1997

Dear Ms. Peters:

Please refer to your new drug application dated July 24, 1997, received July 25, 1997, submitted under section 505 of the Federal Food, Drug, and Cosmetic Act for PREVPAC™, a patient compliance pack which contains the triple therapy regimen of PREVACID® (lansoprazole) Delayed-Release Capsules. We note that the this product is subject to the exception provisions of section 125 (2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated August 14, August 15, September 18 and September 22, 1997. The User Fee goal date for this application is July 25, 1998.

This new drug application provides for a compliance pack which contains PREVACID® (lansoprazole) Delayed-Release Capsules, clarithromycin tablets and amoxicillin capsules for the eradication of *Helicobacter pylori* in patients with active duodenal ulcer disease or a one-year history of a duodenal ulcer.

We have completed the review of this application, including the submitted draft labeling, 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 draft labeling in the submission dated December 1, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on December 1, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case 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 "FINAL PRINTED LABELING" for approved NDA 50-757. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit one market package of the drug product when it is available.

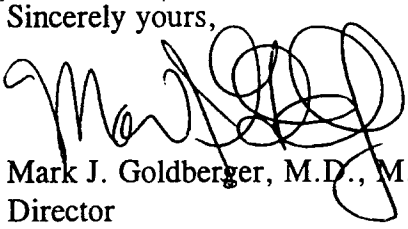
In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Special Pathogens and Immunologic Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 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, please contact Robin Anderson, Project Manager, at (301) 827-2335.

Sincerely yours,



Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens
and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 50-757
HFD-590/Div. files
HFD-590/CSO/R.Anderson
HFD-520/MO/L. Giradi
HFD-520/CHEM/J. Timper
HFD-590/A. Med. TL/R. Hopkins
HFD-180/CSO/M. Walsh (with labeling)
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-205 / FOI / C. Hatton (with labeling)

Concurrence Only:
HFD-590/Act.SuperCSO/LHubbard
HFD-590/Director/MGoldberger

Drafted by: RA/November 28, 1997/approval.pre
Initialed by:
final:

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050757

MEDICAL REVIEW(S)

NOV 20 1997

Medical Officer's Review of NDA 50-757
PREVPAC

Sponsor: TAP Holdings, Inc.

Contact Person: Linda J. Peters, M.S.
Bannockburn Lake Office Plaza
22355 Waukegan Road
Deerfield, IL 60015
(847) 374-5481

Date of Application: July 24, 1997

Date of Receipt by CDER: July 25, 1997

Date of Review: October 29, 1997

Revised: November 12, 1997

Purpose of Submission: This NDA is intended to support the use of PREVPAC™, a patient compliance pack which contains the triple therapy regimen of PREVACID (lansoprazole), TRIMOX (amoxicillin, USP) and BIAXIN Filmtab (clarithromycin tablets), for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year).

Regulatory History: On June 17, 1997, TAP received FDA approval for the 14-day triple therapy regimen of lansoprazole/amoxicillin/clarithromycin, as well as the dual therapy regimen of lansoprazole/amoxicillin (NDA 50-876 and 50-877, respectively).These NDA's were later designated as Type 6 NDA's and became part of PREVACID NDA 20-406, held by the Division of Gastrointestinal and Coagulation Drug Products, HFD-180. These NDA's contain the clinical information to support PREVPAC.

This submission contains information on Chemistry, Manufacturing and Controls (CMC) and Methods Validation, Samples and Labeling. This review will comment on the proposed draft labeling for PREVPAC. There is no new clinical information. The reader is referred to the Chemistry review by Dr. Jim Timper for other pertinent information.

The sponsor submitted the following proposed labeling. The MO will comment after each major section. Sections or their parts that are identical to the PREVACID labeling approved on June 17, 1997, will not be commented upon.

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

THESE PRODUCTS ARE INTENDED ONLY FOR USE AS DESCRIBED. The individual products contained in this package should not be used alone or in combination for other purposes. The information described in this labeling concerns only the use of these products as indicated in this daily administration pack. For information on use of the individual components when dispensed as individual medications outside this combined use for treating *Helicobacter pylori (H. pylori)*, please see the package inserts for each individual product.

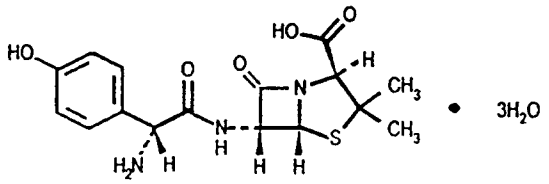
MO Comment: This is acceptable.

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

MO Comment: This is acceptable.

The following descriptive information has been added:

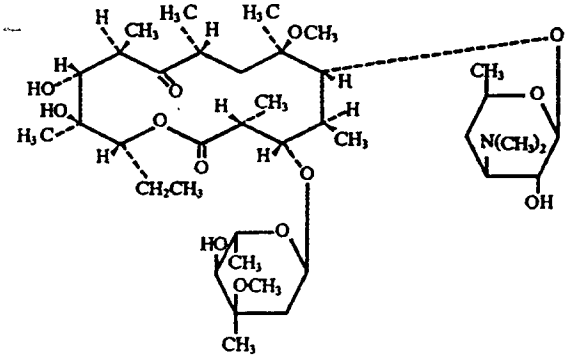
TRIMOX® (amoxicillin, USP)
Amoxicillin, USP, [2S-[2α,5α, 6β (S*)]]-6-[[amino(4-hydroxyphenyl)-acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate, is a semisynthetic penicillin, an analogue of ampicillin. It has the following chemical structure:



The empirical formula is $C_{16}H_{18}N_3O_5S \bullet 3H_2O$, and the molecular weight is 419.45.

The maroon and light-pink capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin. The inactive ingredient in the capsules is magnesium stearate.

BIAXIN® Filmtab® (clarithromycin tablets)
Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.
Each yellow oval film-coated tablet contains 500 mg of clarithromycin and the following inactive ingredients: cellulosic polymers, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin.

MO Comment: These additions are acceptable.

In the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section the following additions have been made:

Amoxicillin:
Amoxicillin is stable in the presence of gastric acid and is well absorbed from the gastrointestinal tract and may be given with no regard to food. 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 to 7.5 μg/mL.

Detectable serum levels are observed up to eight 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.

MO Note: This addition is acceptable; it comes from the TRIMOX (amoxicillin, USP) package insert, April, 1996.

Clarithromycin:
Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. Food slightly delays both the onset of clarithromycin absorption and the formation of the antimicrobially active metabolite, 14-OH clarithromycin, but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food.

In fasting healthy human subjects, peak serum concentrations were attained within two hours after oral dosing. Steady-state peak serum clarithromycin concentrations were attained in two to three days and were approximately 2 to 3 μg/mL with a 500 mg dose administered every 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 12 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin, the principal 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 days.

After a 500-mg tablet every 12 hours, the urinary excretion of clarithromycin is approximately 30%. The renal clearance of clarithromycin approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with a 500-mg tablet administered every 12 hours.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. (See **PRECAUTIONS and DOSAGE AND ADMINISTRATION.**)

MO Note: This addition comes from the BIAXIN (clarithromycin) package insert, January, 1997. In the second paragraph, within the second and third sentences, "500 mg dose" should be changed to "500-mg dose."

The following has been added to the Microbiology subsection:

Pharmacodynamics

Microbiology

Susceptibility Testing for Helicobacter pylori

Development of resistance to amoxicillin and/or clarithromycin did not occur with coadministration of PREVACID, amoxicillin, and clarithromycin in clinical studies. However, susceptibility testing should be done, if possible, in patients who fail therapy. If resistance to amoxicillin or clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy is recommended.

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

MO Comment: The first sentence should be deleted. The above should be changed to the following to reflect the original language in the approved PREVACID labeling:

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If resistance to amoxicillin or clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy is recommended.

Under the subsection, ***Antisecretory activity, the following sentence has been added:***

"Higher levels of acid suppression have been predicted to potentiate the activity of antibiotics in eradicating *Helicobacter pylori (H. pylori).*"

MO Comment: This sentence should be deleted to reflect the approved labeling of June 17,1997.

The **INDICATIONS AND USAGE SECTION** has been revised to read as follows:

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

"PREVPAC (PREVACID, amoxicillin, and clarithromycin) is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**)."

MO Comment: This should be revised to read as follows:

"The components in PREVPAC (PREVACID, amoxicillin, and clarithromycin) are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION.**)"

The **CONTRAINDICATIONS** section has been worded as follows:

CONTRAINDICATIONS
PREVPAC is contraindicated in patients with known hypersensitivity to any component of the formulation of PREVACID, any macrolide antibiotic, or any penicillin.

Concomitant administration of PREVPAC with cisapride, pimozide, or terfenadine is contraindicated. There have been postmarketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

MO Comment: This change is acceptable.

The **WARNINGS** section has been worded as follows:

Amoxicillin:
Serious and occasionally fatal hypersensitivity (anaphylactoid) 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 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. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

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

Clarithromycin:
CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. CLARITHROMYCIN HAS DEMONSTRATED ADVERSE EFFECTS OF PREGNANCY OUTCOME AND/OR EMBRYO-FETAL DEVELOPMENT IN MONKEYS, RATS, MICE, AND RABBITS AT DOSES THAT PRODUCED PLASMA LEVELS 2 TO 17 TIMES THE SERUM LEVELS ACHIEVED IN HUMANS TREATED AT THE MAXIMUM RECOMMENDED HUMAN DOSES. (See PRECAUTIONS - *Pregnancy.*)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.
MO Comment: This change is acceptable and reflects the TRIMOX as well as the BIAXIN package inserts.

The **PRECAUTIONS** section has been worded as follows:

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

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

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

Information for Patients: Each dose of PREVPAC contains four pills: one pink and black capsule (PREVACID), two 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.

The **Drug Interactions** subsection under **PRECAUTIONS** has been changed to include information on BIAXIN as follows:

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated. (See **CONTRAINDICATIONS.**)

Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

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

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.

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, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P_{450} system should be monitored closely in patients concurrently receiving these drugs.

MO Note: This addition is acceptable.

The **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section has been changed to include information on TRIMOX and BIAXIN as follows:

Amoxicillin:
Long-term studies in animals have not been performed with amoxicillin.

Clarithromycin:
The following *in vitro* mutagenicity tests have been conducted with clarithromycin:

Salmonella/Mammalian Microsomes Test
Bacterial Induced Mutation Frequency Test
In Vitro Chromosome Aberration Test
Rat Hepatocyte DNA Synthesis Assay
Mouse Lymphoma Assay
Mouse Dominant Lethal Study
Mouse Micronucleus Test

All tests had negative results except the *In Vitro* Chromosome Aberration Test which was weakly positive in one test and negative in another.

In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day (1.3 times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally at 150 mg/kg/day (2.4 times the recommended maximum human dose based on mg/m^2), clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits, *in utero* fetal loss occurred at an intravenous dose of 33 mg/m^2, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m^2.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

MO note: This is acceptable.

The **Pregnancy** subsection has been altered to reflect the BIAXIN labeling as follows:

Pregnancy
Teratogenic Effects. Pregnancy Category C
Category C is based on the pregnancy category for clarithromycin.

Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to 125 mg/kg/day (approximately 2 times the recommended maximum human dose based on mg/m^2) or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2, respectively) during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m^2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

MO Comment: This is acceptable. In addition, the following has been added to the section:

There were no adequate and well-controlled studies of PREVPAC in pregnant women. PREVPAC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS.**)

MO Comment: This is acceptable.

Changes to the ***Labor and Delivery, Nursing mothers, Pediatric Use, and Geriatric Use*** subsections were made as follows:

Labor and Delivery
Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether use of these drugs in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers
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.

Pediatric Use
Safety and effectiveness of PREVPAC in children infected with *H. pylori* have not been established (See **CONTRAINDICATIONS** and **WARNINGS**).

MO Note: The period should be placed inside the parentheses. Also, "children" should be changed to "pediatric patients." This is based on the pediatric rule.

Geriatric Use
Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering PREVPAC to this patient population.

MO Note: These changes are acceptable.

The **Laboratory Values** subsection under **ADVERSE REACTIONS** section has been changed to include the following information on Amoxicillin:

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.

The following adverse reactions have been reported as associated with the use of penicillin:

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

MO Note: This should be revised to read as follows: "Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea have been reported. (These reactions are usually associated with oral dosage forms.)

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

Liver - A moderate rise in serum glutamic oxaloacetic transaminase (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.

MO Note: The following was also included under the amoxicillin portion of the **Laboratory Values** subsection under **ADVERSE REACTIONS:**

Rarely, erythromycin and clarithromycin have been associated with 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 are from adult studies only.

MO Comment: The above is actually from the BIAXIN labeling and should be placed after the paragraph below on clarithromycin.

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.

The following post-marketing experience for clarithromycin was added to the PREVPAC labeling:

Postmarketing Experience:
Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis and Stevens-Johnson syndrome have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, vomiting, tongue discoloration, 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 have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, depersonalization, disorientation, hallucinations, insomnia, nightmares, psychosis, tinnitus, 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.

MO Comment: This addition is acceptable.

The **OVERDOSAGE** section has been changed to the following:

OVERDOSAGE
In case of an overdose, patients should contact a physician, poison control center, or emergency room. There is neither a pharmacologic basis nor data suggesting an increased toxicity of the combination compared to individual components.

MO Note: This change is acceptable.

The following information on amoxicillin has been added to the same section:

Amoxicillin:
In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. Amoxicillin can be removed from circulation by hemodialysis.

MO Note: This change is acceptable.

The **DOSAGE AND ADMINISTRATION** section has been changed as follows:

DOSAGE AND ADMINISTRATION
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**
The recommended adult oral dose is 30 mg PREVACID, 1 g amoxicillin, and 500 mg clarithromycin administered together twice daily (morning and evening) for 14 days. (See **INDICATIONS AND USAGE**).

PREVPAC is not recommended in patients with creatinine clearance less than 30 mL/min.

MO Comment: The period should be placed within the parentheses, after the word USAGE.

The **HOW SUPPLIED** section was changed to the following:

HOW SUPPLIED
PREVPAC is supplied as an individual daily administration pack, each containing:

PREVACID:
- two opaque, hard gelatin, black and pink PREVACID 30 mg capsules, with the TAP logo and "PREVACID 30" imprinted on the capsules.

TRIMOX:
- four maroon and light-pink amoxicillin 500 mg capsules, USP, with " BRISTOL 7279" imprinted on the capsules.

BIAXIN Filmtab:
- two yellow oval film-coated clarithromycin 500 mg tablets with the Abbott logo and " KL" imprinted in blue on one side of the tablets.

MO Note: "30 mg," "500 mg", "500 mg" should be changed to "30-mg," "500-mg," and "500-mg."

Conclusions and Recommendations:

This NDA for PREVPAC should be approved provided the sponsor makes the changes outlined in the above review. An approval letter should be sent to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

Luigi S. Girardi, M.D.

CC:
NDA 50-757
HFD-520/590 Division Files
GChikami Act Div Dir HFD-520 Gary K Chikami 11/13/97
MGoldberger Div Dir HFD-590 MJC 11/13/97
MAlbuerne Team Leader HFD-520 MDA 11/12/97
JTimper Chem HFD-520
DKatague Team Leader Chem HFD-520
JCintron Proj Man HFD-520
RAnderson Proj Man HFD-590
LUtrup Micro HFD-590
LGirardi MO HFD-520
RHopkins MO HFD-590

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050757

CHEMISTRY REVIEW(S)

AUG 2 8 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 50-757

CHEM.REVIEW #: 1 **REVIEW DATE:** 8/19/97

User Fee date is 1/25/97.

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	**7/24/97**	**7/25/97**	**8/19/97**
Amendment (by FAX)	8/15/97	To be submitted to the file	8/19/97

NAME & ADDRESS OF APPLICANT:

Tap Holdings Inc.
2355 Waukegan Road
Deerfield, IL 60015

DRUG SUBSTANCE NAME

Established: PREVPAC: a patient compliance pack that will contain PREVACID (lansoprazole), TRIMOX (amoxicillin) and BIAXIN Filmtab (clarithromycin tablets).
USAN: (See list below.)
Code #: n/a

PREVACID (lansoprazole, TAP) 30 mg capsule NDA 20-406	**BIAXIN (clarithromycin, Abbott Labs) 500 mg tablet NDA 50-662**	**TRIMOX (amoxicillin, APOTHECON) 500 mg capsule AADA 61-885**	***PREVPAC (lansoprazole/ clarithromycin/ amoxicillin) TAP NDA 50-757***

PHARMACOLOGICAL CATEGORY/INDICATION:

For the eradication of *Helicobacter pylori*

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: **Rx** The three component parts of the compliance pack are commercially available by prescription only. Upon approval of this NDA the physician will have the option to write a single prescription for a triple therapy package.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

PREVACID (lansoprazole) Delayed-Release Capsules

The active ingredient in PREVACID capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole, a compound that inhibits gastric acid secretion. Its empiracle formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. CAS-103577-45-3.

BIAXIN Filmtab (clarithromycin tablets)

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-O-methyl-erythromycin. CAS-81103-11-9. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96.

TRIMOX (amoxicillin USP)

Amoxicillin, USP, [2S-[2α,5α,6β(S*)]]-6-[[amino(4-hydroxyphenyl)-acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate, is a semisynthetic penicillin, an analog of ampicillin. CAS-61336-70-7.

RELATED DOCUMENTS:

Lansoprazole drug substance is manufactured by Takeda Chemical Industries Ltd., at their Hikari, Japan, facility. All respective information for lansoprazole drug substance is contained in the PREVACID, NDA 20-406, which is held by TAP Holdings Inc. Both the IND and NDA for PREVACID are on file with the Division of Gastrointestinal and Coagulation Drug Products (HFD-180).

Clarithromycin drug substance information is contained in the BIAXIN NDA 50-662, which is held by Abbott Laboratories. The NDA for BIAXIN is in HFD-520.

Amoxicillin drug substance is contained in the AADA 61-885, which is held by Apothecon, a Bristol-Myers Squibb company.

CONSULTS: This review is performed as a consult to HFD-590. The following items were requested with this review:

- EER submitted 8/15/97; District goal date is 11/20/97; userfee date is 1/25/98.
- Labeling and Nomenclature Committee consult found the trade name acceptable, 6/23/97.
- Environmental Assessment Waiver statement should be requested form the firm.
- All the products that constitute this compliance pack are approved and require no method validation submissions.

REMARKS/COMMENTS:

Letter from Eric Sheinin, ONDC, dated 12/16/97 agreed that the least expiration date among the three component products in PREVPAC would be granted with commitment for reporting the PREVPAC blister in an annual report as well as verifying that the blister packaging was as least as protective as the currently marketed blisters for the individual products. In addition three months of stability data should be provided. This stability data has been provided and it is adequate.

CONCLUSIONS & RECOMMENDATIONS:

There is a pending inspection of the dedicated penicillin packaging site; the firm should provide a statement to waiver the environmental assessment. The application is approvable until these two criteria are met.

JT 8/19/97

J. Timper

APPEARS THIS WAY
ON ORIGINAL

cc: Org. NDA 50-757
HFD-520/Division File
HFD-520/Katague/Team Leader, Chem DBK 8/25/97
HFD-520/Timper/Chem 6/26/97
HFD-520/Girardi/MO
HFD-520/Utrup/Micro
HFD-520/Cintron/CSO
HFD-590/Anderson/CSO
HFC-130/JAllen

Consult #796

PREVPAC HP
PREVPAC lansoprazole/clarithromycin/amoxicillin

The Committee noted one look alike/sound alike conflict: PREVACID. However, since this is a companion product by the same sponsor, the potential for conflict is low. There were no misleading or fanciful aspects found in the proposed name. The Committee discourages the use of suffixes without a definite medical or pharmaceutical meaning and also using the indication as part of the brand name. Therefore the Committee discourages the use of HP in the proprietary name.

The Committee has no reason to find the proposed name unacceptable.

Dwaring B 5/23/97

Chair, CDER Labeling and Nomenclature Committee

NOV 14 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 50-757

Addendum to Review #1

REVIEW DATE: 11/14/97
User Fee date is 1/25/97.

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	**7/24/97**	**7/25/97**	**8/19/97**
Amendment (by FAX)	8/15/97	8/18/97	8/19/97
Correspondence	9/22/97	9/23/97	11/14/97

NAME & ADDRESS OF APPLICANT:

Tap Holdings Inc.
2355 Waukegan Road
Deerfield, IL 60015

DRUG SUBSTANCE NAME

Established: PREVPAC: a patient compliance pack that will contain PREVACID (lansoprazole), TRIMOX (amoxicillin) and BIAXIN Filmtab (clarithromycin tablets).

USAN: (See list below.)

Code #: n/a

PREVACID (lansoprazole, TAP) 30 mg capsule NDA 20-406	**BIAXIN (clarithromycin, Abbott Labs) 500 mg tablet NDA 50-662**	**TRIMOX (amoxicillin, APOTHECON) 500 mg capsule AADA 61-885**	***PREVPAC (lansoprazole/ clarithromycin/ amoxicillin) TAP NDA 50-757***

PHARMACOLOGICAL CATEGORY/INDICATION:

For the eradication of *Helicobacter pylori*

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: **Rx** The three component parts of the compliance pack are commercially available by prescription only. Upon approval of this NDA the physician will have the option to write a single prescription for a triple therapy package.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

PREVACID (lansoprazole) Delayed-Release Capsules

The active ingredient in PREVACID capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole, a compound that inhibits gastric acid secretion. Its empiracle formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. CAS-103577-45-3.

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TRIMOX (amoxicillin USP)

Amoxicillin, USP, [2S-[2α,5α,6β(S*)]]-6-[[amino(4-hydroxyphenyl)-acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate, is a semisynthetic penicillin, an analog of ampicillin. CAS-61336-70-7.

RELATED DOCUMENTS:

Lansoprazole drug substance is manufactured by Takeda Chemical Industries Ltd., at their Hikari, Japan, facility. All respective information for lansoprazole drug substance is contained in the PREVACID, NDA 20-406, which is held by TAP Holdings Inc. Both the IND and NDA for PREVACID are on file with the Division of Gastrointestinal and Coagulation Drug Products (HFD-180).

Clarithromycin drug substance information is contained in the BIAXIN NDA 50-662, which is held by Abbott Laboratories. The NDA for BIAXIN is in HFD-520.

Amoxicillin drug substance is contained in the AADA 61-885, which is held by Apothecon, a Bristol-Myers Squibb company.

CONSULTS: This review is performed as a consult to HFD-590. The following items were requested with this review:

- EER submitted 8/15/97; Acceptable 8/18/97.
- Labeling and Nomenclature Committee consult found the trade name acceptable, 6/23/97.
- Environmental Assessment Waiver statement has been submitted and is adequate.
- All the products that constitute this compliance pack are approved and require no method validation submissions.

REMARKS/COMMENTS:

In review #1 the remaining issues were environmental assessment waiver request for categorical exclusion and inspections were not complete.
Both these items are completed and acceptable at this time.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval with regard to chemistry, manufacturing, and controls.

11/14/97

J. Timper

cc: Org. NDA 50-757
HFD-520/Division File
HFD-520/Katague/Team Leader, Chem 11/14/97
HFD-520/Timper/Chem 11/14/97
HFD-520/Girardi/MO
HFD-520/Utrup/Micro
HFD-520/Cintron/CSO
HFD-590/Anderson/CSO
HFC-130/JAllen

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050757

ADMINISTRATIVE DOCUMENTS

Section 14.0

PATENT STATEMENT UNDER 21 CFR §314.53

No Relevant Patents

The undersigned declares that it has no patent which claims the drug or drug product or which claims a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the product.

EXCLUSIVITY SUMMARY for NDA # 50-757 SUPPL # _____

Trade Name PREVPAC Generic Name lansoprazole, clarithromycin and amoxicillin
Applicant Name TAP Holdings, Inc. HFD-590

Approval Date 12/2/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /_X__/

   If your answer is "no" because you believe the study is a bioavailability study and therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /__X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /_X__/ NO /___/

If yes, NDA #50-662 _____ Drug Name Biaxin_____
NDA# 20-406 Prevacid
AADA # 61-885 Amoxicillin

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____
_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____
_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____
_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

! _____

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Robin Anderson

Robin Anderson 12/4/97
Signature Date
Title: Project Manager

APPEARS THIS WAY
ON ORIGINAL

12/4/97
Signature of Division Director Date

cc: Original NDA 50-757
HFD-590 Division File
HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-757 Supplement # ____Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-590 Trade and generic names/dosage form: __PREVPAC®, contains PREVACID®(lansoprazole) Delayed-Release Capsules labeling for the use of lansoprazole in combination with clarithromycin and amoxicillin

Action
: AP
AE
NA

Applicant TAP Holding Therapeutic Class H.pylori

Indication(s) previously approved: Short Term Maintenance Treatment of Erosive Esophagitis, Phatological Condition including Zollinger-Ellison Syndrome, Maintenance of Healed Duodenal Ulcers, Short-Term Treatment of Active Benign Gastric Ulcer, Short-Term of Erosive Esohagitis, Maintenance of Healing of Erosive Esophagitis

Pediatric information in labeling of approved indication(s) is adequate ____ inadequate___

Indication in this application : for the eradication of *Helicobacter pylori* in patients with active duodenal ulcer disease (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED**. There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

XX 5. **If none of the above apply**, attach an explanation, as necessary. **Safety and effectiveness in pediatric patients have not been established.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Signature of Preparer and Title
Robin Anderson, Project Mananger

Date
December 2, 1997

cc: Orig NDA/PLA/PMA # 50-757
HFD-590 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 12/4/97)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: 12/1/97
Time: 2:15pm
Application: NDA 50-757 (Prevpac)
Type of Meeting: FDA initiated teleconference
Meeting Chair: Dr. Gino Girardi/Medical Officer/HFD-520
Meeting Recorder: Robin Anderson/Project Manager/HFD-590

FDA Attendees, Titles, and Office/Division:
Gino Girardi/Medical Officer/HFD-520
Robin Anderson/Project Manager/HFD-590
Mary Dempsey/Project Manager/HFD-590
Jose Cintron/Project Manager/HFD-520
Robert Hopkins/Acting TL/Medical Officer/HFD-590
James Timper/Chemist/HFD-520
Karen Storms/CSO/HFD-590

TAP Holdings Attendees and Titles:
Janis Baldwin, Senior Operations Manager
Laura Blackowicz, Rph., Medical Services Project Manager
Doug Colè, Group Marketing Manager, Gastroenterology Business Unit
Debra Karvois, Clinical Research Manager
Linda Peters, Senior Regulatory Products Manager
Art Rice, Director of Marketing, Gastroenterology Business Unit
Jenny Rohde, Project Manager, Strategic Development
Pam Rose, Associate Director, Clinical
Nancy Siepman, Ph.D., Section Head, Statistics
Judy Decker Wargel, Assistant Director, Regulatory Affairs

Background:
Dr. Girardi's review with his recommended labeling changes were faxed to the applicant on 11/20/97. The applicant incorporated these changes and submitted revised labeling to the Agency on 11/26/97.

Purpose of teleconference:
To discuss and finalize the proposed label for this NDA with the applicant.

Discussion Points:
- FDA's Chemist noted that chemical name for Amoxicillin should be documented per the USP Dictionary of USAN and International Drug names. The applicant agreed to revise this in the label. The Agency agreed to fax the correct terminology to the applicant immediately following the meeting.

- Since all participants were in agreement that the proposed label was acceptable, there was no further discussion. The Applicant agreed to fax the revised label to the Agency, and to formally submit it to the NDA. The applicant also agreed to submit the proposed label on diskette in both annotated and non-annotated versions.

Post Meeting Corrigenda:
The applicant faxed the revised label to the Agency on 12/1/97, and a desk copy of the revised label in hard copy and on diskette was received by the Agency on 12/2/97.

NDA 50-757

cc:
NDA 50-757
HFD-590/Division file
HFD-590/PM/R. Anderson
HFD-590/Acting Medical TL/R. Hopkins 12/5/97
HFD-520/MO/L. Girardi
HFD-520/Chemist/J. Timper
HFD-520/PM/J. Cintron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050757

CORRESPONDENCE

ORIG AMENDMENT

ORIGINAL

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lake Office Plaza
Deerfield Rd.
IL 60015

September 22, 1997

Division of Special Pathogens & Immunologic Drug Products (HFD-590)
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, 1st Floor
9201 Corporate Boulevard
Rockville, MD 20850

Attn: Mark Goldberger, MD, Division Director

RE: PREVPAC™ (lansoprazole, amoxicillin and clarithromycin) for the Eradication of *Helicobacter pylori*
NDA 50-757
Amendment No. 003

Chemistry, Manufacturing and Controls
- Request for EA Categorical Exclusion -

Dear Dr. Goldberger:

In accordance with Section 507 of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.60, TAP Holdings Inc. submits this amendment to the pending New Drug Application for PREVPAC™ (lansoprazole, amoxicillin and clarithromycin) for the eradication of *H. pylori*.

The purpose of this communication is to request categorical exclusion for the environmental assessment contained in the PREVPAC NDA, No. 50-757, originally submitted to HFD-590 on July 24, 1997 (Volume 2, pages 1 - 257). This request is based on information recently published in the Federal Register, dated July 29, 1997 (Volume 62, No. 145), in which the FDA amended its regulations governing compliance with the National Environmental Policy Act of 1969 (NEPA) as implemented by the regulations of the Council on Environmental Quality (CEQ). These amended regulations became effective on August 28, 1997. Based on the information presented, TAP believes that PREVPAC falls under the option of categorical exclusion, and therefore requests exclusion in accordance with §25.15(d) of this final

rule. In addition, TAP waives the claim for categorical exclusion if a finding of no significant impact (FONSI) has been signed on or before August 28, 1997.

Please do not hesitate to contact me if you have any questions regarding this submission. Thank you for your assistance in this matter.

Sincerely,

Linda J. Peters

Linda J. Peters, M.S.
Senior Regulatory Products Manager
(847) 374-5481
(847) 317-5795 FAX

cc: Maria Walsh (HFD-180)

APPEARS THIS WAY
ON ORIGINAL

LJP/ljp c:\winword\hpylori\50-757.doc

TAP HOLDINGS INC.

August 15, 1997

Division of Special Pathogens & Immunologic Drug Products (HFD-590)
Food and Drug Administration
Document Control Room, 1st Floor
9201 Corporate Boulevard
Rockville, MD 20850

Attn: Mark Goldberger, MD, Division Director

RE: PREVPAC™ (lansoprazole, amoxicillin and clarithromycin) for the Eradication of *Helicobacter pylori*
NDA 50-757
Amendment No. 001

Chemistry, Manufacturing and Controls
PREVPAC™ Stability Report

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Goldberger:

In accordance with Section 507 of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.60, TAP Holdings Inc. submits this amendment to the pending New Drug Application for PREVPAC™ (lansoprazole, amoxicillin and clarithromycin) for the eradication of *Helicobacter pylori* (*H. pylori*).

The purpose of this communication is to provide the Agency with the three-month stability report for PREVPAC™. This report contains stability data for PREVACID® (lansoprazole) 30-mg capsules, TRIMOX® (amoxicillin, USP) 500-mg capsules and BIAXIN® Filmtab® (clarithromycin tablets) 500-mg. Three month stability data for one lot of PREVPAC under accelerated conditions at 10% the commercial production batch size was accepted by Dr. Eric Sheinin, Director, Office of New Drug Chemistry (HFD-800), in his December 16, 1996 correspondence to TAP Holdings Inc. A copy of Dr. Sheinin's December 16th letter can be found in NDA 50-757, Volume 1, pages 69-70.

BEST POSSIBLE COPY

A copy of the enclosed stability report was also submitted to the FDA/Chicago District Office on August 15, 1997. Please do not hesitate to contact me if you have any questions regarding this submission. Attached hereto is the information required for the completion of this form.

Sincerely,

Linda J. Peters

Linda J. Peters, M.S.
Senior Regulatory Products Manager
(847) 374-5481
(847) 317-5795 FAX

LJP/ljp c:\winword\hpylori\hpmem162
attachments

APPEARS THIS WAY
ON ORIGINAL

TAP HOLDINGS INC.

August 14, 1997

Division of Special Pathogens & Immunologic Drug Products (HFD-590)
Food and Drug Administration
Document Control Room, 1st Floor
9201 Corporate Boulevard
Rockville, MD 20850

Attn: Mark Goldberger, MD, Division Director

RE: **PREVPAC™ (lansoprazole, amoxicillin and clarithromycin) for the Eradication of *Helicobacter pylori***
NDA 50-757

- General Correspondence -

Dear Dr. Goldberger:

The purpose of this communication is to notify the Agency of an error in the cover page of the original NDA for PREVPAC™ (NDA 50-757), submitted to the Division of Special Pathogens & Immunologic Drug Products on July 24, 1997. Per a telephone conversation with Mr. Jose Cintron, Project Manager, Anti-Infective Drug Products Division (HFD-520), TAP Holdings Inc. was made aware that the NDA submission for PREVPAC should have been cited under the provisions of Section 507 of the Federal Food, Drug and Cosmetic Act. TAP inadvertently cited Section 505(i) of the Federal Food, Drug and Cosmetic Act for PREVPAC. In addition, TAP incorrectly referred to the NDA numbers for PREVACID® (lansoprazole) in combination with clarithromycin and amoxicillin for the eradication of *H. pylori* as 50-876, 50-877 and 50-878. The correct NDA numbers are 20-876, 20-877 and 20-878, respectively.

We would like to thank the Agency for bringing this information to our attention. Please do not hesitate to contact me if you have any questions regarding this submission.

Sincerely,

Linda J. Peters, M.S.
Senior Regulatory Products Manager
(847) 374-5481
(847) 317-5795 FAX

CC: Mr. Jose Cintron HFD-520

LJP/ljp c:\winword\hpylori\hpmem159