CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 20876

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Clinical Pharmacology Biopharmaceutics Review(s)	X			
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Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 20876

Trade Name: Prevacid Delayed-Release Capsules

Generic Name:(lansoprazole)

Sponsor:Tap Holdings, Inc.

Approval Date:June 17, 1997

Indication: Provides for the addition of a new indication to the PREVACID (lansoprazole) Delayed-Release Capsules labeling for the use of lansoprazole in combination with clarithromycin and amoxicillin for the eradication of Helicobacter pylori in patients with active duodenal ulcer disease or a one-year history of a duodenal ulcer.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20876

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-876

JUN 17 1997

TAP HOLDINGS, INC
Attention: Ms. Linda J. Peters, M.S.
Regulatory Products Manager
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Peters:

Please refer to your new drug application dated September 30, 1996, received on October 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREVACID®(lansoprazole) Delayed-Release Capsules.

The User Fee goal date for this application is October 1, 1997.

This new drug application provides for the addition of a new indication to the PREVACID® (lansoprazole) Delayed-Release Capsules labeling for the use of lansoprazole in combination with clarithromycin and amoxicillin 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 June 9, 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 June 9, 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 20-876. 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.

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 Anti-Infective 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 call Mr. Jose R. Cintron, R.Ph., M.A., Project Manager, at (301) 827-2120.

Sincerely yours,

David W. Feigál, Jr., M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and
Research

cc:

Original NDA 20-876
HFD-520/Div. files
HFD-520/Div. files
HF-2/Medwatch (with labeling)
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFI-20/Press Office (with labeling)
HFD-101/LCarter
HFD-104/TNearing
HFD-520/MO/LGirardi 6/11/97
HFD-520/TLPharm/ROsterberg
HFD-520/TLChem/DKatague
HFD-520/Chem/JTimper
HFD-520/TLMicro/ASheldon
HFD-590/Micro/LUtrup
HFD-725/TLStat/DLin
HFD-725/ATLStat/NSilliman
HFD-830/ONDC Division Director
HFD-880/TLBiopharm/FPelsor
HFD-880/Biopharm/HSun
DISTRICT OFFICE
HFD-520/PMS/JCintron
HFD-520/

Concurrence Only:
HFD-520/CMPS/JBona 6/10/97
HFD-520/TLMO/MAlbuerne 6/11/97
HFD-520/Act.Div/GChikami 6/12/97
HFD-590/Act.Div/MGoldberger 6/12/97

Drafted by: jrc/June 5, 1997/
Initialed by:
final:

APPROVAL (AP)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-877

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Sincerely yours,

David W. Feigál, Jr., M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and
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cc:
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HFD-520/Chem/JTimper
HFD-520/TLMicro/ASheldon
HFD-590/Micro/LUtrup
HFD-725/TLStat/DLin
HFD-725/ATLStat/NSilliman
HFD-830/ONDC Division Director
HFD-880/TLBiopharm/FPelsor
HFD-880/Biopharm/HSun
DISTRICT OFFICE
HFD-520/PMS/JCintron
HFD-520/

Drafted by: jrc/June 5, 1997/
Initialed by:
final:

APPROVAL (AP)

Concurrence Only:
HFD-520/CMPS/JBona 6/10/97
HFD-520/TLMO/MAlbuerne 6/11/97
HFD-520/Act.Dir/GChikami 6/14/97
HFD-590/Act.Dir/MGoldberger 6/24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20876

MEDICAL REVIEW(S)

Medical and Statistical Review of NDA

1. General Information

Applicant Identification

Name: Tap Holdings, Inc.

Address and Telephone Number: 2355 Waukegan Road
Deerfield, Illinois 60015
(847) 374-5481

Contact Person: Linda J. Peters, M.S. Regulatory Products Manager

Submission/Review Dates

Date of Submission: September 30, 1996

CDER Stamp Date: October 1, 1997

Date Submission Received by Reviewer: October 3, 1996

Date Review Begun: February 15, 1997

Date Review Completed: June 1, 1997

Drug Identification

Generic Name: Lansoprazole, Clarithromycin, and Amoxicillin

MO Note: Three separate prescriptions will have to be written, one for each product.

Current trade names of the components: PREVACID, Biaxin Filmtab®, and Amoxicillin. (The sponsor will seek approval for a compliance pack containing three medications in a subsequent submission).

Pharmacologic Category: Lansoprazole is a proton-pump inhibitor, clarithromycin is a macrolide antibiotic, amoxicillin is a beta-lactam antibiotic.

Dosage Form: delayed-release capsules (lansoprazole), capsules (amoxicillin), tablets (clarithromycin)

Route of Administration: oral

Proposed Indication and Usage Section

MO Comment: Recent history of duodenal ulcer disease is defined as endoscopic diagnosis of DU within 1 year of enrollment. This should be stated in the eventual package insert under the **INDICATIONS AND USAGE** *section.*
Statistician Comment: The studies in the literature that show a correlation between eradication of H. pylori and reduction in the risk of ulcer recurrence, and thus that suggest eradication of H. pylori is a reasonable surrogate measure for the reduction in the risk of ulcer recurrence, were conducted in patients with an active ulcer. Little information exists for patients with a history of ulcer.

Dual Therapy
PREVACID Delayed-Release Capsules, in combination with clarithromycin or amoxicillin as dual therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (current or recent history of a duodenal ulcer) to eradicate *H. pylori.* Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Proposed Dosage and Administration Section:

MO Note: The sponsor wishes to market the combination of the above three products which are approved individually. Lansoprazole is approved for short-term treatment of active duodenal ulcer, short-term treatment of erosive esophagitis, and maintenance of healing of erosive esophagitis. Most recently, an approval was issued for maintenance of healing of duodenal ulcer. The approved dosage is 15mg once daily for maintenance of healing of erosive esophagitis, and 30mg once daily for treatment of active duodenal ulcer and erosive esophagitis. Lansoprazole is approved for pathological hypersecretory conditions including Zollinger-Ellison Syndrome at dosages ranging from 60mg once daily to 90mg twice daily.

Material Reviewed: A computer-assisted new drug application (CANDA) consisting of a data base of 1242 patients was reviewed. The patients were divided among 4 principal

studies to support the use of triple as well as dual therapy regimens for the treatment of duodenal ulcers in patients infected with *H. pylori.*

Note: Throughout this review, the dosing frequecies q.d., b.i.d., t.i.d., will, at times, be abbreviated QD, BID, TID for emphasis.

2. Commercial Marketing History:

Lansoprazole, used in combination with two antibiotics, has been approved for the eradication of *H. pylori* in the Untied Kingdom, France, Austria and Denmark. The approved antibiotics used in combination with lansoprazole are clarithromycin, amoxicillin and metronidazole. No dual therapy regimens have been approved. An example of the approved labeling of lansoprazole in combination with antibiotics from the United Kingdom follows:

Eradication of H. pylori: "The following combinations have been shown to be effective when given for 7 days: Lasoprazole 30 mg twice daily plus two of the following antibiotics: clarithromycin 250 mg twice daily, amoxycillin 1 g twice daily, or metronidazole 400 mg twice daily. The best eradication results are obtained when clarithromycin is combined with either amoxycillin or metronidazole. When used in combination with the recommended antibiotics, lansoprazole is associated with *H. pylori* eradication rates of up to 90%."

3. Chemistry/ Manufacturing Controls
Please see Chemistry Review.

4. Animal Pharmacology/Toxicology
Please see Pharm/Tox Review.

5. Microbiology

In the principal studies included in this submission, the presence of *H. pylori* was detected using several different methodologies including histology, culture, CLOtest, ^{13}C-urea breath test, and serology. Patients were evaluated at screening to assess the presence of *H. pylori* and four to six weeks after completion of treatment (Week 6 Visit) to assess the eradication of *H. pylori*. For a complete review of this section, please see the microbiology review by Dr. Linda Utrup.

The E-test® (Epsilometer test,) was used to conduct susceptibility tests on recovered isolates. The microbiology review contains information on breakpoint interpretation using this methodology. It is important to note that there is no standard breakpoint established for E-test and *H. pylori*.

Other applications for *H. pylori* therapies have employed agar dilution in determining susceptibility of strains. Data correlating the use of E-test® with agar dilution were obtained from study M93-131. Biopsies were collected at screening and at 4 to 6 weeks posttreatment. Susceptilbility testing was performed using Mueller-Hinton agar with 5% sheep blood for both agar dilution and E-test® methodologies. E-test® strips for clarithromycin (Clr), ampicillin (Am), and metronidazole were applied to the plates for susceptibility testing. The percent of susceptible, intermediate, and resistant organisms was calculted for each of the antimicrobials as follows:

	Clarithromycin E-test®/Agar dil.	**Amoxicillin** E-test®/Agar dil	**Metronidazole** E-test®/Agar dil
Susceptible	86%/88%	98%/100%	26%/55%
Intermediate	0%/1%	ND/ND	ND/ND
Resistant	14%/11%	ND/ND	74%/45%

ND= not defined
Susceptible= Clr $\leq$ 0.5 μg/mL; Am $\leq$ 0.25μg/mL; Met < 8 μg/mL
Intermediate= Clr > 0.5 - $\leq$ 2μg/mL; Am and Met not defined.
Resistant= Clr > 2 μg/mL; Am not defined; Met $\geq$ 8μg/mL

MO note: Based on these data, the sponsor concludes that the interpretation of Clr and Am susceptibility is similar between the two methods. E-test® reports more isolates as resistant for metronidazole than does the agar dilution method.

For a discussion on the development of resistance among the therapies see the safety review of this document.

6. Human Pharmacokinetics/ Pharmacodynamics
Please see review by Dr. He Sun

In support of the administration of lansoprazole with one or two antibiotics, two potential drug interaction studies were performed. Study M93-063 assessed the effects of coadministration of lansoprazole with clarithromycin. Study M94-168 assessed the effects of coadministration of lansoprazole with amoxicillin. The safety and pharmacodynamic results from these studies are described in the Clinical Pharmacology Section of the NDA submission. During a meeting on March 18, 1996 with FDA, TAP Holdings, Inc. asked for the Agency's guidance regarding whether a lansoprazole/clarithromycin/amoxicillin interaction study would be required, in light of the fact that separate interaction studies had been previously conducted with clarithromycin and amoxicillin. The Agency expressed that it would not be necessary to conduct such an interaction study evaluating all three drugs together. The Consumer Safety Officer also later confirmed by telephone, that the Agency would not require such a study. MO Note: *This was also agreed to by the biopharmaceutics team leader.*

A detailed overview of the pharmacokinetics of lansoprazole was included in the original NDA (NDA 20-406) for the compound. That submission included studies addressing the bioequivalence and relative bioavailability between lansoprazole formulations, dose proportionality, absolute bioavailability, the effects of food, effects of morning and evening dosing, pharmacokinetics after multiple dosing, pharmacokinetics in special populations (elderly, hepatically-impaired, renally-impaired, and dialysis subjects), metabolism and disposition, and drug-drug interactions (warfarin, theophylline, phenytoin, prednisone, diazepam, indomethacin, ibuprofen, aspirin, Maalox®, Riopan®, sucralfate, vitamin B_{12} and oral contraceptives, as well as antipyrine and indocyanine green). The reader is referred to that document for detailed discussions of those topics and pertinent references. In general, no clinically significant drug interactions were found.

The effects of dose size (15, 30 or 60 mg) and dosing regimen (QD, BID or TID) on the pharmacokinetics of lansoprazole were investigated since lansoprazole may be administered either BID or TID in combination with antibiotics for the eradication of *H. pylori*. In general, the pharmacokinetics of lansoprazole administered in BID or TID

dosing regimens were consistent with the results of previous studies which primarily employed QD dosing. The dosing regimen (QD, BID, or TID) did not significantly affect the T_{max} values, implying similarity in the rates of absorption irrespective of dose or time of dosing, and minimal influence of residual drug from the previous dose. Intra-group comparisons demonstrated small, but statistically significant, increases in the dose-normalized C_{max} and AUC values from the larger or more frequent dosing regimens. These changes suggested earlier and improved absorption, which could be related to the greater acid suppression caused by the greater doses of lansoprazole. However, when the dose-normalized AUC values for the entire study were considered, no consistent trends were evident and there was no indication of nonlinearity in the pharmacokinetics of lansoprazole.

The effects of dosing regimen on the half-life values for lansoprazole were small and of no therapeutic significance. In the context of BID or TID dosing, the time of dosing (a.m. vs p.m.) had no effect on the T_{max} or half-life values. Although there were small differences in the dose-normalized C_{max} and AUC values between morning (8 a.m.) and evening (6 p.m.) dosing, any decrease in absorption appeared to be minimal when lansoprazole was administered at 6 p.m., and 30 minutes prior to the evening meal.

Coadministration of clarithromycin (500 mg TID) significantly increased the AUC for lansoprazole (30 mg TID) after the morning and evening doses on Day 5. However, none of the other pharmacokinetic parameters for lansoprazole was significantly affected by clarithromycin. Lansoprazole had no significant effect on any of the absorption and disposition parameters for clarithromycin. The pharmacokinetic parameters for the microbiologically active 14-[*R*]-hydroxy-clarithromycin were not affected by coadministration of lansoprazole, with the exception of a small increase in the AUC of the metabolite during the evening dosing period. However, the minor changes in the pharmacokinetics of lansoprazole and 14-[*R*]-hydroxy-clarithromycin that were observed in this study would not be expected to affect the activity of either compound.

The steady-state pharmacokinetic parameters for lansoprazole (30 mg TID) were not affected by concomitant administration of amoxicillin (1000 mg TID), with the exception of a minor reduction in the AUC for the second (1 p.m.) dose. Since the total AUC for lansoprazole during the 24-hour period was not altered by amoxicillin, the slight change in the AUC for the second dosing interval should not affect the suppression of acid production by lansoprazole. Coadministration of lansoprazole appeared to slow the absorption of amoxicillin, as reflected by increased T_{max} and decreased C_{max} values. The AUC and half-life of amoxicillin during the evening (third) dosing period were increased, but the total AUC for the antibiotic during the entire 24-hour period was not significantly affected by coadministration of lansoprazole.

In general, the sponsor maintains that the results of these two interaction studies with clarithromycin and amoxicillin were consistent with the previous findings which have demonstrated minor pharmacokinetic interactions between lansoprazole and several other drugs.

7. Clinical Studies

Four separate U.S. pivotal studies were performed to support the use of a triple therapy regimen (Lansoprazole + clarithromycin + amoxicillin) or 2 dual therapy regimens (lansoprazole + clarithromycin and lansoprazole + amoxicillin) for eradication of *Helicobacter pylori* in patients with a duodenal ulcer. The first study was used to support the triple therapy as well as the dual therapy regimens. The study names and numbers follow.

1. Study M93-131: A Study to Evaluate the Effects of Therapy with Lansoprazole and Clarithromycin and/or Amoxicillin on the Eradication of *Helicobacter pylori* and the Recurrence of Duodenal Ulcer

2. Study M95-392: A Study to Evaluate the Effects of Triple Therapy of Lansoprazole, Clarithromycin and Amoxicillin on Eradication of *Helicobacter pylori*

3. Study M93-130: A Study to Evaluate the Effects of Dual Therapy with Lansoprazole and Clarithromycin on the Eradication of *H. pylori*

4. Study M93-125. A Study to Evaluate the Effects of Dual Therapy with Lansoprazole and Amoxicillin on the Eradication of *H. pylori*

The database consisted of 1242 patients

- 995 (80%) evaluable patients across all 4 protocols
- (92%) "MITT" patients (worst case analysis): patients excluded if baseline infection not present or duodenal ulcer not present (active or history of DU within past year).
- All studies were randomized, double-blind, parallel-group, active controlled
- Treatment arms consisted of: Single agent (PPI or abx alone), dual (PPI+Abx, or dual abx) and triple therapy (PPI+amox+clari). All treatments administered for 14 days.
- Infection defined as 2 positive tests (Clo, histology, culture)
- Eradication defined as negative culture and histology performed at week 6 (4 weeks post-treatment).

Overview of total number of patients enrolled across the four pivotal studies.

Number of Patients Enrolled by Dosing Regimen and Study in the Four Principal Studies Designed to Assess the Safety and Efficacy of Lansoprazole as Part of Triple- and Dual-Therapy Regimens for the Eradication of *H. pylori*

Dosing Regimens (14 days each)	M93-125	M93-130	M93-131	M95-392	Total
Cla 500 mg TID	-	103	-	-	103
Amx 1 gm TID	67	-	-	-	67
Lan 30 mg TID	73	-	69	-	142
Lan 30 mg BID	-	100	-	-	100
Cla 500 mg BID/Amx 1 gm BID	-	-	-	83	83
Lan 30 mg BID/Cla 500 mg BID	-	99	66	-	165
Lan 30 mg BID/Cla 500 mg TID	-	107	66	-	173
Lan 30 mg BID/Amx 1 gm TID	68	-	66	-	134
Lan 30 mg TID/Amx 1 gm TID	72	-	65	-	137
Lan 30 mg BID/Cla 500 mg BID/ Amx 1 gm BID	-	-	64	74	138
Overall Number of Patients	280	409	396	157	1242

MO Note: The number of study arms and the type of treatment regimen were the only differences in terms of study design among the four pivotal studies. Each study had the same primary efficacy endpoint (eradication of H. pylori). Treatment regimens were administered for 14 days. Patients were to have an active duodenal ulcer or a history of duodenal ulcer disease, endoscopically confirmed, within the past year, and documented presence of H. pylori. A description of each protocol follows. Unique features of each protocol will be highlighted.

M93-131

Title: A Study to Evaluate the Effects of Therapy With Lansoprazole and Clarithromycin and/or Amoxicillin on the Eradication of *Helicobacter pylori* and the Recurrence of Duodenal Ulcer

Objective: The objective of this Phase 3 study was to compare the safety and efficacy of monotherapy with lansoprazole, dual therapy with lansoprazole and amoxicillin or lansoprazole and clarithromycin, and triple therapy with lansoprazole, clarithromycin, and amoxicillin for the eradication of

Helicobacter pylori from the gastric mucosa of patients with active duodenal ulcer disease or a history of duodenal ulcer disease. A secondary objective was to compare the duodenal ulcer prevalence rates after treatment for the eradication of *H. pylori* with the aforementioned therapies.

Study Design: This was a stratified, randomized, double-blind, parallel-group, active-controlled, multicenter study comparing the effectiveness of:

- two dual therapy regimens of lansoprazole and clarithromycin (lansoprazole 30 mg BID with clarithromycin 500 mg BID or TID);
- two dual therapy regimens of lansoprazole and amoxicillin (lansoprazole 30 mg BID or TID with amoxicillin 1 gm TID);
- one triple therapy regimen of lansoprazole 30 mg BID, clarithromycin 500 mg BID, and amoxicillin 1 gm BID; and,
- one monotherapy regimen of lansoprazole 30 mg TID.

All regimens were to be given for 14 consecutive days in patients with either active duodenal ulcer disease or a history of endoscopically documented duodenal ulcer disease within the past year, and documented presence of *H. pylori*. Patients were stratified according to their baseline duodenal ulcer status (active or historical) prior to randomization.
MO Comment: *Inclusion of patients with an endoscopically confirmed duodenal ulcer within a year of enrollment was agreed to by the Division during IND development.*

Patients were to be evaluated at screening, on Study Day 1 (baseline), at the end of the two-week course of therapy (Week 2 Visit), and four to six weeks after completion of treatment (Week 6 Visit). Patients with healed DU at the Week 6 Visit were to return 12 to 14 weeks after completion of treatment (Month 3 Visit), and six months after completion of treatment (Month 6 Visit).
MO Comment: *This last visit is not included in the evaluation of efficacy as per agreement with the Division.*

All of the treatment regimens were evaluated for the primary endpoint, eradication of *H. pylori*. Endoscopic examinations were to be performed for all patients at the screening and Week 6 Visits to obtain biopsies and to document the presence, size, location, and status of duodenal ulcer(s) and other lesions. The presence of *H. pylori* was to be confirmed at screening by rapid urease test (CLOtest®) or histological detection from gastric biopsy specimens. Culture or histology results positive for *H. pylori* were required for the patient to have remained in the study. Eradication of *H. pylori* was defined as no *H. pylori* isolated from cultured biopsy specimens and no

H. pylori visualized on stained biopsy specimens at the Week 6 Visit. Additional efficacy parameters included ulcer prevalence, gastritis findings, assessment of symptoms associated with duodenal ulcer disease, and frequency of concomitant antacid use.

INVESTIGATORS

The study was conducted at 58 investigational sites. The principal investigator and study location are listed. The last column lists the number of patients enrolled at each site followed by the number evaluable. A breakdown of enrolled /evaluable patients based on study arm will not be presented.

Investigator	Affiliation/Site	Total Enrolled/Evaluable
Dennis Avner, M.D.	Private Practice/Salt Lake City, UT	7/7
Canan Avunduk, M.D.	Baystate Medical Center/Springfield, MA	4/2
Charles Bedard, M.D.	Advanced Research Management/ Seattle, WA	2/0
Arnold Berlin, M.D.	Institute of Healthcare Assessment, Inc./ San Diego, CA	8/7
Brian M. Fennerty, M.D.	Oregon Health Sciences University/ Portland, OR	1/1
Ronald P. Fogel, M.D.	Henry Ford Hospital/Detroit, MI	2/0
Andrew Fridberg, M.D.	Clinical Research Group of Maryland/ Elkton, MD	1/1
Walter Gaman, M.D.	Private Practice/Irving, TX	13/6
Howard Gogel, M.D.	Southwest Gastroenterology Associates, P.C./Albuquerque, NM	1/1
Colin W. Howden, M.D.	University of South Carolina School of Medicine/Columbia, S.C.	4/2
Mazen M. Jamal, M.D.	University of New Mexico Hospital/ Albuquerque, NM	5/2
Neil Kassman, M.D.	Statesville Medical Group/Statesville, NC	6/4
Mukui Khandelw	Hershey Medical Center/Hershey, PA	6/4

al, M.D.		
Kerry King, M.D.	Private Practice	1/1
Phillip K. Kiyasu, M.D.	The Portland Clinic/Portland, OR	3/3
Phillip Koszyk, M.D.	Southern Illinois School of Medicine/ Springfield, IL	1/1
Richard Krause, M.D.	Parkridge Professional Plaza/ Chattanooga, TN	21/18
Michael D. Kurtz, M.D.	Clinical Investigator Network/ Oceanside, CA	3/3
Mark Lamet, M.D.	Center for Gastrointestinal Disorders/ Hollywood, FL	15/9
Michael Levine, M.D.	Kennestone Hospital at Windy Hill/ Marietta, GA	8/2
Thomas Lieberman n, M.D.	Center for Clinical Research of the Austin Diagnostic Clinic/Austin, TX	2/0
Ira Lobis, M.D.	Medical Research Institute of Delaware/ Newark, DE	5/5
Ralph T. Lyerly, M.D.	Research Center/Birmingham. AL	7/7
David M. Maccini, M.D.	Private Practice/Spokane, WA	2/2
Ranjit C. Mathew, M.D., Ph.D.	Athens Regional Medical Center and NuCare Clinical Trials, Inc./Duluth, GA	1/0
Barry Mills, M.D.	Associated Medical Research/ Melbourne, FL	3/2
Nemat Moussavia n, M.D.	Private Practice/Cincinnati, OH	7/2
Jack Nudel, M.D.	Private Practice/Pembroke Pines, FL	3/3
Daniel Pambianc o, M.D.	Charlottesville Gastrointestinal Association and Martha Jefferson Hospital/ Charlottesville, VA	11/10
Norman Panitch, M.D.	Western Clinical Research, Inc./ Torrance, CA	7/6
Steven Peiken, M.D.	Cooper Hospital/Camden, NJ	2/1
Robert L. Pintozzi, M.D.	Cedarwood Medical Center/ St. Joseph, MI	3/2
Alan Posner, M.D.	Harriman Jones Medical Group/ Long Beach, CA	1/1
Mark J. Provenza, M.D.	Shreveport Endoscopy Center/ Shreveport, LA	10/7
A.B.	Tuscaloosa Endoscopy Center/	12/8

Reddy, M.D.	Tuscaloosa, AL	
Robert Rhame, M.D.	Carolina Research/Orangeburg, SC	5/5
Lee Richman, M.D.	Rocky Mountain Gastroenterology, P.C./ Wheatridge, CO	2/2
Malcolm Robinson, M.D.	Oklahoma Foundation for Digestive Research/Oklahoma City, OK	13/12
Bruce Sahba, M.D.	California Research Foundation/ San Diego, CA	20/17
Luis Salas, M.D.	Clinical Research Group of Maryland/ Baltimore, MD	1/0
Howard I. Schwartz, M.D.	South Florida Center for Digestive Disease/Miami, FL	38/33
Louis Shane, M.D.	Physicians Clinical Research Service/ White Plains, NY	1/0
Howard Siegel, M.D.	Eastside Comprehensive Medical Services/ New York, NY	21/15
Douglas Simon, M.D.	Jacobi Hospital/Bronx, NY	17/13
William B. Smith, M.D.	Louisiana Cardiovascular Research Center/New Orleans, LA	2/2
Thomas Sobieski, M.D.	McGuire Medical Group/Richmond, VA	3/2
Roger Soloway, M.D.	Clinical Studies Unit/Galveston, TX	10/7
Malcolm J. Sperling, M.D.	EMG Clinical Research/ Fountain Valley, CA	12/11
Lewis Strong, M.D.	Aspen Medical Center/Loveland, CO	4/4
John A. Thesing, M.D.	Heart of America Research/Mission, KS	3/3
Raymond Tidman, M.D.	Private Practice/Blue Ridge, GA	2/0
Esther A. Torres, M.D.	University of Puerto Rico/San Juan, PR	7/5
Amy M. Tsuchida, M.D.	Madigon Army Medical Center/ Tacoma, WA	10/7
Stuart Weissman, M.D.	Private Practice/Redwood City, CA	8/6
Sandra Lee Wilborn, M.D.	Metropolitan Clinic/Portland, OR	1/1
Peter Witt, M.D.	Greeley Medical Clinical, P.A./ Greeley, CO	4/4
Robert A. Wohlman,	Northwest Gastroenterology Associates/ Bellevue, WA	9/4

M.D.		
Salam Zakko, M.D.	University of Connecticut Health Center/ Farmington, CT	15/14

396/297

STUDY POPULATION

Male or female patients at least 18 years of age with either endoscopically proven duodenal ulcer (DU) of at least 3 mm in diameter (an upper size linit was not defined), or history of DU disease endoscopically documented within the previous year, and a positive rapid urease test (CLOtest®) and/or positive histology for detection of *H. pylori* from a gastric biopsy specimen were eligible for participation in the study. Other selection criteria for study patients included the following:

- No evidence of co-existing gastric ulcer or erosive reflux esophagitis; no evidence of current esophageal stricture requiring dilatation (the endoscope must have passed freely into the stomach during endoscopy); no evidence of Zollinger-Ellison syndrome or esophageal varices; no history of gastric, duodenal, or esophageal surgery (except for simple oversew of an ulcer).

- No evidence of symptomatic pancreatobiliary tract disease, cholecystitis, scleroderma, rheumatoid arthritis, lupus, or malignancy (with the exception of basal cell carcinoma) requiring active treatment. Patients with Gilbert's disease or Barrett's epithelium were eligible for study.

- No receipt of any antimicrobial agents (i.e., clarithromycin, amoxicillin, tetracycline, metronidazole, etc.) at any time within four weeks prior to initiating study treatment for any reason.

- No receipt of treatment for *H. pylori* eradication with an antimicrobial (e.g., clarithromycin, or another macrolide compound, amoxicillin, or metronidazole) and/or bismuth within six weeks prior to initiating study treatment.

- No receipt of any other antiulcer medication in dosages indicated for ulcer disease (i.e., omeprazole, famotidine, nizatidine, cimetidine, ranitidine, sucralfate, misoprostol) for more than a total of five days within two weeks prior to initiating study treatment. Did not require maintenance therapy for an ulcer.

- No chronic use of any ulcerogenic drug, including nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin, except as allowed by the protocol; no chronic anticoagulant therapy; no need to begin a new course of chronic tricyclic antidepressant therapy; no requirement for terfenadine or

astemizole therapy; and no corticosteroid therapy at dosages greater than the equivalent of 10 mg prednisone per day. Monitoring of serum drug levels was required for patients requiring continuous treatment with theophylline derivatives, carbamazepine, and/or digoxin.

- No evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurologic or endocrine disease or other abnormality other than the disease being studied.

- No receipt of blood products within 12 weeks before initiating study medication.

- No evidence of current alcohol abuse, illegal drug use, or drug abuse in the past 12 months.

- No receipt of any investigational drug(s) within 12 weeks prior to initiating study treatment. No participation in any other lansoprazole/*H. pylori* study.

- For women, no capability of bearing children; or a negative serum pregnancy test along with previous use and agreement of continued use of appropriate means of contraception for the duration of the study. Women were not to be lactating.

- No history of hypersensitivity or allergic reaction to macrolides (e.g., clarithromycin or erythromycin), penicillin derivatives and/or amoxicillin or substituted benzimidazole compounds.

- No laboratory results outside of normal limits specified by or if abnormal, judged clinically acceptable by the investigator and approved by the sponsor. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) must have been less than twice the upper limit of normal with no concurrent elevations above the normal limit for study entry. Also, creatinine was to have been ≤ 2 mg/dL. No known significant renal impairment by calculated creatinine clearance (CrCl) <40 mL/min.

- Informed consent was to be signed and understood by the participant prior to screening procedures and the patient was to be able to understand and cooperate with study requirements.

DOSING SCHEDULE

Study medications were to be administered for 14 consecutive days. Patients were to self-administer five capsules and one tablet per dose prior to breakfast, lunch, and dinner. Appropriate dummy pills were to be given to maintain blinding. Each daily dose was self-administered in the order indicated in the patient's package. Patients also received Gelusil to take as needed for symptom relief.

EVALUATIONS AND SCHEDULING

Study Procedures	Screening (Study Days -7 to -1)	Baseline (Study Day 1)	Week 2 Visit (End of Treatment)	Week 6 Visit (4 to 6 Weeks Posttreatment) [a]
Informed Consent Signed	X			
Complete Medical and Social Histories	X			
Complete Physical Examination	X			X
Brief Physical Examination			X	
Vital Signs	X	X	X	X
Endoscopy	X			X
Gastric Biopsies (culture, histology, rapid urease)[b]	X			X
Serology[c]	X			
Routine Fasting Laboratory Evaluation	X		X	X
Fasting Serum Gastrin[d]	X		X	X
Theophylline, Carbamazepine, and/or Digoxin Levels (if applicable)	X		X	X
Serum Pregnancy Test (Females)	X			X
Symptom Assessment		X	X	X
Diary Review and Comment			X	X
Concurrent Medications	X	X	X	X
Adverse Event Assessment			X	X
Dispense Study Medication, Gelusil, and Diary		X	X	X
Return Study Medication and Diary			X	X

a Visit was to have been scheduled a minimum of four weeks after completing treatment.
b Six biopsies specimens were taken at the screening visit for culture, histology, and rapid urease and five were taken at each of the Week 6, Month 3, and Month 6 Visits for culture and histology.
c A positive serology result was to have been obtained prior to the endoscopy.
d Fasting (eight hours) and before endoscopy or 24 hours after endoscopy.

Screening Period (Study Days -7 to -1)

The results of these procedures were reviewed by the investigator before the patient entered the treatment period.

A positive serology test for the determination of the presence of antibodies to *H. pylori* must have been obtained prior to the screening endoscopy. An endoscopy was to be performed and duodenal ulcer, if present, was to be documented. In addition, gastric biopsy samples were to be obtained from the corpus and antrum to determine the presence of *H. pylori* infection. A positive rapid urease test or positive histology for *H. pylori* must have been obtained before study medication was dispensed. Culture or histology results positive for *H. pylori* must have been obtained for the patient to have remained in the study. If a patient was negative for *H. pylori* by rapid urease test, but was subsequently determined to be *H. pylori* positive by histology, the patient was to be considered *H. pylori* positive and qualified for the study entry. Conversely, if a patient was positive for *H. pylori* by rapid urease test and both subsequent culture and histology results from the gastric biopsies were determined to be negative for *H. pylori*, the patient could not continue in the study.

Study Day 1

Study Day 1 of the treatment period was defined as the first day study medication was administered.

Treatment Period

During the treatment period, patients were asked to complete a daily diary to document day and night abdominal pain and self-administration of study medication and Gelusil.

Follow-up Period

Patients were to be seen at the end of the two-week treatment period.

Posttreatment Period

Patients who completed the two-week treatment period were eligible to enter the posttreatment period. Patients were not permitted to take any antiulcer medication (other than Gelusil) or any antibiotic for any reason during the posttreatment period. In addition, no changes in tricyclic antidepressant therapy were to have been made, and no anticoagulants, ulcerogenic drugs, or corticosteroids were to be used except as allowed by protocol.

Patients were to be seen at a minimum of four weeks following the completion of study drug therapy. Only patients who were free of active duodenal ulcer were to be continued in the posttreatment period after the Week-6 Visit. Patients who were free of active duodenal ulcer at the Week-6 Visit were seen at a minimum of 12 weeks following the completion of study drug therapy. Patients who were free of active duodenal ulcer at the Month-3 Visit were seen at six months following the completion of study drug therapy. Unscheduled Visit Forms were to be completed if a patient returned to the clinic at any time during the treatment and/or posttreatment periods of the study for evaluation of symptoms or side effects. If adverse events occurred, the Adverse Event Form was to be completed.

The Week-6 Visit procedures were to be completed if the patient was prematurely terminated from the study on or before the Week-6 Visit. The Month-6 Visit procedures were to be completed if a patient was terminated from the study at any point after the Week-6 Visit.

A patient was considered to have completed the study when any of the following occurred:

- The patient completed the two-week treatment period plus the six-month posttreatment period.
- The patient's ulcer(s) was (were) not healed at the Week 6 Visit.
- The patient experienced recurrence of duodenal ulcer.
- Adverse events warranted termination as judged by the investigator and/or TAP Holdings, Inc., personnel.
- The patient withdrew from the study for any reason.
- The patient experienced any gastrointestinal disease requiring antiulcer medication (e.g., erosive reflux esophagitis, gastric ulcer).
- The patient experienced disease requiring any antibiotic therapy.

Endoscopy

Endoscopies were performed at screening, and at the Week-6, Month-3, and Month-6 Visits to document the presence, location, size, and healing status of duodenal ulcer(s) and other lesions. Gastric biopsies were obtained at the time of endoscopy. Additional endoscopies were to be performed at unscheduled visits if deemed appropriate by the investigator. All endoscopies were to be performed by the same endoscopist, if possible.

Gastric Biopsy Specimens

Six biopsy samples were to be taken at the screening visit: one for the rapid urease test; two for culture of *H. pylori*; and three for the detection of *H. pylori* by histology. Five biopsy specimens were taken at the Week-6, Month-3, and Month-6 Visits. Of these five specimens, two were taken for culture of *H. pylori,* and three were to be used for the detection of *H. pylori* by histology.

•Gastric Biopsy Specimens for the Rapid Urease Test

One biopsy specimen was to be taken from the greater curvature of the antrum for the rapid urease test at screening only. The preparation of the rapid urease test (CLOtest) slide and procedure for the test were to be performed according to the package instructions.

•Gastric Biopsy Specimens for Culture

Two biopsy specimens were to be taken for culture of *H. pylori* at the screening, Week-6, Month-3, and Month-6 Visits. One biopsy specimen was to be taken from the greater curvature of the antrum and one was to be taken from the corpus. The specimens were to be placed in individual vials containing appropriate transport media and shipped to The specimens were to be inoculated to both selective and nonselective media and incubated at 37°C in microaerobic conditions. *H. pylori* was to be identified by Gram stain morphology and the production of catalase, oxidase, and urease.

Susceptibility tests were to be performed on *H. pylori* isolated from biopsy specimens collected at all of the study visits using the E-test®
The antimicrobials tested included amoxicillin (ampicillin was used), clarithromycin, and metronidazole.

Serology

A serum sample was collected at the screening visit for the determination of the presence of antibodies to *H. pylori*. The FlexSure™ HP test for serum IgG antibodies to *H. pylori* was provided. A positive serology result was to have been obtained prior to the screening endoscopy.

Symptom Assessment

A symptom assessment was to be performed at each visit by investigator interview to determine the severity of symptoms that a patient may have experienced during the two weeks prior to the visit. Symptoms assessed included primary symptoms of day and night abdominal pain, and secondary symptoms including heartburn, painful swallowing, dysphagia, belching, gastroesophageal regurgitation, fullness/bloating/early satiety, abdominal distention, anorexia, nausea, vomiting, flatulence/abdominal rumbling, diarrhea, constipation, hematemesis, and melena.

Treatment Diary

Patients were to be given a diary at baseline (Study Day 1) and at the Week-2 Visit to be completed daily during the first six weeks of the study. The patient was to

record dosing information, frequency of antacid administration, and episodes of day and night abdominal pain (defined as none, mild, moderate, or severe). The diaries were to be collected and reviewed at the Week-2 Visit and at the Week-6 Visit. Data in the patient diaries were to be used to complete the Diary Summary Form. All diaries were to be retained as part of the patient record at the study site.

STATISTICAL METHODS

Planned Sample Size

This study was designed to enroll approximately 390 patients (65 patients in each treatment group) to obtain 330 evaluable patients (55 patients in each treatment group). This sample size allows for the detection of significant differences in *H. pylori* eradication rates at the Week-6 Visit between dual therapy with lansoprazole and clarithromycin or with lansoprazole and amoxicillin, as compared to monotherapy with lansoprazole at the p=0.05 (two-tailed) level with at least 99% power assuming *H. pylori* eradication rates of 80% and 40%, respectively.

Method of Randomization

Randomization was blocked by site and stratified at each site by the patient's baseline DU status (active or historical).

Evaluation Endpoints

The primary efficacy endpoint was:

H. pylori eradication rate at the Week-6 Visit: The percentage of patients who had eradication of *H. pylori* at the Week-6 Visit. *MO note: This will be the only endpoint evaluated for efficacy.*

The secondary efficacy endpoints were:

Ulcer prevalence rate at the Week-6 Visit: The percentage of patients who had an ulcer present at the Week-6 Visit.

Symptom resolution and improvement rates at the Week-2 and Week-6 Visits: The percentage of patients who experienced resolution of symptoms and the percentage of patients who experienced resolution or improvement of symptoms from baseline to Week-2 or Week-6.

Gastritis resolution and improvement rates at the Week-6 Visit: The percentage of patients who experienced resolution of gastritis and the percentage of patients who experienced resolution or improvement of gastritis from baseline to Week-6.

Diary summaries: Summaries of day and night abdominal pain and Gelusil use during the treatment period and during the posttreatment period.

The safety endpoints were assessments of adverse events, clinical laboratory data, physical examination, vital sign data, and fasting serum gastrin levels.

Efficacy Analyses

All efficacy analyses excluded patients who did not have confirmed evidence of *H. pylori* at baseline or had no duodenal ulcer present or had unconfirmed duodenal ulcer due to undocumented duodenal ulcer size and no history of duodenal ulcer endoscopically documented within the past year. Confirmed evidence of *H. pylori* was defined as at least two positive test results for *H. pylori* from culture, histology, and CLOtest.

The efficacy endpoints of *H. pylori* eradication and ulcer prevalence were analyzed for three groups of patients:

- Evaluable - included patients who met the evaluability criteria per the protocol.

- Intent-to-Treat - all available data, included all patients with confirmed evidence of *H. pylori* and either duodenal ulcer at baseline, or history of duodenal ulcer endoscopically documented within the past year. Patients who did not return for a particular visit or did not have a particular procedure performed and, therefore had no data available, were excluded.

- Modified Intent-to-Treat - worst case, included all patients with confirmed evidence of *H. pylori* and either duodenal ulcer at baseline, or history of duodenal ulcer endoscopically documented within the past year. Patients who did not return for a particular visit or did not have a particular procedure performed were included as treatment failures.

  MO Comment: These analyses are in accordance with the DAIDP Evaluability Criteria. The analyses that will be reviewed will be the evaluable and the modified intent-to-treat. These are the analyses which form the basis of approval for H. pylori regimens as stated in the Division's guidance document on H. pylori-associated trials.

The efficacy endpoints of symptom and gastritis assessments and diary summaries were analyzed for the intent-to-treat (all available data) group of patients only.

Patient Evaluability

Classification of patients regarding acceptability of data for efficacy analyses was carried out by the project team (medical, data management, and statistics) prior to any knowledge of double-blind treatment group assignment. Reasons for excluding patients from efficacy analyses (both *H. pylori* eradication and ulcer prevalence) were established as follows:

Exclusion From Analysis of *H. pylori* Eradication

- Lack of at least two positive test results for *H. pylori* at screening from culture, histology, and CLOtest. (This was also applicable for exclusion from the intent-to-treat analyses.)

- No endoscopically documented duodenal ulcer $\geq$3 mm in diameter at screening and no history of endoscopically documented DU within the past year. (This was also applicable for exclusion from the intent-to-treat analyses.)

- Underwent therapeutic procedures or regimens which interfered with patient evaluation, including administration of antimicrobial agents, or bismuth.

- Less than 70% of prescribed study medication was taken during the 14-day treatment period, and/or less than 10 days of treatment was received.

- Study blind was broken prior to the Week-6 Visit.

- Culture and histology evaluation was not performed at the Week-6 Visit (25 to 60 days posttreatment) and there was no posttreatment documentation of the presence of *H. pylori* prior to this window (i.e., 0 to 24 days posttreatment). If only culture or histology was performed, patients were considered evaluable if the test indicated the presence of *H. pylori*.

Statistical Analyses

For all efficacy and safety endpoints, comparisons were made between the results obtained on triple therapy or monotherapy with lansoprazole to those obtained on each of the dual therapies with lansoprazole and clarithromycin or with lansoprazole and amoxicillin, as well as between the two dual therapies as shown below:

triple therapy	vs	lansoprazole BID/clarithromycin BID
triple therapy	vs	lansoprazole BID/clarithromycin TID
triple therapy	vs	lansoprazole BID/amoxicillin TID
triple therapy	vs	lansoprazole TID/amoxicillin TID

monotherapy	vs	lansoprazole BID/clarithromycin BID
monotherapy	vs	lansoprazole BID/clarithromycin TID
monotherapy	vs	lansoprazole BID/amoxicillin TID
monotherapy	vs	lansoprazole TID/amoxicillin TID
lansoprazole BID/clarithromycin BID	vs	lansoprazole BID/clarithromycin TID
lansoprazole BID/amoxicillin TID	vs	lansoprazole TID/amoxicillin TID

The above ten comparisons between treatment groups are referred to as designated group comparisons in this section. It should be noted that this study was not designed to detect small differences between the clarithromycin dual therapies, or between the amoxicillin dual therapies.

P-values less than or equal to 0.050 (when rounded to three digits) are reported as "significant" in the text and are flagged in tables as "significant at the p=0.05 level of significance". The phrase "no significant difference" indicates that all p-values for the tests are greater than 0.050 (when rounded).

Statistician Comment: If this trial had followed standard factorial design to show the contribution of each component to efficacy in the triple therapy regimen, there would be a triple therapy arm, three corresponding dual therapy arms, and three monotherapy arms. Several of these arms were excluded due to the knowledge that they would prove ineffective. Note, however, that this trial has two extra dual therapy arms compared to the standard design. This is due to the fact that the sponsor wanted to find the best dosing regimen for each dual therapy (lansoprazole plus clarithromycin and lansoprazole plus amoxicillin). To be declared effective, the triple therapy needed to show superiority over all four dual therapy regimens, thus no adjustment is made for multiple comparisons. For the dual therapy regimens to be declared effective, they simply needed to show superiority over the monotherapy regimen. Since there are two additional dual therapy to monotherapy comparisons and the sponsor did not pre-specify which dual therapy regimens were most of interest, FDA analysis will account for multiple comparisons by using the Bonferroni procedure. More specifically, since there are two comparisons of lansoprazole plus clarithromycin to lansoprazole (and lansoprazole plus amoxicillin to lansoprazole), in each case the p-value for the difference will be compared to a 0.025 (=0.05/2) significance level instead of the usual 0.05 significance level.

The baseline value is defined as the last value obtained prior to the start of study medication. In this report, all negative (positive) changes from baseline represent decreases (increases) from baseline.

Note that standard errors presented as part of the summary statistics in this report are estimated within the framework of the particular model and are based on pooled estimates of the variance; i.e., on the mean square error for the model.

Efficacy

H. pylori Eradication Rate at the Week-6 Visit

The eradication of *H. pylori* was defined as negative results from culture and histology. The Week-6 Visit evaluation was defined as the last evaluation obtained in the interval from 25 to 60 days after the end of treatment. If a patient did not have an evaluation within this interval but did have presence of *H. pylori* documented after the end of treatment, the patient was included in the analysis as *H. pylori* positive.

The *H. pylori* eradication rate was summarized by treatment group, and designated group comparisons were performed using Cochran-Mantel-Haenszel methodology for combining (2x2) tables across baseline DU status (active or historical) and across the investigators' geographic regions. Triple therapy was considered statistically superior to dual therapy only if it was significantly better than all four dual therapy regimens. The geographic grouping of sites was determined prior to knowledge of double-blind treatment group assignment and is described in the table below.

Geographic Grouping of Sites

Region	Sites Included
Northwest	Alaska, Idaho, Montana, Nebraska, North Dakota, Oregon, South Dakota, Washington, Wyoming
Southwest	Arizona, California, Colorado, Hawaii, Nevada, New Mexico, Utah
Upper Midwest	Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio, Wisconsin
Lower Midwest	Arkansas, Kansas, Louisiana, Missouri, Oklahoma, Texas
Northeast	Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Washington, D.C.
Southeast	Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, Puerto Rico, South Carolina, Tennessee, Virginia, West Virginia

The 95% exact binomial confidence interval for the *H. pylori* eradication rate was constructed for each treatment group. Homogeneity of treatment differences across baseline DU status and investigator's geographic region was examined using the Breslow-Day test. The *H. pylori* eradication rate at the Week-6 Visit was also

summarized by geographic region and by each investigator within each geographic region.

Designated group comparisons adjusting for concomitant factors (baseline *H. pylori* grade, baseline DU status, baseline DU size, study drug compliance, gender, age, race, weight, tobacco use, alcohol use, and caffeine use) were examined using Cochran-Mantel-Haenszel methodology for combining (2x2) tables across levels of each factor. Homogeneity of treatment difference across levels of each concomitant factor (treatment-by-factor interaction) was examined using the Breslow-Day test.

PATIENT DISPOSITION

Three-hundred ninety-six patients were enrolled at 58 investigative sites. Sixty-four (64) patients were randomized to receive lansoprazole 30 mg BID, clarithromycin 500 mg BID, and amoxicillin 1 gm BID; 69 were randomized to receive lansoprazole 30 mg TID ; 66 were randomized to received lansoprazole 30 mg BID and clarithromycin 500 mg BID; 66 were randomized to receive lansoprazole 30 mg BID and clarithromycin 500 mg TID; 66 were randomized to receive lansoprazole 30 mg BID and amoxicillin 1 gm TID, and 65 were randomized to receive lansoprazole 30 mg TID and amoxicillin 1 gm TID.

Evaluable Patients

A total of 297 (75%) of the 396 enrolled patients were considered evaluable for the analysis of *H. pylori* eradication after exclusion of 99 (25%) of the 396 patients for various deviations from the protocol. The most common reasons for exclusion from the analysis of *H. pylori* eradication rates were no *H. pylori* eradication assessment at the Week-6 Visit (10%, 39/396) and negative *H. pylori* status pretreatment (10%, 39/396).

The reasons patients were excluded from the evaluable analysis of *H. pylori* eradication rates are presented by treatment group in the table below.

MO Note: *The numbers represent the reasons for non-evaluability, not the number of patients who were excluded. A single patient could have been excluded because of more than one reason.*

Reasons for Patient Exclusion From the Evaluable Analysis of *H. pylori* Eradication						
	Treatment Group % (n)					
Reason for Exclusion#	Lan BID/Cla BID/Amx BID (N = 64)	Lan TID (N = 69)	Lan BID/ Cla BID (N = 66)	Lan BID/ Cla TID (N = 66)	Lan BID/ Amx TID (N = 66)	Lan TID/ Amx TID (N = 65)
No *H. pylori* Eradication Assessment at the Week-6 Visit	8% (5)	6% (4)	9% (6)	15% (10)	12% (8)	9% (6)
Negative for *H. pylori* at Baseline	11% (7)	12% (8)	14% (9)	6% (4)	9% (6)	8% (5)
Received <70% of Study Medication	2% (1)	1% (1)	3% (2)	12% (8)	5% (3)	2% (1)
Received <10 Days of Study Medication	2% (1)	1% (1)	2% (1)	12% (8)	2% (1)	0% (0)
Antibiotic Use During Treatment or Posttreatment	2% (1)	3% (2)	0% (0)	5% (3)	3% (2)	2% (1)
H. pylori Negative Documented by Only One Test at the Week-6 Visit	3% (2)	0% (0)	0% (0)	0% (0)	2% (1)	3% (2)
No Evidence of Duodenal Ulcer	3% (2)	0% (0)	0% (0)	0% (0)	0% (0)	2% (1)
Antibiotic Use Prestudy	2% (1)	1% (1)	0% (0)	0% (0)	0% (0)	0% (0)
Unable to Document DU as Ulcer Size Not Documented	0% (0)	0% (0)	2% (1)	2% (1)	0% (0)	0% (0)
Dosing Instructions Not Followed	0% (0)	0% (0)	0% (0)	2% (1)	0% (0)	0% (0)
History of DU Documented >15 Days Beyond Past Year	0% (0)	1% (1)	0% (0)	0% (0)	0% (0)	0% (0)
Total Number of Patients Excluded	27% (17)	23% (16)	26% (17)	27% (18)	26% (17)	22% (14)
Total Included in *H. pylori* Eradication Analysis	73% (47)	77% (53)	74% (49)	73% (48)	74% (49)	78% (51)

Lan = lansoprazole; Cla = clarithromycin; Amx = amoxicillin

Patients could have had more than one reason for exclusion

Intent-to-Treat (All Available Data)

A total of 313 (79%) of the 396 enrolled patients were included in the intent-to-treat (all available data) analysis of *H. pylori* eradication. Among the patients excluded were patients with no *H. pylori* eradication assessment at the Week-6 Visit (10%, 39/396) and patients with negative *H. pylori* status pretreatment (10%, 39/396).

The reasons patients were excluded from the intent-to-treat (all available data) analysis of *H. pylori* eradication rates are presented by treatment group in the table below.

MO Note: The numbers represent the reasons for non-evaluability, not the number of patients who were excluded. A single patient could have been excluded because of more than one reason.

Reason for Exclusion#	Lan BID/Cla BID/Amx BID (N = 64)	Lan TID (N = 69)	Lan BID/ Cla BID (N = 66)	Lan BID/ Cla TID (N = 66)	Lan BID/ Amx TID (N = 66)	Lan TID/ Amx TID (N = 65)
No *H. pylori* Eradication Assessment at the Week-6 Visit	8% (5)	6% (4)	9% (6)	15% (10)	12% (8)	9% (6)
Negative for *H. pylori* at Baseline	11% (7)	12% (8)	14% (9)	6% (4)	9% (6)	8% (5)
No Evidence of Duodenal Ulcer	3% (2)	0% (0)	0% (0)	0% (0)	0% (0)	2% (1)
Unable to Document DU as Ulcer Size Not Documented	0% (0)	0% (0)	2% (1)	2% (1)	0% (0)	0% (0)
History of DU Documented >15 Days Beyond Past Year	0% (0)	1% (1)	0% (0)	0% (0)	0% (0)	0% (0)
Total Number of Patients Excluded	22% (14)	19% (13)	24% (16)	23% (15)	21% (14)	17% (11)
Total Included in *H. pylori* Eradication Analysis	78% (50)	81% (56)	76% (50)	77% (51)	79% (52)	83% (54)

Lan = lansoprazole; Cla = clarithromycin; Amx = amoxicillin

Patients could have had more than one reason for exclusion

Modified Intent-to-Treat (Worst Case)

A total of 352 (89%) of the 396 enrolled patients were included in the modified intent-to-treat (worst case) analysis of *H. pylori* eradication after exclusion of 39 (10%) of the 396 patients with negative *H. pylori* status pretreatment, 3 (1%) patients with no evidence of duodenal ulcer, 2 (<1%) patients with no duodenal ulcer documented due to size not documented, and 1 (<1%) patient with a history of duodenal ulcer documented more than 15 days prior to the past year. One patient (Moussavian , was excluded for negative *H. pylori* status pretreatment and for no evidence of duodenal ulcer.

MO/Statistician Review Strategy for entire database:

- *Reviewed all non-evaluable patients (blinded to treatment)*
- *Reviewed 100 (10%) of evaluable population; randomly selected (blinded to treatment)*
- *This strategy was applied to all four pivotal studies*

Results:

- *Thirty-three non-evaluable patients (across all protocols) were changed to evaluable failures. (Pts dropped from sponsor's analysis due to AE on therapy) This was based on DAIDP evaluability criteria.*
- *No changes in evaluable population as discussed below, for an overall "disagreement" rate of 0% [95% confidence interval (0%, 3.6%)] between the sponsor's and MO's assessment of evaluable patients*
- *MITT results same as sponsor's.*

Review of Patients Included in the Evaluable Analysis

MO Note: A random sample of the evaluable patient subset was generated by the Statistical Reviewer. One-hundred patients were generated from an evaluable population of 995 across all protocols. (Thirty evaluable patients from M93-131, 26 patients from M93-125, 29 patients from M93-130, and 15 from M95-392). No major protocol violations were identified. The MO determined that no patients from this list should be excluded. In addition, no changes in outcome were made.

Review of the Patients Excluded from the Evaluable Analysis

MO Note: A total of 99 patients were excluded from the Sponsor's evaluable analysis for protocol M93-131. A patient could have been excluded for more than one reason. The medical officer considered patients evaluable if they dropped out of the study because of reasons related to the study drug. For example, if a patient had to discontinue treatment because of an adverse event related to the study drug, this patient was considered an evaluable failure. This approach is consistent with the evaluability criteria as developed within DAIDP. The table below lists the number of patients who were changed from non-evaluable to evaluable in protocol M93-131. The patient number, and treatment arm are identified.

Patients who were changed in Protocol M93-131 from non-evaluable to evaluable

Patient ID Number	Treatment Arm
	Lans b.i.d./Clari b.i.d.
	Lans b.i.d./Clari t.i.d.
	Lans b.i.d./Clari b.i.d./Amx b.i.d.
	Lans b.i.d./Clari t.i.d.
	Lans b.i.d./Cla b.i.d.
	Lans b.i.d./Clari t.i.d.
	Lans b.i.d./Clari t.i.d.
	Lans b.i.d./ Clari t.i.d.
	Lans b.i.d / Clari t.i.d.

Total Patients = 9

MO Comment: Only 1 patient from the triple therapy arm was changed from non-evaluable to evaluable. All the above patients were made evaluable failures. In each case, the patients listed above were excluded from the sponsor's evaluable analysis because of either a failure of the patient to take at least 10 days or 70% of the study drug. An additional reason was that there was no H. pylori eradication assessment for several of the patients at the six-week visit. Further examination of these patients revealed that they experienced adverse events related to the study drug which caused them to either miss the six-week visit or not take the required amount of drug.

EFFICACY RESULTS

Statistician's Comment: FDA efficacy results given below and in the remainder of this review were obtained by incorporating the Medical Officer's changes to the sponsor's nonevaluable patient database. No changes were made to the sponsor's evaluable patient database due to the close agreement in assessment between the sponsor and the MO for these patients. Confidence intervals presented for individual FDA eradication rates are constructed using exact binomial confidence limits (i.e., the same methodology used by the sponsor).

Results of Eradication Analyses (Only the Evaluable and MITT analyses will be presented because these analyses form the basis of approval).

The **bolded** regimens are those for which the sponsor seeks approval.

Evaluable Analysis

Treatment Arm	Sponsor's Eradication Rate (95% CI)	FDA Eradication Rate (95% CI)
Lans BID/Clari BID/Amox BID	**94% N=47 (82.5-98.7)**	**92% N=48 (80.0-97.7)**
Lans BID/Clari BID	**57% N=49 (42.2-71.2)**	**55% N=51 (40.3-68.9)**
Lans TID/Amox TID	**77% N=51 (62.5-87.2)**	**77% N=51 (62.5-87.2)**
Lans BID/Clari TID	75%N=48 (60.4-86.4)	67% N=54 (52.5-78.9)
Lans TID	2%N=53 (0.0-10.1)	2% N=53 (0.0-10.1)
Lans BID/Amox TID	53%N=49 (38.3-67.5)	53%N=49 (38.3-67.5)

MO/Statistician note: In both the sponsor and FDA analyses, triple therapy was statistically significantly different from each of the four dual therapy arms. In addition, the dual therapy arms were all statistically significantly different from the monotherapy arm (incorporating the Bonferroni correction for multiple comparisons). There was no significant difference between the two clari dual therapy arms. However, in both the sponsor and FDA analyses, the lans tid/amx tid arm was statistically superior to the lans bid/amx tid arm (note: no correction for multiple comparisons is made here since these are secondary endpoints). Results were similar for the MITT analysis.

MITT Analysis (Worst Case)

Reviewers' Comment: Only the Sponsor's analysis will be presented since no changes were made by the MO in this analysis.

Treatment Arm	Sponsor's Eradication Rate (95% CI)
Lans BID/Clari BID/Amox BID	**86% N=55 (73.3-93.5)**
Lans BID/Clari BID	**50% N=56 (36.3-63.7)**
Lans TID/Amox TID	**70% N=60 (56.8-81.2)**
Lans BID/Clari TID	61% N=61 (47.3-72.9)
Lans TID	3% N=60 (0.4-11.5)
Lans BID/Amox TID	45%N=60 (32.1-58.4)

Reviewers' Comment: The statistically significant differences between the triple therapy treatment group and each of the dual therapy treatment groups, between the lansoprazole monotherapy and dual therapy treatment groups, and between the two amoxicillin dual therapy treatment groups for H. pylori eradication rates at the Week-6 Visit remained after adjustment for other potentially influential factors, including either gender, race, age, weight, study drug compliance, baseline H. pylori grade, baseline duodenal ulcer size, or alcohol, tobacco, or caffeine use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses, with the exception that no statistically significant differences were observed between the triple therapy and lansoprazole TID/amoxicillin TID treatment groups for H. pylori eradication rates after adjusting for gender, baseline H. pylori grade, or baseline duodenal ulcer size for the modified intent-to-treat (worst case) analysis.

Reviewers' Conclusion: This study was a well-designed, well-controlled study which demonstrates a high eradication rate as reported through both the evaluable as well as the MITT analyses. The study supports the use of the triple therapy regimen. In addition, the lansoprazole TID/amoxicillin TID regimen appears to be an effective alternative regimen. The eradication rate for the lansoprazole BID/clarithromycin BID regimen is too low to be acceptable, with the lower-bound 95% confidence interval well below the suggested lower-bound rate of 60%.

Study Number: M95-392

Title: A Study to Evaluate the Effects of Triple Therapy With Lansoprazole, Clarithromycin, and Amoxicillin Versus Dual Therapy with Clarithromycin and Amoxicillin on the Eradication of *Helicobacter pylori*.

Study Dates December 19, 1995 to June 24, 1996.

Objective: The objective of this Phase 3 study was to compare the safety and efficacy of dual therapy with clarithromycin and amoxicillin versus triple therapy with lansoprazole, clarithromycin, and amoxicillin for the eradication of *H. pylori* from the gastric mucosa of patients with active duodenal ulcer or a history of duodenal ulcer.

Study Design: This was a stratified, randomized, double-blind, parallel-group, active-controlled, multicenter study comparing the effectiveness of dual therapy with clarithromycin 500 mg BID and amoxicillin 1 gm BID to that of triple therapy with lansoprazole 30 mg BID, clarithromycin 500 mg BID, and amoxicillin 1 gm BID. Both regimens were to be administered for 14 consecutive days in patients with either active duodenal ulcer disease or a history of endoscopically documented duodenal ulcer disease within the past year, and documented presence of *H. pylori*. Patients were stratified according to their duodenal ulcer status (active or historical) prior to randomization.

Patients were to be evaluated at screening, on Study Day 1 (baseline), at the end of the two-week course of therapy (Week 2 Visit), and four to six weeks after completion of treatment (Week 6 Visit).

Both of the treatment regimens were evaluated for the primary endpoint, eradication of *H. pylori*. Endoscopic examinations were to be performed for all patients at the screening and Week-6 Visits to obtain biopsies and to document the presence, size, location, and status of duodenal ulcer and other lesions. The presence of *H. pylori* was to be confirmed at screening by rapid urease test (CLOtest®) or histological detection from gastric biopsy specimens. Culture or histology results positive for *H. pylori* must have been obtained for the patient to have remained in the study. Eradication of *H. pylori* was defined as no *H. pylori* isolated from cultured biopsy specimens and no *H. pylori* visualized on stained biopsy specimens at the Week 6-Visit. Additional efficacy parameters included ulcer prevalence, gastritis findings, assessment of symptoms associated with duodenal ulcer disease, and frequency of concomitant antacid use.

Safety was monitored through adverse event assessments, routine laboratory evaluations, physical examination, and vital signs data.

INVESTIGATORS

The study was conducted at 33 investigational sites from December 19, 1995 to June 24, 1996. A list of investigators, their study sites and affiliations, and the number of patients enrolled/evaluable for the *H. pylori* eradication analysis is presented.

List of Investigators				
		Enrolled/Evaluable#		
Investigator	Affiliation/Site	Lan/Cla/Amx	Cla/Amx	Total
Donald Abrahm, M.D.	Private Practice/ Newport Beach, CA	2/2	3/3	5/5
Charles F. Barish, M.D., F.A.C.P., F.A.C.G.	Wake Research Associates/ Raleigh, NC	1/1	1/1	2/2
Thomas D. Bianchi, M.D.	Community Medical Arts Center/ Tallassee, AL	4/4	3/3	7/7
Charles Birbara, M.D.	Clinical Pharmacology Study Group/Worcester, MA	2/1	3/2	5/3
Paul C. Bird, M.D.	Research Associates of Norman, Inc./Norman, OK	1/1	3/2	4/3
Jeffery R. Breiter, M.D.	Private Practice/Manchester, CT	2/2	2/1	4/3
Donald L. Bruns, M.D.	The Interstate Medical Center/ Red Wing, MN	2/2	2/2	4/4
Donald R. Campbell, M.D.	Veterans Administration Medical Center/Kansas City, MO	2/2	1/1	3/3
Edward Cheng, M.D.	Northport VAMC Hospital/ Northport, NY	2/1	3/3	5/4
Richard G. Cline, M.D.	Private Practice/Maryville, TN	1/1	1/1	2/2
Stephen R. Freeman, M.D.	St. Joseph Hospital/Denver, CO	2/1	4/4	6/5
Samuel B. Ho, M.D.	VA Medical Center/ Minneapolis, MN	2/2	2/2	4/4
Keith P. Hussey, M.D.	Clinical Pharmacology Investigations/Naples, FL	1/1	0/0	1/1

David S. James, D.O.	Private Practice/Tulsa, OK	3/2	2/0	5/2
Jong K. Kim, M.D.	Edgewater Hospital/Chicago, IL	4/4	4/3	8/7
David Kogut, M.D.	Piedmont Gastroenterology/ Statesville, NC	3/2	2/2	5/4
Thomas Kovacs, M.D.	V.A. Medical Center West Los Angeles/Los Angeles, CA	2/2	2/1	4/3
Daniel M. Kruss, M.D.	Oak Park Hospital/Oak Park, IL	0/0	2/2	2/2
Thomas A. Loludice, D.O.	Akron Gastroenterology Associates, Inc./Akron, OH	1/1	2/0	3/1
David C. Metz, M.D.	Hospital of the University of Pennsylvania/Philadelphia, PA	1/1	1/1	2/2
Uma K. Murthy, M.D.	Veterans Administration Medical Center/Syracuse, NY	1/1	2/2	3/3

List of Investigators (cont'd)

Investigator	Affiliation/Site	Enrolled/Evaluable#		
		Lan/Cla/Amx	Cla/Amx	Total
David C. Pound, M.D.	Indianapolis Gastroenterology and Hepatology, Inc./Indianapolis, IN	1/0	3/2	4/2
Ronald E. Pruitt, M.D.	Nashville Medical Research Institute/ Nashville, TN	3/3	3/3	6/6
Herbert A. Rubin, M.D.	Beverly Hills Gastroenterology Institute/Beverly Hills, CA	5/5	6/5	11/10
Michael A. Safdi, M.D.	Consultants for Clinical Research, Inc./Cincinnati, OH	4/3	3/3	7/6
Michael Schwartz, M.D.	South Florida Center of Gastroenterology/ West Palm Beach, FL	4/3	2/1	6/4
Charles Scowcroft, M.D.	Anderson Area Medical Center/ Anderson, SC	2/2	3/3	5/5
Umed Shah, M.D., F.A.C.G.	Shah Associates, M.D., P.A./ Leonardstown, MD	4/3	4/3	8/6
Bavikatte Shivakumar, M.D.	Gastrointestinal Clinic of Quad Cities/Davenport, IA	4/4	4/3	8/7

David R. Silvers, M.D.	Drug Research Services/ Metairie, LA	1/1	1/1	2/2
William Snape, M.D.	Long Beach Gastroenterology Associates/Long Beach, CA	4/4	5/4	9/8
Thomas Tietjen, M.D.	Internal Medicine Group/ Cheyenne, WY	0/0	1/1	1/1
Barry D. Winston, M.D.	North Houston Gastroenterology Clinic, P.A./Houston, TX	3/3	3/3	6/6
Total		74/65	83/68	157/133

Lan = lansoprazole; Cla = clarithromycin; Amx = amoxicillin
# = number of patients evaluable for *H. pylori* eradication

STUDY POPULATION

Male or female patients at least 18 years of age with either endoscopically proven duodenal ulcer (DU) of at least 3 mm in diameter, or history of DU disease endoscopically documented within the previous year, and a positive rapid urease test (CLOtest®) or positive histology for detection of *H. pylori* from a gastric biopsy specimen were eligible for participation in the study. Other selection criteria for study patients were identical as those listed for the previous study. *MO Note: An upper limit to the size of the ulcer was not specified. In general, however, the upper limit has been 2 cm in diameter.*

Reviewers' Comment: Dosing, evaluations and visit schedules were identical to the previous study. Endpoints and efficacy analyses were also identical.

PATIENT ACCOUNTABILITY

A total of 157 patients were enrolled in the study. The numbers of patients included in each of the efficacy analyses are presented below:

Patient Accountability (Number of Patients)		
	Treatment Group	
	Lan/Cla/Amx	Cla/Amx
Total Enrolled	74	83
Evaluable *H. pylori* Eradication	65 (66)	68 (73)
Modified ITT (Worst Case)	70	80
Lan = lansoprazole; Cla = clarithromycin; Amx = amoxicillin; ITT = intent-to-treat		

The number in parentheses reflects the MO number of evaluable patients.

MO Note: A total of 6 patients were changed from non-evaluable to evaluable. All changes resulted in evaluable failures. Changes in evaluability were based on similar reasons to those listed for protocol M93-131. In general, patients who were deemed non-evaluable by the sponsor because of adverse events that were clearly related to the study drug were considered evaluable by the MO.
Five patients from the Cla/Amx arm were changed from non-evaluable to evaluable failures. One patient from the triple therapy arm was changed from non-evaluable to evaluable failure. A list of the patients from study M95-392 who were changed to evaluable failures and the treatment arm to which they were randomized follows:

Patient ID	Treatment Arm
	Cla b.i.d./Amox b.i.d.
	Cla b.i.d./Amox b.i.d.
	Cla b.i.d./Amox b.i.d.
	Cla b.i.d./Amox b.i.d.
	Lans b.i.d./Clari b.i.d./Amox b.i.d.
	Cla b.i.d./Amox b.i.d.

RESULTS OF ERADICATION ANALYSES FOR M93-392

Evaluable Analysis

Treatment Arm	Sponsor's Eradication Rate (95% CI)	FDA Eradication Rate (95% CI)
Lans BID/Clari BID/Amox BID	**88% N=65 (77.2-94.5)**	**86% N=66 (75.7-93.6)**
Clari BID/Amox BID	74%N=68 (61.4-83.5)	68%N=73 (56.6-78.9)

For both the sponsor and FDA analysis, differences in eradication rates for the triple and dual therapy regimens were statistically significant. Results were similar in the MITT analysis.

MITT (Worst Case)
No changes in the sponsor's rates were made

Treatment Arm	Sponsor's Eradication Rate (95% CI)
Lans BID/Clari BID/Amox BID	**83% N=70 (72.0-90.8)**
Clari BID/Amox BID	64% N=80 (52.2-74.2)

Reviewers' Comment: The statistically significant differences between the treatment groups for H. pylori eradication rates remained after adjustment for other potentially influential factors, including gender, race, age, weight, study drug compliance, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses. After adjustment for alcohol use, the difference between treatment groups for H. pylori eradication rates was not statistically significant for the evaluable patient analysis. Additionally, after adjustment for baseline H. pylori grade and caffeine use, the difference between treatment groups was not statistically significant for the evaluable and intent-to-treat (all available data) analyses. The difference in H. pylori eradication rates between treatment groups were not statistically significant in the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses, after adjusting for baseline duodenal ulcer size. The analysis of H. pylori eradication adjusted for baseline duodenal ulcer size included only those patients with active duodenal ulcer at baseline, which, therefore, decreased the power to detect treatment group differences.

Reviewers' Conclusions: This study also supports the use of lansoprazole triple therapy for the eradication of H. pylori in duodenal ulcer patients.

COMBINED ERADICATION RATES FOR **TRIPLE THERAPY ARMS** IN STUDIES M93-392 AND M93-131 (Each component dosed b.i.d.)

Evaluable Analysis

Treatment Arm	Sponsor's Eradication Rate (95% CI)	FDA Eradication Rate (95% CI)
Lans/Clari/Amox	90% N=112 (83.1-95.0)	89% N=114 (81.3-93.8)

MITT (Worst Case)
No changes in the sponsor's rates were made

Treatment Arm	Sponsor's Eradication Rate (95% CI)
Lans/Clari/Amox	84% N=125 (76.4-89.9)

Study Number: M93-130

Title: A Study to Evaluate the Effects of Dual Therapy With Lansoprazole and Clarithromycin on the Eradication of *Helicobacter pylori*

Study Design: This was a stratified, randomized, double-blind, parallel-group, active-controlled, multicenter study comparing the effectiveness of two dual therapy regimens of lansoprazole and clarithromycin (lansoprazole 30 mg BID with clarithromycin 500 mg BID or TID) to two monotherapy regimens (lansoprazole 30 mg BID or clarithromycin 500 mg TID) given for 14 consecutive days in patients with either active duodenal ulcer disease or a history of duodenal ulcer disease within the past year and documented presence of *H. pylori*.

Statistician Comment: This trial has an extra dual therapy arm compared to the standard factorial design, due to the fact that the sponsor wanted to find the best lansoprazole plus clarithromycin dosing regimen. Since there are two dual therapy to monotherapy comparisons instead of one and the sponsor did not pre-specify which dual therapy regimen was most of interest, FDA analysis will account for multiple comparisons using the Bonferroni procedure. More specifically, for both comparisons of lansoprazole plus clarithromycin to lansoprazole (and lansoprazole plus clarithromycin to clarithromycin), the p-value for the difference will be compared to a 0.025 (=0.05/2) significance level instead of the usual 0.05 significance level.

INVESTIGATORS

The study was conducted at 58 investigational sites from October 3, 1994 through January 15, 1996. A list of investigators, their study sites and affiliations, and the number of patients enrolled/evaluable for the *H. pylori* eradication analysis is presented in the table below:

List of Investigators

Investigator	Affiliation/Site	#Enrolled/#Evaluable			
		Cla	Lan	Lan/ Cla BID	Lan/ Cla TID
Firas H. Al-Kawas, M.D.	Georgetown University Medical Center/Washington, DC	2/1	2/2	2/2	2/1
Bashar M. Attar, M.D., F.A.C.P., F.A.C.G.	Cook County Hospital/Chicago, IL	2/2	1/1	2/1	2/2
Charles F. Barish, M.D., F.A.C.P., F.A.C.G.	Wake Research Associates/Raleigh, NC	1/1	1/1	2/1	1/1
Marcelo A. Barreiro, M.D., M.Sc.	United Medical Associates, PC/ Binghamton, NY	1/1	3/2	1/0	1/1
Robert T. Bass, Jr., M.D.	Health Trials 3000/ Jacksonville Beach, FL	1/1	1/1	1/1	0/0
Richard K. Bath, M.D.	Private Practice/Cincinnati, OH	2/2	2/2	2/2	1/1
Raymond L. Bell, M.D.	Private Practice/Mobile, AL	1/0	0/0	1/1	0/0
Thomas D. Bianchi, M.D.	Community Medical Arts Center/ Tallassee, AL	6/5	5/5	6/6	7/7
Philip C. Bird, M.D.	Research Associates of Norman, Inc./ Norman, OK	0/0	1/1	0/0	2/2
Scott R. Brazer, M.D., M.H.S.	Duke University Medical Center/ Durham, NC	2/2	0/0	1/1	2/2
Jeffery R. Breiter, M.D.	Private Practice/Manchester, CT	2/2	2/1	2/1	2/1
Donald L. Bruns, M.D.	Interstate Medical Center/ Red Wing, MN	1/1	1/1	1/0	2/1
Donald R. Campbell, M.D.	Veterans Administration Medical Center/Kansas City, MO	6/6	5/5	5/4	5/4
Donald O. Castell, M.D.	The Graduate Hospital/ Philadelphia, PA	0/0	0/0	1/1	1/1
Richard G. Cline, M.D.	Tennessee Endoscopy Center/ Maryville, TN	2/1	2/2	3/3	3/3
Charles L. Colip, M.D.	Portland Medical Associates/ Portland, OR	4/3	3/3	3/2	4/3
Gary W. Falk, M.D.	The Cleveland Clinic Foundation/ Cleveland, OH	2/2	3/3	3/2	1/1
Stephen R. Freeman, M.D.	St. Joseph Hospital/Denver, CO	2/2	1/1	2/2	2/0
Ronald Gaskins, M.D.	West Virginia Medical Center Morgantown, WV	1/1	0/0	0/0	1/0
Kevin T. Geraci, M.D., F.A.C.P	University Hospital/Cleveland, OH	0/0	0/0	0/0	1/0
David Y. Graham, M.D.	Veterans Affairs Medical Center/ Houston, TX	1/0	2/1	3/2	3/3

Cla = clarithromycin; Lan = lansoprazole

List of Investigators

Investigator	Affiliation/Site	#Enrolled/#Evaluable			
		Cla	Lan	Lan/ Cla BID	Lan/ Cla TID
Vernon G. Hee, M.D.	The Vancouver Clinic, Inc./ Vancouver, WA	3/2	2/2	2/2	1/1
Edward F. Herlihy, M.D.	Private Practice/New Bedford, MA	1/1	1/1	0/0	0/0
Samuel B. Ho, M.D.	VA Medical Center/Minneapolis, MN	4/1	4/4	4/4	5/3
Keith P. Hussey, M.D.	Clinical Pharmacology Investigations/ Naples, FL	0/0	1/1	0/0	1/1
David S. James, D.O.	Osteopathic Gastroenterology/ Tulsa, OK	0/0	0/0	1/0	1/1
James V. Jones, M.D.	The Green Clinic/Ruston, LA	2/2	2/2	3/3	2/2
Jong K. Kim, M.D.	Edgewater Hospital/Chicago, IL	4/3	5/4	4/3	5/3
Linas M. Klygis, M.D.	MacNeal Hospital/Berwyn, IL	1/1	1/1	0/0	1/1
Kenneth R. Kohagen, M.D.	Raleigh Internal Medicine/Raleigh, NC	1/1	0/0	0/0	1/1
Robert N. Kornfield, M.D.	Private Practice/Rochester, NY	1/1	1/0	1/0	0/0
Thomas Kovacs, M.D.	V.A. Medical Center West Los Angeles/Los Angeles, CA	5/3	5/5	5/5	5/4
Kenneth R. Kranz, M.D.	Internal Medicine Group, P.C./ Cheyenne, WY	2/2	2/2	1/1	2/2
Daniel M. Kruss, M.D.	Oak Park Hospital/Oak Park, IL	2/2	1/1	1/1	2/1
Frank L. Lanza, M.D.	Houston Institute for Clinical Research/ Houston, TX	2/2	2/2	0/0	0/0
Thomas A. LoIudice, D.O.	Akron Gastroenterology Associates, Inc./Akron, OH	2/1	4/3	2/2	2/0
Henry N. Maimon, M.D.	Private Practice/Dayton, OH	1/1	1/1	1/1	1/1
Arthur J. McCullough, M.D.	Metrohealth Medical Center/ Cleveland, OH	2/2	3/3	3/3	3/3
David C. Metz, M.D.	Hospital of the University of Pennsylvania/Philadelphia, PA	3/3	2/2	2/1	2/2
Uma K. Murthy, M.D.	Veterans Administration Medical Center/Syracuse, NY	1/1	3/1	1/1	2/1
James S. Novick, M.D.	The Urology Center at Charles North/ Baltimore, MD	2/1	1/1	1/1	1/1
David C. Pound, M.D.	Indianapolis Gastroenterology and Hepatology, Inc./Indianapolis, IN	1/1	1/1	1/1	1/1
Ronald E. Pruitt, M.D.	Nashville Medical Research Institute/ Nashville, TN	1/1	1/1	1/1	1/1
Dennis S. Riff, M.D.	Associated Gastroenterology Medical Group/Anaheim, CA	2/1	1/1	1/1	1/1
Walter M. Roufail, M.D.	Piedmont Research Associates/ Winston-Salem, NC	1/1	1/1	2/2	1/1

Cla = clarithromycin; Lan = lansoprazole

List of Investigators					
		#Enrolled/#Evaluable			
Investigator	Affiliation/Site	Cla	Lan	Lan/ Cla BID	Lan/ Cla TID
J. David Rowekamp, M.D.	Winona Clinic Ltd./Winona, MN	1/1	2/2	2/2	1/1
Herbert A. Rubin, M.D.	Beverly Hills Gastroenterology Institute/Beverly Hills, CA	0/0	0/0	1/0	0/0
Michael A. Safdi, M.D.	Consultants for Clinical Research, Inc./Cincinnati, OH	3/2	3/3	3/3	3/1
Jerrold L. Schwartz, M.D.	Northwest Gastroenterologists, S.C./ Arlington Heights, IL	0/0	1/1	0/0	0/0
Nayan R. Shah, M.D., F.A.C.G.	Shah Associates, M.D., P.A./ Leonardtown, MD	6/4	5/5	5/5	7/5
Ann L. Silverman, M.D.	William Beaumont Hospital/ Royal Oak, MI	1/1	1/0	1/0	1/1
David R. Silvers, M.D.	Drug Research Services/Metairie, LA	3/3	3/1	2/1	3/3
Robert A. Simmons, M.D.	Poudre Valley Hospital/ Fort Collins, CO	0/0	0/0	1/1	0/0
John W. Singleton, M.D.	University Hospital/Denver, CO	0/0	0/0	1/0	1/1
Kurtis Smith, M.D.	VA Medical Center/Allan Park, MI	1/1	1/1	0/0	1/0
Steven C. Solik, M.D.	Durham Internal Medicine Association/Durham, NC	2/1	2/2	2/2	3/3
Barry D. Winston, M.D.	North Houston Gastroenterology Clinic, P.A./Houston, TX	3/3	2/1	2/2	3/3
Lawrence D. Wruble, M.D.	Memphis Gastroenterology Group/ Memphis, TN	0/0	0/0	1/0	0/0
TOTAL		103/83	100/88	99/81	107/84
Cla = clarithromycin; Lan = lansoprazole					

PATIENT ACCOUNTABILITY

A total of 409 patients were enrolled in the study. The numbers of patients included in each of the efficacy analyses are presented below:

Patient Accountability (Number of Patients)				
	Treatment Group			
	Cla TID	Lan BID	Lan/Cla BID	Lan/Cla TID
Total Enrolled	103	100	99	107
Evaluable *H. pylori* Eradication	83 (88)	88 (90)	81 (85)	84 (86)
Modified ITT (Worst Case)	98	95	94	97
Cla = clarithromycin; Lan = lansoprazole; ITT = intent-to-treat				

The number of FDA evaluable patients per treatment arm is shown in parentheses in the table above.

MO Note: A total of 13 patients were changed from non-evaluable to evaluable failures by the MO. These were done for similar reasons as stated for the prior protocols. Patients were classified as evaluable failures by the MO if they had dropped out because of an adverse event that was clearly related to the study drug. A list of patients and the treatment arm to which they were randomized follows:

No changes in the MITT population were made.

Patient ID	Treatment Arm
	Lans b.i.d.
	Lans b.i.d./clari b.i.d.
	Clari t.i.d.
	Clari t.i.d.
	Lans b.i.d./clari t.i.d.
	Clari t.i.d.
	Lans b.i.d.
	Lans b.i.d./clari t.i.d.
	Lans b.i.d./clari b.i.d.
	Lans b.i.d./clari b.i.d
	Clari t.i.d.
	Clari t.i.d.
	Lans b.i.d./clari b.i.d.

EFFICACY ANALYSIS

Evaluable Analysis

Treatment Arm	Sponsor's Eradication Rate	FDA Eradication Rate
Lans BID/Clari BID	**68% N=81 (56.6-77.8)**	**65% N=85 (53.6-74.8)**
Lans BID /Clari TID	55% N=84 (43.5-65.7)	53% N=~~86~~ (42.4-64.3)
Lans BID	0% N=88 (0.0-4.1)	0% N=90 (0.0-4.0)
Clari TID	31% N=83 (21.6-42.4)	30% N=88 (20.3-40.2)

For both sponsor and FDA analyses, there was a statistically significant difference in eradication rates between each dual therapy and each monotherapy arm (*note: using the Bonferroni procedure to correct for multiple comparisons in the FDA analysis*). However, there was no significant difference between the two dual therapy arms. This remained true in the MITT analysis.

MITT Analysis (Worst Case)

Treatment Arm	Sponsor's Eradication Rate
Lans BID/Clari BID	**60% N=94 (49.0-69.6)**
Lans BID/Clari TID	52% N=97 (41.2-61.8)
Lans BID	0% N=95 (0.0-3.8)
Clari TID	31% N=98 (19.9-38.6)

The statistically significant differences between the treatment groups for *H. pylori* eradication rates remained after adjustment for other potentially influential factors, including either gender, race, age, weight, study drug compliance, baseline *H. pylori* grade, baseline duodenal ulcer size, or alcohol, tobacco, or caffeine use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

Reviewers' Conclusion: The eradication rate for the lansoprazole BID/clarithromycin BID regimen is too low to be acceptable, with the lower-bound 95% confidence interval well below the suggested lower-bound rate of 60%.

Study Number: M93-125

Title: A Study to Evaluate the Effects of Dual Therapy With Lansoprazole and Amoxicillin on the Eradication of *Helicobacter pylori*

Study Dates: August 29, 1994 to August 14, 1995

Objective: The objective of this Phase 2 study was to compare the safety and efficacy of dual therapy with lansoprazole and amoxicillin to monotherapy with lansoprazole or amoxicillin on the eradication of *H. pylori* from the gastric mucosa of patients with active duodenal ulcer disease or a history of duodenal ulcer disease.

Study Design: This was a randomized, double-blind, parallel-group, active-controlled, multicenter study comparing the effectiveness of two dual therapy regimens of lansoprazole and amoxicillin (lansoprazole 30 mg BID or TID with amoxicillin 1 gm TID) to two monotherapy regimens (lansoprazole 30 mg TID or amoxicillin 1 gm TID) given for 14 consecutive days in patients with either active duodenal ulcer disease or a history of duodenal ulcer disease within the past year, and documented presence of *H. pylori*.

Statistician Comment: This trial has an extra dual therapy arm compared to the standard factorial design, due to the fact that the sponsor wanted to find the best lansoprazole plus amoxicillin dosing regimen. Since there are two dual therapy to monotherapy comparisons instead of one and the sponsor did not pre-specify which dual therapy regimen was most of interest, FDA analysis will account for multiple comparisons using the Bonferroni procedure. More specifically, for both comparisons of lansoprazole plus amoxicillin to lansoprazole (and lansoprazole plus amoxicillin to amoxicillin), the p-value for the difference will be compared to a 0.025 (=0.05/2) significance level instead of the usual 0.05 significance level.

Patients were evaluated at screening, on Study Day 1 (baseline), at the end of the two-week course of therapy (Week-2 Visit), and four to six weeks after completion of treatment (Week-6 Visit).

Safety was monitored by adverse events, routine laboratory evaluations, changes in Grimelius-positive cell density, fasting serum gastrin values, physical examination, and vital signs data.

The study was conducted at 41 investigational sites from August 29, 1994 to August 14, 1995. A list of investigators, their study sites and affiliations, and the number of patients enrolled/evaluable for the *H. pylori* eradication analysis is presented in the table below:

List of Investigators

Investigator	Affiliation/Site	# Enrolled / # Evaluable			
		Amx	Lan	Lan BID/ Amx	Lan TID/ Amx
Ajit S. Arora, M.D.	Private Practice/Fresno, CA	3/1	4/4	4/3	3/2
Charles F. Barish, M.D.	Wake Research Associates/Raleigh, NC	2/2	2/2	2/2	2/2
William R. Berry, M.D.	Longmont Clinic, P.C./Longmont, CO	0/0	0/0	0/0	1/0
Charles A. Birbara, M.D.	Clinical Pharmacology Study Group/ Worcester, MA	1/1	1/1	1/1	1/0
Philip C. Bird, M.D.	Research Associates of Norman, Inc./ Norman, OK	3/3	1/1	2/2	2/2
An-Yu Chen, M.D.	The Monroe Clinic/Monroe, WI	3/3	2/1	3/2	3/3
Edward H. Cheng, M.D.	Northport V.A. Medical Center/Northport, NY	1/1	3/2	1/1	2/1
Roland B. Christian, M.D.	West Side Clinic, S.C./Green Bay, WI	1/1	1/1	1/0	1/1
Alan F. Cutler, M.D.	Sinai Hospital/Detroit, MI	2/2	3/3	3/3	2/2
Robert S. Fisher, M.D.	Temple University Health Sciences Center/ Philadelphia, PA	1/0	1/0	1/1	0/0
Duane D. Fitch, M.D.	Triangle East Gastroenterology, P.A./ Wilson, NC	1/1	2/2	1/0	2/2
David Y. Graham, M.D.	Veterans Affairs Medical Center/Houston, TX	2/2	2/2	2/0	1/0
Jon D. Green, M.D.	Private Practice/West Orange, NJ	0/0	1/1	0/0	1/1
Miles E. Gresham, M.D.	Private Practice/Birmingham, AL	2/2	2/1	1/0	2/1
Robert A. Hammer, M.D.	Private Practice/New Orleans, LA	0/0	1/1	1/0	0/0
William Harford, M.D.	Dallas VA Medical Center/Dallas, TX	4/4	4/4	4/4	3/2
Basil I. Hirschowitz, M.D.	University of Alabama at Birmingham Medical Center/Birmingham, AL	2/2	3/2	2/1	2/1
Peter J. Kahrilas, M.D.	Northwestern Memorial Hospital/Chicago, IL	0/0	1/1	1/1	1/1
David G. Kogut, M.D.	Piedmont Gastroenterology/Statesville, NC	2/1	1/1	2/2	2/2
George Koval, M.D.	West Hills Gastroenterology Associates/ Portland, OR	1/1	2/1	1/0	2/2
Frank T. Kucer, M.D.	Upper Bucks Medical Arts Building/ Sellersville, PA	0/0	1/0	1/1	0/0
Frank L. Lanza, M.D.	Houston Institute for Clinical Research/ Houston, TX	4/4	4/3	3/1	3/2
David H. Lebioda, M.D.	Private Practice/Altomonte Springs, FL	2/2	3/2	2/2	2/2
Fredrich C. Loura, M.D.	Private Practice/Everett, WA	1/1	0/0	1/1	1/0
Timothy R. Morgan, M.D.	V.A. Medical Center/Long Beach, CA	1/1	1/1	1/1	1/1

Amx = amoxicillin; Lan = lansoprazole

Table 4.a (Continued)

List of Investigators

Investigator	Affiliation/ Site	# Enrolled / # Evaluable			
		Amx	Lan	Lan BID/ Amx	Lan TID/ Amx
Rao V. Movva, M.D.	Private Practice/Moline, IL	1/1	1/1	1/0	2/1
Ronald E. Pruitt, M.D.	Nashville Medical Research Institute/ Nashville, TN	3/3	3/3	3/2	3/3
Dennis S. Riff, M.D.	Associated Gastroenterology Medical Group/Anaheim, CA	3/2	3/3	3/2	3/2
Herbert A. Rubin, M.D.	Beverly Hills Gastroenterology Institute/ Beverly Hills, CA	3/3	3/3	3/2	3/3
Seymour M. Sabesin, M.D.	Rush-Presbyterian St. Luke's Medical Center/ Chicago, IL	2/2	2/2	1/1	3/3
Richard E. Sampliner, M.D.	V.A. Medical Center/Tuscon, AZ	1/1	0/0	0/0	1/1
Timothy T. Schubert, M.D.	Allenmore Medical Center/Tacoma, WA	1/1	0/0	0/0	1/1
Jerrold L. Schwartz, M.D.	Northwest Gastroenterologists, S.C./ Arlington Heights, IL	3/3	2/2	3/3	3/2
Ronald P. Schwarz, M.D.	Raleigh Medical Group/Raleigh, NC	1/1	1/1	1/1	1/0
Charles Scowcroft, M.D.	Private Practice/Anderson, SC	2/2	3/2	2/2	2/2
Bavikatte N. Shivakumar, M.D.	Gastrointestinal Clinic of Quad Cities/ Davenport, IA	2/1	3/3	3/3	3/3
William J. Snape, Jr., M.D.	Long Beach Gastroenterology Associates/ Long Beach, CA	1/0	2/2	3/3	2/2
Stephen J. Sontag, M.D.	Hines Veterans Administration Hospital/ Hines, IL	1/0	1/0	1/1	1/1
Patrick R. Volak, M.D.	Midwest Foundation for Digestive Health/ Tulsa, OK	1/1	0/0	1/0	1/0
Steven J. Wegley, M.D.	Seattle Gastroenterology Associates, P.S./ Seattle, WA	0/0	1/1	1/1	2/2
Lawrence D. Wruble, M.D.	Memphis Gastroenterology Group/ Memphis, TN	3/3	2/2	1/1	1/1
Total		67/59	73/62	68/51	72/57

Amx = amoxicillin; Lan = lansoprazole

PATIENT ACCOUNTABILITY

A total of 280 patients were enrolled in the study. The numbers of patients included in each of the efficacy analyses are presented below:

Patient Accountability (Number of Patients)

	Treatment Group			
	Amx	**Lan**	**Lan BID/Amx**	**Lan TID/Amx**
Total Enrolled	**67**	**73**	**68**	**72**
Evaluable				
Eradication Analysis	59(60)	62(63)	51(53)	57(58)
Ulcer Prevalence	55	57	48	52
ITT (All Available Data)				
Eradication Analysis	65	66	51	61
Ulcer Prevalence	65	66	52	61
Modified ITT (Worst Case)	66	69	60(60)	67(67)

Amx = amoxicillin; Lan = lansoprazole; ITT = intent-to-treat Amx was given t.i.d. in all instances.

MO Note: The number in parentheses reflect the MO evaluable patients. A total of five patients were changed to evaluable failures among the treatment arms. All patients who were made evaluable failures by the MO were changed because they dropped out due to an adverse event that was clearly related to the study drug. A listing of the patients and the treatment they received follows: The MITT numbers did not change from the sponsor's numbers.

Patient ID	Treatment Arm
	Amoxicillin t.i.d.
	Lans b.i.d./Amox t.i.d.
	Lans t.i.d.
	Lans b.i.d./Amox t.i.d.
	Lans t.i.d./Amox t.i.d.

EFFICACY RATES FOR M93-125

Evaluable analysis

Treatment Arm	Sponsor's Eradication Rate	FDA Eradication Rate
Lans TID/AmxTID	**67% N=57 (52.9-78.6)**	**66% N=58 (51.9-77.5)**
Lans BID/Amx TID	57% N=51 (42.2-70.7)	55% N=53 (40.4-68.4)
Lans TID	0% N=62 (0.0-5.8)	0% N=63 (0.0-5.7)
Amx TID	0% N=59 (0.0-6.1)	0% N=60 (0.0-6.0)

For both sponsor and FDA analyses, there was a statistically significant difference in eradication rates between each dual therapy and each monotherapy arm (*note: using the Bonferroni procedure to correct for multiple comparisons in the FDA analysis*). However, there was no significant difference between the two dual therapy arms. Results were similar in the MITT analysis.

MITT Analysis (Worst Case)

Treatment Arm	Sponsor's Eradication Rate
Lans TID/AmxTID	**61% N=67 (48.5-72.9)**
Lans BID/Amx TID	48% N=60 (35.2-61.6)
Lans TID	0% N=69 (0.0-5.2)
Amx TID	0% N=66 (0.0-5.4)

Reviewers' comment: The statistically significant differences between the treatment groups for H. pylori eradication rates remained after adjustment for other potentially influential factors, including either gender, race, age, weight, study drug compliance, baseline H. pylori grade, baseline duodenal ulcer size, or alcohol, tobacco, or caffeine use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

Reviewers' Conclusions: The rates are somewhat lower in this study for the lans tid/amx tid arm than in Study M93-131.

EFFICACY CONCLUSIONS:
A graphical representation of the eradication rates (both evaluable and MITT) for the various treatment arms across the four pivotal studies is appended at the end of this review. From an efficacy standpoint, the triple therapy regimen should be approved. The dual therapy of lans t.i.d./amx t.i.d. also appears to have adequate efficacy. This latter regimen would be useful in patients with allergy to clarithromycin or in those patients who have difficulty tolerating clarithromycin. In addition, this therapy can be used in patients who might have clarithromycin resistant isolates. (See section 9 under integrated summary of safety).

8. Overview of Safety

INTRODUCTION

Lansoprazole is considered safe and well-tolerated, with the most frequently reported possibly or probably treatment-related adverse events including headache, diarrhea, abdominal pain, and nausea. Long-term studies in Zollinger-Ellison patients given lansoprazole doses up to 180 mg/day for up to 64 months demonstrated no increased frequency or severity of adverse events compared with short-term studies in which lansoprazole 30 mg was administered daily.

The most frequently reported possibly or probably treatment-related adverse events seen in adult patients receiving clarithromycin include diarrhea, nausea, taste perversion, dyspepsia, abdominal pain, and headache. In pediatric patients, the most frequently reported adverse events include diarrhea, vomiting, abdominal pain, rash, and headache.

Amoxicillin provides 20 years of safety experience. In addition, there have been no resistant *H. pylori* isolates to amoxicillin documented as of the writing of this review.The most frequently reported adverse events seen in patients receiving amoxicillin include rash, nausea, diarrhea, and anaphylactic reactions.

All studies included in the Integrated Summary of Safety (ISS) are listed by treatment regimen and study type in the following table.

Studies Included in the Integrated Summary of Safety			
	Eradication Therapy Regimen		
Type of Study	**Triple Lan BID/ Cla BID/Amx BID**	**Dual Lan BID/ Cla BID**	**Dual Lan TID/ Amx TID**
Principal Studies	M93-131 (U.S.) M95-392 (U.S.)	M93-131 (U.S.) M93-130 (U.S.)	M93-131 (U.S.) M93-125 (U.S.)
Supportive Studies	M95-307 (U.S.)	M95-268 (U.S.) M95-269 (U.S.) M95-287 (U.S.)	M95-270 (U.S.) M95-271 (U.S.)
	AG/III/93/026* (France) GB 94/110 (U.K.)	GB 92/169 (U.K.) GB 94/002 (U.K.) GB 93/106 (U.K.) GB 92/168 (U.K.)	ZA/92/749/05 (S. Africa) AG/III/91/013 (France) AG/III/93/026* (France) GB 92/118 (U.K.) GB 93/107 (U.K.) GB 93/105 (U.K.)
Clinical Pharmacology Studies	M93-006 (U.S.) M93-063 (U.S.) M94-168 (U.S.)		

Lan = lansoprazole; Cla = clarithromycin; Amx = amoxicillin

* Study AG/III/93/026 is supportive for both the triple Lan/Cla/Amx and dual Lan/Amx regimens.

In the analysis of safety for the triple-therapy regimen with lansoprazole 30 mg BID, clarithromycin 500 mg BID, and amoxicillin 1 gm BID, triple therapy was compared to three dual-therapy regimens (two regimens for which approval is sought and the dual-antibiotic regimen) combined from the principal studies as follows:

Regimen	Studies
• lansoprazole 30 mg BID/clarithromycin 500 mg BID/amoxicillin 1 gm BID	M93-131, M95-392
• lansoprazole 30 mg BID/clarithromycin 500 mg BID	M93-130, M93-131
• lansoprazole 30 mg TID/amoxicillin 1 gm TID	M93-125, M93-131
• clarithromycin 500 mg BID/amoxicillin 1 gm BID	M95-392

For the dual-therapy regimen with lansoprazole 30 mg BID and clarithromycin 500 mg BID, comparisons of this regimen were made to one dual-therapy regimen and two monotherapy regimens combined from the principal studies as follows:

Regimen	Studies
• lansoprazole 30 mg BID/clarithromycin 500 mg BID	M93-130, M93-131
• lansoprazole 30 mg BID/clarithromycin 500 mg TID	M93-130, M93-131
• lansoprazole 30 mg BID or TID	M93-125, M93-130, M93-131
• clarithromycin 500 mg TID	M93-130

For the dual-therapy regimen with lansoprazole 30 mg TID and amoxicillin 500 mg TID, comparisons of this regimen were made to one dual therapy regimen and two monotherapy regimens combined from the principal studies as follows:

Regimen	Studies
• lansoprazole 30 mg TID/amoxicillin 1 gm TID	M93-125, M93-131
• lansoprazole 30 mg BID/amoxicillin 1 gm TID	M93-125, M93-131
• lansoprazole 30 mg BID or TID	M93-125, M93-130, M93-131
• amoxicillin 500 mg TID	M93-125

For all comparisons in this safety overview, treatment groups being compared may consist of patients combined from different sets of studies. Thus, treatment differences could be confounded with differences between studies. However, the studies combined are all from identical study designs, were conducted and monitored in the same fashion, and used the same central laboratories. Review of the individual study results showed that the conclusions from the combined analysis in this ISS are consistent with those from the individual studies.

Statistician's Comment: Combining data across studies is acceptable and is actually preferred for the analyses in this ISS.

A summary of patients enrolled in the four principal studies by treatment regimen is presented in the following table.

Number of Patients Enrolled by Dosing Regimen and Study in the Four Principal Studies Designed to Assess the Safety and Efficacy of Lansoprazole as Part of Triple- and Dual-Therapy Regimens for the Eradication of *H. pylori*

Dosing Regimens (14 days each)	M93-125	M93-130	M93-131	M95-392	Total
Cla 500 mg TID	-	103	-	-	103
Amx 1 gm TID	67*	-	-	-	67
Lan 30 mg TID	73	-	69	-	142
Lan 30 mg BID	-	100	-	-	100
Cla 500 mg BID/Amx 1 gm BID	-	-	-	83	83
Lan 30 mg BID/Cla 500 mg BID	-	99	66	-	165
Lan 30 mg BID/Cla 500 mg TID	-	107	66	-	173
Lan 30 mg BID/Amx 1 gm TID	68	-	66	-	134
Lan 30 mg TID/Amx 1 gm TID	72	-	65	-	137
Lan 30 mg BID/Cla 500 mg BID/ Amx 1 gm BID	-	-	64	74*	138
Overall Number of Patients	280	409	396	157	1242

Lan = lansoprazole; Cla = clarithromycin; Amx = amoxicillin

* One patient received amoxicillin monotherapy in Study M93-125 as Kogut #6629 and triple therapy in Study M95-392 as Kogut #2145.

METHODS

All patients who received at least one dose of study drug were included in the safety analyses. In these studies, adverse events were monitored throughout the study; laboratory determinations were performed at the screening, Week-2, and Week-6 Visits. Gastritis findings were evaluated at the screening and Week 6 Visits. In Studies M93-125, M93-130, and M93-131, serum gastrin values were collected at the screening, Week-2, and Week-6 Visits. In Study M93-125, gastric endocrine cell changes were evaluated at the screening and Week-6 Visits.

P-values less than or equal to 0.050 (when rounded to three digits) were reported by the sponsor as "significant" in the text and are flagged in tables as "significant at the p=0.05 level of significance". The phrase "no significant difference" indicates that all p-values for the tests are greater than 0.050 (when rounded).

Adverse Events

Adverse events were defined as any evidence of drug intolerance or any clinical or laboratory adverse experience, whether or not thought to be drug-related and whether observed by the investigator or reported by the patients during the treatment period (or within three days after the last dose of double-blind study medication) and during the posttreatment period. Each of the adverse events was mapped to the COSTART dictionary. Patients with one or more adverse events (COSTART term) within a specified body system were counted only once within that body system. Multiple episodes of the same event (COSTART term) for a

single patient were counted only once within that COSTART term. Frequency tabulations grouped by COSTART term and by COSTART body system were made for the incidence of adverse events during the treatment period and during the posttreatment period. Tabulations were also made for all possibly or probably treatment-related adverse events. The proportions of patients reporting adverse events were compared between treatment groups using Fisher's exact test. Analyses of adverse events rates during the treatment period by age (less than 45, 45 to 65, greater than 65 years), gender, and race (Caucasian, Black, other) were also performed. Differences between the categories within a treatment group were evaluated using Fisher's exact test.

In the tabulations of adverse events by severity, patients who had more than one designation of severity for the same event were counted only once based on the most severe occurrence of that event; patients with multiple events of varying severity were counted only once in the overall total based on their most severe event.

Similarly, in the tabulations of adverse events by relationship to study drug, patients with multiple events of varying relation to study drug were counted only once in the overall total based on the event(s) with the "worst case" attribution, i.e., greatest degree of relationship to study drug.

The severity of each adverse event was rated by the investigator according to the following definitions:

- Mild: The adverse event was transient and easily tolerated by the patient.
- Moderate: The adverse event caused the patient discomfort and interrupted the patient's usual activities.
- Severe: The adverse event caused considerable interference with the patient's usual activities and may have been incapacitating or life threatening.

The relationship between an adverse event and study medication was assessed by the investigator and recorded on the case report form according to the following definitions:

- Probable: The adverse event had a timely relationship to study drug administration, and a potential alternative etiology was not apparent.
- Possible: The adverse event had a timely relationship to study drug administration. However, a potential alternative etiology existed, which may have been responsible for the adverse event.
- No Relationship: Evidence existed that the adverse event was definitely related to an etiology other than study drug.

Clinical Laboratory Parameters

All analyses of clinical laboratory test results are based on the principal and U.S. supportive studies. Clinical laboratory evaluations were conducted at a central laboratory, for all principal and U.S. supportive studies.

For all clinical trials, clinical laboratory values for hematology, serum chemistry, and urinalysis tests were assessed pretreatment (within one week prior to dosing), immediately posttreatment (Week 2), and 4 to 6 weeks posttreatment (Week 6). Clinical laboratory data were collected for patients who received at least one dose of study drug(s).
Laboratory tests included the following:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

- Blood Chemistry:
  Electrolyte: sodium, potassium, and chloride
  Hepatic: aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), gamma glutamyl transferase (GGT), alkaline phosphatase, and total bilirubin
  Metabolic: albumin, total protein, glucose, total cholesterol, and calcium
  Renal: blood urea nitrogen (BUN), creatinine, inorganic phosphorus, and uric acid

- Urinalysis: specific gravity, pH, glucose, ketones, protein, and microscopic examination.

Three types of analyses were performed for the laboratory data including mean change from baseline, percent change from baseline, and incidence of laboratory values requiring further clinical review.

Other Safety Evaluations

Fasting Serum Gastrin Determinations

In Studies M93-125, M93-130, and M93-131, serum gastrin samples were drawn following an eight-hour fast and prior to, or 24 hours after, the endoscopy procedure. The percent changes from baseline to the Week-2 and Week-6 Visits were calculated for all patients with available fasting gastrin levels. Fasting gastrin levels were defined as those derived from samples obtained after at least an eight-hour fast.

The Kruskal-Wallis test and Wilcoxon two-sample test were used to test for "no significant difference" in gastrin values among the treatment groups at baseline and for pairwise treatment comparisons of percent changes from baseline, respectively.

Grimelius-Positive Cell Density and Solcia Classification

Extensive data on the effects of lansoprazole on Grimelius-positive cell density are on file with the Agency in NDA 20-406 (submitted November 12, 1993). Most of these data, however, address single daily doses of lansoprazole 15 mg or 30 mg. Because of these extensive data for Grimelius-positive cell density with lansoprazole in single daily doses, this factor was evaluated in only one study in the clinical program for eradication of *H. pylori*. Study M93-125 was selected because it incorporated a monotherapy arm of lansoprazole 30 mg TID, the highest daily dose used in the principal studies.

Gastric biopsies from the greater curvature of the corpus were evaluated quantitatively and qualitatively for endocrine cell (namely ECL cell) changes. Statistical analyses of changes from baseline to the Week-6 Visit in the density of nucleated Grimelius-positive cells in gastric corpus biopsies were conducted with a one-way analysis of covariance model with treatment as the main effect and baseline density as the "covariate".

In all of the principal studies, acute and chronic inflammation and gastric atrophy were evaluated at baseline and the Week-6 Visit. Two full mucosal thickness biopsies were sampled from the antrum, one each from the greater and lesser curvature, and one from the corpus. All biopsies were fixed in formalin and sent to the for evaluation. Paraffin-embedded tissue sections were stained with Hematoxylin and Eosin stain and graded for acute and chronic inflammation and gastric atrophy.

Additionally, in Study M93-125, the greater curvature slides stained with Grimelius silver stain were evaluated using the Solcia Classification, to qualitatively evaluate the corpus morphology.

SAFETY DATA FOR TRIPLE THERAPY WITH LANSOPRAZOLE, CLARITHROMYCIN, AND AMOXICILLIN

Triple-Therapy: Patient Accountability in the Principal Studies

A total of 523 patients received treatment with the regimens selected for analysis of safety with triple therapy. Of these, 138 patients received triple therapy with lansoprazole 30 mg BID, clarithromycin 500 mg BID, and amoxicillin 1 gm BID; 165 patients received dual therapy with lansoprazole 30 mg BID and clarithromycin 500 mg BID; 137 patients received dual therapy with lansoprazole 30 mg TID and amoxicillin 1 gm TID; and 83 patients received dual therapy with clarithromycin 500 mg BID and amoxicillin 1 gm BID.

Triple Therapy: Demographic Characteristics in the Principal Studies

A summary of demographic data for patients who received treatment with the regimens selected for the safety analyses of triple therapy is presented below.

Patient Demographics for Patients Included in the Safety Analyses of Triple Therapy in the Principal Studies				
Demographic Characteristics	**Lan BID/Cla BID/Amx BID (N = 138)**	**Lan BID/ Cla BID (N = 165)**	**Lan TID/ Amx TID (N = 137)**	**Cla BID/ Amx BID (N = 83)**
Gender:				
Female	30% (41)	30% (50)	31% (42)	36% (30)
Male	70% (97)	70% (115)	69% (95)	64% (53)
Race:				
Black	22% (31)	23% (38)	18% (25)	17% (14)
Caucasian	58% (80)	57% (94)	58% (79)	64% (53)
Hispanic	14% (20)	10% (17)	18% (24)	11% (9)
Other	5% (7)	10% (16)	7% (9)	8% (7)
Age (years):#				
<45	46% (64)	39% (65)	41% (56)	30% (25)
45-65	41% (56)	45% (74)	45% (62)	59% (49)
>65	13% (18)	16% (26)	14% (19)	11% (9)
Mean (SD)	48.1 (14.2)	50.1 (13.9)	49.6 (13.0)	51.7 (12.5)
Range				
Weight - Females (lbs):#	(N = 41)	(N = 50)	(N = 41)	(N = 30)
<150	41% (17)	42% (21)	32% (13)	43% (13)
≥150	59% (24)	58% (29)	68% (28)	57% (17)
Mean (SD)	162.3 (43.3)	158.6 (36.9)	160.0 (30.8)	163.5 (43.3)
Range				
Weight - Males (lbs):#	(N = 97)	(N = 115)	(N = 95)	(N = 53)
<150	14% (14)	17% (19)	16% (15)	11% (6)
≥150	86% (83)	83% (96)	84% (80)	89% (47)
Mean (SD)	183.4 (34.2)	185.7 (37.3)	176.2 (30.1)	188.5 (31.9)
Range				
Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm Studies included: M93-125, M93-130, M93-131, and M95-392 # At baseline.				

There were no statistically significant differences among the triple-therapy and the dual-therapy regimens for any demographic variable.

Triple Therapy: Treatment Exposure in the Principal Studies

A summary of treatment duration and percent compliance among patients who received treatment with the regimens selected for the safety analyses of triple therapy is presented in the following table.

Extent of Treatment Exposure for Patients Included in the Safety Analyses of Triple Therapy in the Principal Studies				
	Lan BID/Cla BID/Amx BID (N = 138)	Lan BID/ Cla BID (N = 165)	Lan TID/ Amx TID (N = 137)	Cla BID/ Amx BID (N = 83)
Treatment Duration (days)				
<10	2% (3)	3% (5)	1% (2)	5% (4)
10-15	96% (133)	93% (154)	96% (131)	95% (79)
>15	1% (2)	4% (6)	3% (4)	0
Mean (SD)	13.8 (1.98)	13.8 (2.03)	14.1 (1.10)	13.5 (2.21)
Range				
Percent Compliance for Number of Capsules/Tablets Taken#				
<70	2% (3)	3% (5)	2% (3)	5% (4)
70-90	5% (7)	3% (5)	5% (7)	5% (4)
> 90	93% (128)	94% (155)	93% (127)	90% (75)
Mean (SD)	96.4% (13.83)	96.2% (14.12)	97.6% (7.02)	95.3% (16.89)
Range				

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm
Studies included: M93-125, M93-130, M93-131, and M95-392
Patients who did not return study drug containers but reported full compliance are included as >90% compliant.

There were no statistically significant differences among the triple-therapy and the dual-therapy regimens analyzed for either mean duration of treatment or mean percent compliance.

Triple-Therapy: Adverse Event Comparisons Across Treatment Groups in the Principal Studies

The percent of patients reporting adverse events among all patients who received the triple-therapy regimen of lansoprazole 30 mg BID/clarithromycin 500 mg BID/amoxicillin 1 gm BID was compared with that of patients who received the dual-therapy regimens for which approval is sought (lansoprazole 30 mg BID/clarithromycin 500 mg BID and lansoprazole 30 mg TID/amoxicillin 1 gm TID) and with that of patients who received the dual-antibiotic regimen (clarithromycin 500 mg BID/amoxicillin 1 gm BID). Results of these analyses are presented below.

Treatment Period

A summary of treatment-emergent and possibly or probably treatment-related adverse events occurring in ≥3% of patients in any treatment group is presented below.

Most Frequently Reported[a] Adverse Events During the Treatment Period for Patients Included in the Safety Analyses of Triple Therapy in the Principal Studies

COSTART Term	Treatment Group % (n)			
	Lan BID/Cla BID/Amx BID (N = 138)	Lan BID/ Cla BID (N = 165)	Lan TID/ Amx TID (N = 137)	Cla BID/ Amx BID (N = 83)
Treatment-Emergent Adverse Events				
Any Event	32% (44)	38% (62)	33% (45)	45% (37)
Diarrhea	7% (10)	9% (15)	8% (11)	11% (9)
Taste Perversion	5% (7)	7% (11)	2% (3)	20% (17)*
Headache	6% (8)	4% (6)	7% (9)	4% (3)
Nausea	3% (4)	5% (9)	2% (3)	2% (2)
Abdominal Pain	1% (2)	6% (10)	3% (4)	1% (1)
Dizziness	3% (4)	3% (5)	1% (2)	2% (2)
Pharyngitis	3% (4)	1% (2)	1% (1)	4% (3)
Rash	1% (2)	0	1% (2)	4% (3)
Possibly or Probably Treatment-Related Adverse Events				
Any Event	21% (29)	22% (37)	20% (27)	36% (30)*
Diarrhea	7% (9)	8% (13)	7% (10)	10% (8)
Taste Perversion	5% (7)	7% (11)	2% (3)	20% (17)*
Headache	4% (5)	3% (5)	4% (6)	2% (2)
Nausea	1% (2)	3% (5)	2% (2)	2% (2)
Dizziness	2% (3)	3% (5)	1% (1)	2% (2)

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm
Studies included: M93-125, M93-130, M93-131, and M95-392
[a] Reported by ≥3% of patients in any treatment group.
* Statistically significant difference versus triple-therapy treatment group ($p \leq 0.05$).

Among the 138 patients who received triple therapy, only one patient (1/138, 1%) had an adverse event (dizziness) considered severe by the investigator.

Among the triple-therapy patients who had possibly or probably treatment-related adverse events, only one severe adverse event of dizziness was reported, which was considered possibly related to treatment (1/138, 1%).

Posttreatment Period

The following table presents a summary of treatment-emergent and possibly or probably treatment-related adverse events during the posttreatment period reported by ≥3% of patients in any treatment group.

Most Frequently Reported[a] Adverse Events During the Posttreatment Period for Patients Included in the Safety Analyses of Triple Therapy in the Principal Studies

COSTART Term	Treatment Group % (n)			
	Lan BID/Cla BID/ Amx BID (N = 138)	Lan BID/ Cla BID (N = 165)	Lan TID/ Amx TID (N = 137)	Cla BID/ Amx BID (N = 83)
Treatment-Emergent Adverse Events				
Any Event	18% (25)	21% (35)	15% (20)	13% (11)
Abdominal Pain	5% (7)	3% (5)	3% (4)	1% (1)
Pharyngitis	3% (4)	2% (4)	1% (2)	4% (3)
Possibly or Probably Treatment-Related Adverse Events				
Any Event	1% (2)	2% (4)	2% (3)	1% (1)

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm

Studies included: M93-125, M93-130, M93-131, and M95-392

[a] Reported by ≥3% of patients in any treatment group.

No statistically significant differences between the triple-therapy and any of the dual-therapy regimens.

Among the 138 patients who received triple therapy, only two patients (1%, 2/138) each experienced one severe adverse event (accidental injury or neck pain).

All of the possibly or probably treatment-related adverse events reported during the posttreatment period for patients treated with triple therapy were of mild or moderate severity.

Triple Therapy: Adverse Events by Demographic Subsets for Patients Treated With Lansoprazole BID/Clarithromycin BID/Amoxicillin BID in the Principal Studies

Treatment-Emergent Adverse Events by Gender

Of the 138 patients who received triple therapy, 97 (70%) were male and 41 (30%) were female. No statistically significant differences were seen between males and females for the percent of patients reporting treatment-emergent adverse events, possibly or probably treatment-related adverse events, or any specific adverse event that could be experienced by both males and females.

Treatment-Emergent Adverse Events by Race

Of the 138 patients who received treatment with triple therapy, 80 (58%) were Caucasian, 31 (22%) were Black, and 27 (20%) were of other races. No statistically significant differences were seen among race categories for the percent of patients reporting treatment-emergent adverse events, possibly or probably treatment-related adverse events, or any specific adverse event.

Treatment-Emergent Adverse Events by Age

Of the 138 patients treated with triple therapy, 64 (46%) were less than 45 years of age, 56 (41%) were 45-65 years of age, and 18 (13%) were greater than 65 years of age. No statistically significant differences were seen among age categories for the percent of patients reporting treatment-emergent adverse events or the percent of patients reporting possibly or probably treatment-related adverse events. A statistically significant difference was seen among age categories for the incidence of treatment-emergent dizziness, with older patients (i.e., greater than 65 years of age) showing increased incidence of dizziness (11%) compared with younger patients (i.e., 45-65 years, 4%); no patients less than 45 years of age experienced dizziness. Similarly, a statistically significant difference was seen among age categories for the incidence of possibly or probably treatment-related dizziness, with older patients (i.e., greater than 65 years of age) showing increased incidence of dizziness (11%) compared with younger patients (i.e., 45-65 years, 2%); no patients less than 45 years of age experienced dizziness.

Adverse Events During the Posttreatment Period by Gender

No statistically significant differences were seen between genders for the percent of patients reporting treatment-emergent adverse events, the percent of patients reporting possibly or probably treatment-related adverse events, or any specific adverse event.

Adverse Events During the Posttreatment Period by Race

No statistically significant differences were seen among race categories for the percent of patients reporting treatment-emergent adverse events, the percent of patients reporting possibly or probably treatment-related adverse events, or any specific adverse event.

Adverse Events During the Posttreatment Period by Age

No statistically significant differences were seen among age categories for the percent of patients reporting treatment-emergent adverse events, the percent of patients reporting possibly or probably treatment-related adverse events, or any specific adverse event.

Triple-Therapy: Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events in Treatment Groups Used for the Triple Therapy Safety Analyses in the Principal Studies

A summary of the number of deaths, patients reporting serious adverse events, pregnancies, and premature discontinuations due to adverse events reported for patients included in the safety analyses of triple therapy in the principal studies is presented below.

Deaths, Serious Adverse Events, Pregnancies, and Discontinuations Due to Adverse Events Reported for Patients Included in the Safety Analyses of Triple Therapy in the Principal Studies				
	Treatment Group % (n)			
Safety Parameter	Lan BID/Cla BID/ Amx BID (N = 138)	Lan BID/ Cla BID (N = 165)	Lan TID/ Amx TID (N = 137)	Cla BID/ Amx BID (N = 83)
Deaths	0	0	0	0
Number of Patients With Serious Adverse Events	2% (3)	1% (1)	3% (4)	4% (3)
Pregnancies	0	0	0	0
Premature Discontinuation Due to Adverse Events	4% (5)	4% (7)	4% (5)	6% (5)
Lan = lansoprazole 30 mg, Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm Studies included: M93-125, M93-130, M93-131, and M95-392				

Of the 138 patients treated with triple therapy, three reported serious adverse events (dizziness, coronary artery disease, and accidental injury). The adverse event of dizziness was the only event considered possibly related to study medication. In addition, one patient who received lansoprazole BID/clarithromycin BID dual therapy (melena), four patients who received lansoprazole TID/amoxicillin TID dual therapy (pleural effusion and atrial arrhythmia; carcinoma of liver; abdominal pain, diarrhea, and melena; and cerebrovascular accident), and three patients who received clarithromycin BID/amoxicillin BID (esophageal ulcer, abdominal pain, and chest pain) reported serious adverse events which were considered unrelated to study medication. However, one case of abdominal pain (in the lansoprazole TID/amoxicillin TID dual therapy group) was considered possibly related to study medication.

Of the 138 patients treated with triple therapy lansoprazole BID/clarithromycin BID/amoxicillin BID, three patients discontinued from the study during the treatment period and two discontinued during the posttreatment period due to adverse events. Events leading to discontinuation during the treatment period included dizziness and nausea; headache; and rash, all of which were considered possibly or probably treatment-related. Events leading to discontinuation during the posttreatment period included accidental injury and coronary artery disease, both of which were considered unrelated to study medication.

No statistically significant differences were observed between the triple-therapy and any of the dual-therapy treatment groups for the percent of patients reporting treatment-emergent adverse events, or possibly or probably treatment-related adverse events which led to discontinuation.

Triple-Therapy: Adverse Events in the Supportive Studies

In the U.S. supportive triple-therapy study of 30 patients (M95-307), the most frequently reported adverse events during the treatment period were diarrhea (7%) and stomatitis (7%). No patient died, reported a serious adverse event, or prematurely discontinued due to an adverse event in the U.S. supportive triple-therapy study. One patient (Riff, , became pregnant during the supportive triple-therapy study and subsequently underwent a therapeutic abortion.

Triple-Therapy: Conclusions of Clinical Laboratory Determinations in the Principal Studies

Some statistically significant differences in mean and percent changes from baseline were observed among treatment groups and the demographic subsets for some laboratory parameters. These changes were small and not considered clinically significant. No statistically significant differences were observed between treatment groups for the proportions of patients with laboratory values requiring further clinical review.

Although there were statistically significant differences between treatment groups in mean and percent changes for some hematology parameters (neutrophils, lymphocytes, basophils, hematocrit, and WBC), these changes were small and not considered clinically significant. No statistically significant differences were observed between treatment groups for the proportions of patients with hematology values requiring further clinical review.

For electrolyte parameters, a statistically significant mean change from baseline was observed between the dual-antibiotic and triple therapy treatment groups in chloride at Week 6; however, the difference was small and not considered clinically significant. There were no statistically significant differences between the triple-therapy and any of the dual-therapy treatment groups for percent change from baseline in any electrolyte parameter.

When hepatic chemistry parameters were evaluated, statistically significant differences were observed for alkaline phosphatase and GGT between treatment groups for both mean and percent change from baseline; however, each of these differences were not considered clinically significant. No statistically significant differences were observed between the triple-therapy and any of the dual-therapy treatment groups for the proportions of patients with hepatic chemistry values requiring further clinical review.

For metabolic/nutritional chemistry parameters, statistically significant differences were observed between treatment groups for mean and percent change from baseline in glucose, cholesterol, and calcium. No statistically significant differences were observed between the triple-therapy and any of the dual-therapy

treatment groups for the proportions of patients with metabolic/nutritional chemistry values requiring further clinical review.

For renal chemistry parameters, statistically significant differences were observed between treatment groups for mean and percent change from baseline in uric acid and creatinine. No statistically significant differences were observed between the triple-therapy and any of the dual-therapy treatment groups for the proportions of patients with renal chemistry values requiring further clinical review.

For urinalysis parameters, no statistically significant differences were observed between the triple-therapy and any of the dual-therapy treatment groups for mean or percent change from baseline or for the proportions of patients with renal urinalysis values requiring further clinical review.

SAFETY DATA FOR DUAL THERAPY WITH LANSOPRAZOLE AND CLARITHROMYCIN

Lansoprazole/Clarithromycin Dual-Therapy: Patient Accountability in the Principal Studies

A total of 683 patients received treatment with the regimens selected for analysis of safety with lansoprazole BID/clarithromycin BID dual therapy. Of these, 165 patients received dual therapy with lansoprazole 30 mg BID and clarithromycin 500 mg BID; 173 patients received dual therapy with lansoprazole 30 mg BID and clarithromycin 500 mg TID; 242 patients received monotherapy with lansoprazole 30 mg BID or TID; and 103 patients received monotherapy with clarithromycin 500 mg TID.

Lansoprazole/Clarithromycin Dual-Therapy: Demographic Characteristics in the Principal Studies

A summary of demographic data for patients who received treatment with the regimens selected for the safety analyses of lansoprazole BID/clarithromycin BID dual therapy is presented below.

Patient Demographics for Patients Included in the Lansoprazole BID/Clarithromycin BID Safety Analyses of Dual Therapy in the Principal Studies

Demographic Characteristics	Lan BID/ Cla BID (N = 165)	Lan BID/ Cla TID (N = 173)	Lan BID or TID (N =242)	Cla TID (N = 103)
Gender:				
Female	30% (50)	34% (59)	30% (73)	29% (30)
Male	70% (115)	66% (114)	70% (169)	71% (73)
Race:				
Black	23% (38)	21% (37)	18% (43)	17% (18)
Caucasian	57% (94)	56% (97)	67% (162)	63% (65)
Hispanic	10% (17)	13% (22)	10% (25)	9% (9)
Other	10% (16)	10% (17)	5% (12)	11% (11)
Age (years):#				
<45	39% (65)	40% (70)	37% (89)	43% (44)
45-65	45% (74)	43% (74)	51% (122)	42% (43)
>65	16% (26)	17% (29)	13% (31)	16% (16)
Mean (SD)	50.1 (13.9)	49.9 (14.7)	49.0 (13.3)	49.2 (13.9)
Range				
Weight - Females (lbs):#	(N = 50)	(N = 59)	(N = 73)	(N = 29)
<150	42% (21)	46% (27)	45% (33)	45% (13)
≥150	58% (29)	54% (32)	55% (40)	55% (16)
Mean (SD)	158.6 (36.9)	160.6 (37.9)	164.4 (43.3)	161.4 (39.1)
Range				
Weight - Males (lbs):#	(N = 115)	(N = 114)	(N = 169)	(N = 72)
<150	17% (19)	11% (13)	14% (23)	14% (10)
≥150	83% (96)	89% (101)	86% (146)	86% (62)
Mean (SD)	185.7 (37.3)	184.1 (34.5)	179.4 (31.6)	183.5 (34.8)
Range				

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg
Studies included: M93-125, M93-130, and M93-131
At baseline.

There were no statistically significant differences among the lansoprazole BID/clarithromycin BID and other regimens analyzed for any demographic variable.

Lansoprazole/Clarithromycin Dual-Therapy: Treatment Exposure in the Principal Studies

A summary of treatment duration and percent compliance for patients who received treatment with the regimens selected for the safety analyses of lansoprazole BID/clarithromycin BID dual therapy is presented in the following table.

Extent of Treatment Exposure for Patients Included in the Lansoprazole BID/Clarithromycin BID Safety Analyses of Dual Therapy in the Principal Studies				
	Lan BID/ Cla BID (N = 165)	Lan BID/ Cla TID (N = 173)	Lan BID or TID (N =242)	Cla TID (N = 103)
Treatment Duration (days)				
<10	3% (5)	7% (12)	2% (6)	8% (8)
10-15	93% (154)	92% (160)	96% (232)	92% (95)
>15	4% (6)	1% (1)	2% (4)	0
Mean (SD)*	13.8 (2.03)	13.3 (2.72)	13.9 (1.63)	13.1 (3.10)
Range				
Percent Compliance for Number of Capsules/Tablets Taken#				
<70	3% (5)	7% (12)	2% (6)	8% (8)
70-90	3% (5)	6% (10)	1% (2)	5% (5)
> 90	94% (155)	87% (151)	97% (234)	87% (90)
Mean (SD)*	96.2% (14.12)	92.9% (19.51)	97.2% (12.05)	91.8% (22.53)
Range				

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg
Studies included: M93-125, M93-130, and M93-131
Patients who did not return study drug containers but reported full compliance are included as >90% compliant.
* Statistically significant difference among treatment groups ($p \leq 0.05$).

Lansoprazole/Clarithromycin Dual-Therapy: Adverse Event Comparisons Across Treatment Groups in the Principal Studies

Treatment Period

The following table presents treatment-emergent and possibly or probably treatment-related adverse events reported during the treatment period by ≥3% of patients in any treatment group.

Most Frequently Reported[a] Adverse Events During the Treatment Period for Patients Included in the Lansoprazole BID/Clarithromycin BID Safety Analyses of Dual Therapy in the Principal Studies

COSTART Term	Treatment Group % (n)			
	Lan BID/Cla BID (N = 165)	Lan BID/Cla TID (N = 173)	Lan BID or TID (N = 242)	Cla TID (N = 103)
Treatment-Emergent Adverse Events				
Any Event	38% (62)	45% (78)	31% (74)	57% (59)*
Taste Perversion	7% (11)	19% (33)*	1% (2)*	26% (27)*
Diarrhea	9% (15)	8% (13)	6% (15)	14% (14)
Nausea	5% (9)	8% (14)	1% (2)*	5% (5)
Abdominal Pain	6% (10)	5% (8)	2% (4)*	5% (5)
Headache	4% (6)	2% (4)	5% (12)	5% (5)
Pharyngitis	1% (2)	1% (2)	2% (5)	8% (8)*
Dizziness	3% (5)	1% (2)	1% (2)	1% (1)
Dry Mouth	1% (2)	4% (6)	0	0
Constipation	1% (2)	0	<1% (1)	4% (4)
Flatulence	0	1% (1)	1% (2)	4% (4)*
Possibly or Probably Treatment-Related Adverse Events				
Any Event	22% (37)	35% (60)*	11% (27)*	45% (46)*
Taste Perversion	7% (11)	19% (33)*	<1% (1)*	26% (27)*
Diarrhea	8% (13)	6% (11)	4% (10)	11% (11)
Nausea	3% (5)	6% (11)	1% (2)	4% (4)
Abdominal Pain	1% (1)	2% (3)	1% (3)	4% (4)
Headache	3% (5)	0*	1% (2)	3% (3)
Dizziness	3% (5)	1% (2)	<1% (1)*	0

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg
Studies included: M93-125, M93-130, and M93-131
[a] Reported by ≥3% of patients in any treatment group.
* Statistically significant difference versus lansoprazole BID/clarithromycin BID treatment group ($p \leq 0.05$).

Among the 165 patients who received dual therapy with lansoprazole BID/clarithromycin BID, only two patients (1%, 2/165) had adverse events (abdominal pain, pain, vomiting) considered severe by the investigator.

Among the patients treated with dual therapy lansoprazole BID/clarithromycin BID who had possibly or probably treatment-related adverse events, only one patient (1%, 1/165) had an adverse event (pain) that was considered by the investigator to be severe.

Posttreatment Period

A summary of all and possibly or probably treatment-related adverse events reported during the posttreatment period by ≥3% of patients in any treatment group is presented below.

Most Frequently Reported[a] Adverse Events During the Posttreatment Period for Patients Included in the Lansoprazole BID/Clarithromycin BID Safety Analyses of Dual Therapy in the Principal Studies

	Treatment Group % (n)			
COSTART Term	**Lan BID/Cla BID (N = 165)**	**Lan BID/Cla TID (N = 173)**	**Lan BID or TID (N = 242)**	**Cla TID (N = 103)**
Treatment-Emergent Adverse Events				
Any Event	21% (35)	19% (32)	19% (45)	20% (21)
Pharyngitis	2% (4)	2% (4)	5% (11)	3% (3)
Abdominal Pain	3% (5)	1% (1)	1% (3)	1% (1)
Possibly or Probably Treatment-Related Adverse Events				
Any Event	2% (4)	2% (4)	2% (4)	3% (3)

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg
Studies included: M93-125, M93-130, and M93-131
[a] Reported by ≥3% of patients in any treatment group.
No statistically significant differences between the lansoprazole BID/clarithromycin BID and other treatment groups analyzed.

Among the 165 patients who received dual therapy with lansoprazole BID/clarithromycin BID, four patients (2%, 4/165) had severe adverse events. The most frequently reported severe adverse event was migraine, reported by two (1%) patients. Other severe adverse events (abdominal pain, accidental injury, melena, vomiting, myalgia, and breast pain) were reported by one patient each.

Lansoprazole/Clarithromycin Dual Therapy: Adverse Events by Demographic Subsets for Patients Treated With Lansoprazole BID/Clarithromycin BID in the Principal Studies

Treatment-Emergent Adverse Events by Gender

Of the 165 patients who received dual therapy with lansoprazole BID/clarithromycin BID, 115 (70%) were male and 50 (30%) were female . The percentage of females (52%, 26/50) with adverse events was statistically significantly higher than the percentage of males (31%, 36/115). A statistically significant difference was also seen between genders for the percent of patients reporting treatment-emergent adverse events associated with the body as a whole (7%, 8/115 males; 24%, 12/50 females). No other statistically significant differences were seen between genders for the percent of patients reporting any

other body system or specific adverse event. Among patients with possibly or probably treatment-related adverse events, no statistically significant differences were seen between genders for the percent of patients reporting treatment-related adverse events, or for any specific adverse event.

Treatment-Emergent Adverse Events by Race

Race was categorized as Caucasian, Black, and other. Of the 165 patients who received treatment with lansoprazole BID/clarithromycin BID, 94 (57%) were Caucasian, 38 (23%) were Black, and 33 (20%) were of other races. No statistically significant differences were seen among race categories for the overall percent of patients reporting treatment-emergent adverse events. A statistically significant difference was seen among races for the incidence of dry mouth. Two (6%) patients of other races reported dry mouth, while no Caucasian or Black patients reported this adverse event. No other statistically significant differences were seen among race categories for the percent of patients reporting any specific treatment-emergent adverse event. No statistically significant differences were seen among race categories for the percent of patients reporting possibly or probably treatment-related adverse events.

Treatment-Emergent Adverse Events by Age

Age was categorized as less than 45 years, 45-65 years, and greater than 65 years. Of the 165 patients treated with dual therapy lansoprazole BID/clarithromycin BID, 65 (39%) were less than 45 years of age, 74 (45%) were 45-65 years of age, and 26 (16%) were greater than 65 years of age. No statistically significant differences were seen among age categories for the percent of patients reporting treatment-emergent adverse events. A statistically significant difference was seen among age categories for the incidence of events associated with the respiratory system (1/65, 2% patients less than 45 years; 1/74, 1% patients 45-65 years; 3/26, 12% patients greater than 65 years). No other statistically significant differences were seen among age categories for the percent of patients reporting any specific treatment-emergent adverse event. No statistically significant differences were seen among age categories for the percent of patients reporting possibly or probably treatment-related adverse events.

Adverse Events During the Posttreatment Period by Gender

No statistically significant differences were seen between genders for the percent of patients reporting at least one adverse event. However, a statistically significant difference was seen for body as a whole; the percentage of females (16%, 8/50) with one or more symptoms associated with the body as a whole was statistically significantly higher than the percentage of males (5%, 6/115). No statistically significant differences were seen between genders for the percent of patients with possibly or probably treatment-related adverse events.

Adverse Events During the Posttreatment Period by Race

No statistically significant differences were seen among races categories for the percent of patients reporting treatment-emergent adverse events or possibly or probably treatment-related adverse events.

Adverse Events During the Posttreatment Period by Age

No statistically significant differences were seen among age categories for the percent of patients reporting at least one treatment-emergent adverse event or possibly or probably treatment-related adverse events. In the analysis of all adverse events, the percentage of older (greater than 65 years of age) patients with constipation was statistically significantly higher than younger (less than or equal to 45 years of age) patients. No occurrence of constipation was reported as a possibly or probably treatment-related adverse event. No statistically significant differences were seen among age categories for the percent of patients reporting any other specific adverse events.

Lansoprazole/Clarithromycin Dual-Therapy: Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events in the Treatment Groups Used for the Lansoprazole/Clarithromycin Safety Analyses in the Principal Studies

A summary of the number of deaths, patients reporting serious adverse events, pregnancies, and premature discontinuations due to adverse events reported for patients included in the lansoprazole BID/clarithromycin BID safety analyses of dual therapy in the principal studies is presented below.

Deaths, Serious Adverse Events, Pregnancies, and Discontinuations Due to Adverse Events Reported for Patients Included in the Lansoprazole BID/Clarithromycin BID Safety Analyses of Dual Therapy in the Principal Studies

	Treatment Group % (n)			
Safety Parameter	**Lan BID/Cla BID (N = 165)**	**Lan BID/Cla TID (N = 173)**	**Lan BID or TID (N = 242)**	**Cla TID (N = 103)**
Deaths	0	1% (1)	0	0
Number of Patients With Serious Adverse Events	1% (1)	1% (1)	1% (2)	2% (2)
Pregnancies	0	1% (2)	0	0
Premature Discontinuation Due to Adverse Events	4% (7)	6% (11)	2% (4)	8% (8)

Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg
Studies included: M93-125, M93-130, and M93-131

No patient died receiving lansoprazole BID/clarithromycin BID dual therapy, however, one patient (M93-130; Breiter) died of lung cancer 88 days after completion of treatment with lansoprazole BID/clarithromycin TID. A detailed narrative for this patient is now presented.

Study M93-130/Breiter a 75-year-old Caucasian female nondrinker who received lansoprazole 30 mg BID and clarithromycin 500 mg TID for 15 days, was an ex-smoker for 20 years who had previously smoked less than one package of cigarettes for 15 years. The patient was prematurely discontinued from the study during the posttreatment period on Study Day 43, when a lung mass [COSTART Term: Carcinoma of Lung], deemed a severe and serious adverse event, was revealed on a chest X-ray and CT scan. A needle biopsy confirmed lung carcinoma. She died two months later (88 days after her last dose of double-blind medication) from lung cancer. In the investigator's opinion, the adverse event and subsequent death due to the disease had no relationship to study drug. Prior to the diagnosis of lung cancer, the patient also experienced mild nausea, moderate vomiting, and a moderate cough. At the time of the adverse event, the patient was not taking any concurrent medications.

Among the 165 patients treated with lansoprazole BID/clarithromycin BID dual therapy, one patient reported three serious adverse events (abdominal pain, vomiting, and melena) which were considered unrelated to study medication. In addition, two patients who received clarithromycin monotherapy (prostatic disorder and pharyngitis), two patients who received lansoprazole monotherapy (accidental injury and carcinoma), and one patient who received lansoprazole BID/clarithromycin TID (carcinoma and increased cough) reported serious adverse events, all of which were considered unrelated to study medication.

Additionally, two patients (M93-130; LoIudice lansoprazole BID/clarithromycin TID and M93-131; Lamet lansoprazole BID/clarithromycin TID) became pregnant during treatment; Lamet became pregnant prior to the Week-6 Visit of Study M93-131 and experienced a severe spontaneous abortion on Study Day 44. LoIudice experienced an uncomplicated pregnancy and gave birth to a healthy baby.

Of the 165 patients treated with dual therapy lansoprazole BID/clarithromycin BID, four patients discontinued from the study during the treatment period and three discontinued during the posttreatment period due to adverse events. Events leading to discontinuation during the treatment period included tremor, taste perversion, headache, and nausea; tongue edema, nausea, and dizziness; abdominal pain; and pruritis, all of which were considered possibly or probably treatment-related, except for one case of abdominal pain. Events leading to discontinuation during the posttreatment period included abdominal pain, hematemesis, nausea, and vomiting, all of which were considered unrelated to study medication.

Among all lansoprazole BID/clarithromycin BID-treated patients, all treatment-emergent and all possibly or probably treatment-related adverse events leading to premature discontinuation during the treatment period were considered by the

investigator to be mild or moderate in severity. For the three patients who discontinued the study due to adverse events during the posttreatment period, two patients had events of moderate severity (abdominal pain, nausea, and hematemesis) and one patient had events that were considered by the investigator to be severe (abdominal pain and vomiting). None of the adverse events leading to discontinuation during the posttreatment period were considered treatment-related.

No statistically significant differences were observed between the lansoprazole BID/clarithromycin BID and other treatment groups analyzed for the percent of patients reporting treatment-emergent adverse events. The percent of patients reporting digestive system adverse events leading to premature discontinuation was statistically significantly higher among patients treated with lansoprazole BID/clarithromycin BID (3%) compared with lansoprazole monotherapy-treated patients (0%). There were no other statistically significant differences observed between the lansoprazole BID/clarithromycin BID and any other treatment group for adverse events leading to premature discontinuation.

The percent of patients reporting possibly or probably treatment-related adverse events leading to premature discontinuation was statistically significantly lower among patients treated with lansoprazole BID/clarithromycin BID (2%, 3/165) than those treated with clarithromycin monotherapy (7%, 7/103).

Lansoprazole/Clarithromycin Dual-Therapy: Adverse Events in the Supportive Studies

In the U.S. supportive lansoprazole BID/clarithromycin TID dual-therapy studies of 88 patients (M95-268, M95-269, and M95-287), the most frequently reported adverse events during the treatment period were taste perversion (39%), diarrhea (8%), dry mouth (7%), abdominal pain (5%), dizziness (5%), nausea (5%), constipation (3%), and insomnia (3%). No patient died and two patients reported three serious adverse events of chest pain, back pain, and myalgia in these studies. Chest pain and back pain were considered by the investigator as unrelated to study medication, while myalgia was considered possibly related to study medication. Eight patients prematurely discontinued from the U.S. supportive lansoprazole BID/clarithromycin TID studies.

Lansoprazole/Clarithromycin Dual-Therapy: Conclusions of Clinical Laboratory Determinations in the Principal Studies

Some statistically significant differences in mean and percent changes from baseline were observed across treatment groups and the demographic subsets for some laboratory parameters; however, these changes were small and not considered clinically significant. No statistically significant differences were observed between treatment groups for the proportions of patients with laboratory values requiring further clinical review.

Although there were statistically significant differences in mean and percent changes for some hematology analytes between both lansoprazole BID/clarithromycin BID and lansoprazole monotherapy treatment groups (hemoglobin, hematocrit, RBC count, WBC count, neutrophils, lymphocytes, basophils, and platelet count) and between lansoprazole BID/clarithromycin BID and clarithromycin monotherapy treatment groups (platelet count), these changes were small and not considered clinically significant. No statistically significant differences were observed between treatment groups for the proportions of patients with hematology values requiring further clinical review.

No statistically significant differences were observed between the treatment groups for mean change from baseline to the Week-2 or Week-6 Visit in any electrolyte parameters. There were no statistically significant differences between the treatment groups, except for percent change from baseline to the Week-2 Visit in potassium between the lansoprazole BID/clarithromycin BID and the clarithromycin monotherapy treatment groups. This difference was small not considered clinically significant.

When hepatic chemistry parameters were evaluated, statistically significant differences were noted between the lansoprazole BID/clarithromycin BID and the lansoprazole monotherapy treatment groups for total bilirubin, AST/SGOT, and ALT/SGPT for mean change from baseline, which were not considered clinically significant. No statistically significant differences were observed between treatment groups for the proportions of patients with hepatic chemistry values requiring further clinical review.

For metabolic/nutritional chemistry parameters, statistically significant differences were observed between the lansoprazole BID/clarithromycin BID and the lansoprazole monotherapy treatment groups for mean change from baseline in albumin and for percent change from baseline for albumin, calcium, and glucose; however each of these differences in mean and percent changes was small and not considered clinically significant. No statistically significant differences were observed between treatment groups for the proportions of patients with metabolic/nutritional chemistry values requiring further clinical review.

For renal chemistry parameters, statistically significant differences were observed between the lansoprazole BID/clarithromycin BID and the lansoprazole BID/clarithromycin TID treatment groups for mean change from baseline BUN; however, this difference in mean changes was small and not considered clinically significant. No statistically significant differences were observed between treatment groups for percent change from baseline in any renal chemistry parameter. No statistically significant differences were observed between treatment groups for the proportions of patients with renal chemistry values requiring further clinical review.

For urinalysis parameters, statistically significant differences were observed between the lansoprazole BID/clarithromycin BID and the clarithromycin monotherapy treatment groups for mean change from baseline for urine specific gravity; however, this difference in mean change was small and not considered clinically significant. No statistically significant differences were observed between the treatment groups for percent change from baseline or for the proportions of patients with urinalysis values requiring further clinical review in any urinalysis parameter.

SAFETY DATA FOR DUAL-THERAPY WITH LANSOPRAZOLE AND AMOXICILLIN

Lansoprazole/Amoxicillin Dual-Therapy: Patient Accountability in the Principal Studies

A total of 580 patients received treatment with the regimens selected for analysis of safety with lansoprazole TID/amoxicillin TID dual therapy. Of these, 137 patients received dual therapy with lansoprazole 30 mg TID and amoxicillin 1 gm TID; 134 patients received dual therapy with lansoprazole 30 mg BID and amoxicillin 1 gm TID; 242 patients received monotherapy with lansoprazole 30 mg BID or TID; and 67 patients received monotherapy with amoxicillin 1 gm TID.

Lansoprazole/Amoxicillin Dual-Therapy: Demographic Characteristics in the Principal Studies

A summary of demographic data for patients who received treatment with the regimens selected for the safety analyses of lansoprazole TID/amoxicillin TID dual therapy is presented in the following table.

Patient Demographics for Patients Included in the Lansoprazole TID/Amoxicillin TID Safety Analyses of Dual Therapy in the Principal Studies

Demographic Characteristics	Lan TID/ Amx TID (N =137)	Lan BID/ Amx TID (N =134)	Lan BID or TID (N =242)	Amx TID (N = 67)
Gender:				
Female	31% (42)	34% (45)	30% (73)	28% (19)
Male	69% (95)	66% (89)	70% (169)	72% (48)
Race:				
Black	18% (25)	25% (33)	18% (43)	30% (20)
Caucasian	58% (79)	58% (78)	67% (162)	61% (41)
Hispanic	18% (24)	13% (17)	10% (25)	8% (5)
Other	7% (9)	5% (6)	5% (12)	2% (1)
Age (years):#				
<45	41% (56)	42% (56)	37% (89)	39% (26)
45-65	45% (62)	46% (62)	50% (122)	51% (34)
>65	14% (19)	12% (16)	13% (31)	10% (7)
Mean (SD)	49.6 (13.0)	47.8 (14.3)	49.0 (13.3)	48.1 (12.3)
Range				
Weight - Females (lbs):#	(N = 41)	(N = 45)	(N = 73)	(N = 19)
<150	32% (13)	42% (19)	45% (33)	42% (8)
≥150	68% (28)	58% (26)	55% (40)	58% (11)
Mean (SD)	160.0 (30.8)	158.5 (31.7)	164.4 (43.3)	171.6 (50.2)
Range				
Weight - Males (lbs):#	(N = 95)	(N = 89)	(N = 169)	(N = 48)
<150	16% (15)	15% (13)	14% (23)	10% (5)
≥150	84% (80)	85% (76)	86% (146)	90% (43)
Mean (SD)	176.2 (30.1)	182.0 (33.2)	179.4 (31.6)	181.3 (29.1)
Range				

Lan = lansoprazole 30 mg; Amx = amoxicillin 1 gm
Studies included: M93-125, M93-130, and M93-131
At baseline.

There were no statistically significant differences among the lansoprazole TID/amoxicillin TID and the regimens analyzed for any demographic variable.

Lansoprazole/Amoxicillin Dual-Therapy: Treatment Exposure in the Principal Studies

A summary of treatment duration and percent compliance for patients who received treatment with the regimens selected for the safety analyses of lansoprazole TID/amoxicillin TID dual therapy is presented below.

Extent of Treatment Exposure for Patients Included in the Lansoprazole TID/Amoxicillin TID Safety Analyses of Dual Therapy in the Principal Studies				
	Lan TID/ Amx TID (N =137)	Lan BID/ Amx TID (N =134)	Lan BID or TID (N =242)	Amx TID (N = 67)
Treatment Duration (days) <10 10-15 >15	 1% (2) 96% (131) 3% (4)	 3% (4) 97% (130) 0	 2% (6) 96% (232) 2% (4)	 1% (1) 93% (62) 6% (4)
Mean (SD) Range	14.1 (1.10)	13.8 (1.52)	13.9 (1.63)	14.2 (1.35)
Percent Compliance for Number of Capsules/Tablets Taken# <70 70-90 > 90	 2% (3) 5% (7) 93% (127)	 4% (6) 3% (4) 93% (124)	 2% (6) 1% (2) 97% (234)	 1% (1) 1% (1) 97% (65)
Mean (SD) Range	97.6% (7.02)	96.9% (9.21)	97.2% (12.05)	98.2% (5.90)
Lan = lansoprazole 30 mg; Amx = amoxicillin 1 gm Studies included: M93-125, M93-130, and M93-131 # Patients who did not return study drug containers but reported full compliance are included as >90% compliant.				

There were no statistically significant differences between the lansoprazole TID/amoxicillin TID and the regimens analyzed for either mean duration of treatment or mean percent compliance.

Lansoprazole/Amoxicillin Dual-Therapy: Adverse Event Comparisons Across Treatment Groups in the Principal Studies

Treatment Period

The following table presents treatment-emergent and possibly or probably treatment-related adverse events reported during the treatment period by ≥3% of patients in any treatment group.

Most Frequently Reported[a] Adverse Events During the Treatment Period for Patients Included in the Safety Analyses of Dual Therapy With Lansoprazole TID/Amoxicillin TID in the Principal Studies

	Treatment Group % (n)			
COSTART Term	Lan TID/Amx TID (N = 137)	Lan BID/Amx TID (N = 134)	Lan BID or TID (N = 242)	Amx TID (N = 67)
Treatment-Emergent Adverse Events				
Any Event	33% (45)	34% (46)	31% (74)	19% (13)*
Diarrhea	8% (11)	5% (7)	6% (15)	9% (6)
Headache	7% (9)	6% (8)	5% (12)	4% (3)
Pharyngitis	1% (1)	4% (5)	2% (5)	1% (1)
Taste Perversion	2% (3)	1% (2)	1% (2)	3% (2)
Possibly or Probably Treatment-Related Adverse Events				
Any Event	20% (27)	18% (24)	11% (27)*	15% (10)
Diarrhea	7% (10)	5% (7)	4% (10)	7% (5)
Headache	4% (6)	4% (5)	1% (2)*	0
Taste Perversion	2% (3)	1% (2)	<1% (1)	3% (2)

Lan = lansoprazole 30 mg; Amx = amoxicillin 1 gm
Studies included: M93-125, M93-130, and M93-131
[a] Reported by ≥3% of patients in any treatment group.
* Statistically significant difference versus lansoprazole TID/amoxicillin TID treatment group ($p \leq 0.05$).

Among the 137 patients who received dual therapy with lansoprazole TID/amoxicillin TID, two patients (1%, 2/137) had adverse events (migraine and rash) considered severe by the investigator.

Among the patients treated with dual therapy lansoprazole TID/amoxicillin TID who had possibly or probably treatment-related adverse events, only one patient (1%, 1/137) had a treatment-related adverse event (rash) considered severe by the investigator.

Posttreatment Period

The following table presents a summary of treatment-emergent and possibly or probably treatment-related adverse events reported during the posttreatment period by ≥3% of patients in any treatment group.

Most Frequently Reported[a] Adverse Events During the Posttreatment Period for Patients Included in the Safety Analyses of Dual Therapy With Lansoprazole TID/Amoxicillin TID in the Principal Studies

COSTART Term	Treatment Group % (n)			
	Lan TID/Amx TID (N = 137)	Lan BID/Amx TID (N = 134)	Lan BID or TID (N = 242)	Amx TID (N = 67)
Treatment-Emergent Adverse Events				
Any Event	15% (20)	22% (29)	19% (45)	24% (16)
Pharyngitis	1% (2)	1% (2)	5% (11)	6% (4)
Abdominal Pain	3% (4)	3% (4)	1% (3)	4% (3)
Insomnia	0	0	1% (2)	3% (2)
Possibly or Probably Treatment-Related Adverse Events				
Any Event	2% (3)	4% (5)	2% (4)	3% (2)

Lan = lansoprazole 30 mg; Amx = amoxicillin 1 gm
Studies included: M93-125, M93-130, and M93-131
[a] Reported by ≥3% of patients in any treatment group.
No statistically significant differences between the lansoprazole TID/amoxicillin TID and other treatment groups analyzed.

Among the 137 patients who received dual therapy with lansoprazole TID/amoxicillin TID, three patients (2%, 3/137) had at least one adverse event categorized as severe. The most frequently reported severe adverse event was abdominal pain, reported by two patients. Other severe adverse events (carcinoma, diarrhea, melena, and pleural effusion) were each reported by one patient.

There were three possibly or probably treatment-related adverse events reported during the posttreatment period for patients treated with dual therapy lansoprazole TID/amoxicillin TID. Two of the events were categorized as mild in severity and one (abdominal pain) was categorized as severe.

Lansoprazole/Amoxicillin Dual Therapy: Adverse Events by Demographic Subsets for Patients Treated With Lansoprazole TID/Amoxicillin TID in the Principal Studies

Treatment-Emergent Adverse Events by Gender

Of the 137 patients treated with dual-therapy lansoprazole TID/amoxicillin TID, 95 (69%) were male and 42 (31%) were female. No statistically significant differences were seen between males and females for the percent of patients reporting treatment-emergent adverse events or possibly or probably treatment-related adverse events. No statistically significant differences were seen between genders for the percent of patients reporting any specific adverse event that could be experienced by both males and females.

Treatment-Emergent Adverse Events by Race

Of the 137 patients treated with dual-therapy lansoprazole TID/amoxicillin TID, 79 (58%) were Caucasian, 25 (18%) were Black, and 33 (24%) were of other races. A statistically significant difference was observed among races for the percent of patients reporting treatment-emergent adverse events (51%, 40/79 Caucasian; 72%, 18/25 Black; 36%, 12/33 other) as well as for the specific adverse events of nausea and rhinitis, which were only reported by Black patients.

A statistically significant difference was seen among races for the incidence of possibly or probably treatment-related nausea. No statistically significant differences were seen among race categories for the percent of patients reporting possibly or probably treatment-related adverse events or for any other specific treatment-related adverse event.

Treatment-Emergent Adverse Events by Age

Of the 137 patients treated with dual-therapy lansoprazole TID/amoxicillin TID, 56 (41%) were less than 45 years of age, 62 (45%) were 45-65 years of age, and 19 (14%) were greater than 65 years of age. No statistically significant differences were observed among age categories for the percent of patients reporting treatment-emergent adverse events or for any specific treatment-emergent adverse event. However, the incidence of treatment-related headache was statistically significantly different among age categories, with younger patients (i.e., less than 45 years of age) showing increased headache (9%) compared with older patients (i.e., greater than 65 years of age, 5%); no patients 45-65 years of age experienced headache. No other statistically significant differences were seen among age categories for the percent of patients reporting possibly or probably treatment-related adverse events.

Adverse Events During the Posttreatment Period by Gender

No statistically significant differences were seen between genders for the percent of patients reporting treatment-emergent adverse events, the percent of patients reporting possibly or probably treatment-related adverse events, or any specific adverse event.

Adverse Events During the Posttreatment Period by Race

No statistically significant differences were seen among race categories for the percent of patients reporting treatment-emergent adverse events, the percent of patients reporting possibly or probably treatment-related adverse events, or any specific adverse event.

Adverse Events During the Posttreatment Period by Age

No statistically significant differences were seen among age categories for the percent of patients reporting treatment-emergent adverse events, the percent of patients reporting possibly or probably treatment-related adverse events, or any specific adverse event.

Lansoprazole/Amoxicillin Dual-Therapy: Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events in the Treatment Groups Used for the Lansoprazole/Amoxicillin Safety Analyses in the Principal Studies

A summary of the number of deaths, patients reporting serious adverse events, pregnancies, and premature discontinuations due to adverse events reported for patients included in the lansoprazole TID/amoxicillin TID safety analyses of dual therapy in the principal studies is presented below.

Deaths, Serious Adverse Events, Pregnancies, and Discontinuations Due to Adverse Events Reported for Patients Included in the Lansoprazole TID/Amoxicillin TID Safety Analyses of Dual Therapy in the Principal Studies

	Treatment Group % (n)			
Safety Parameter	Lan TID/Amx TID (N = 137)	Lan BID/Amx TID (N = 134)	Lan BID or TID (N = 242)	Amx TID (N = 67)
Deaths	0	0	0	0
Number of Patients With Serious Adverse Events	3% (4)	2% (3)	1% (2)	0
Pregnancies	0	0	0	0
Premature Discontinuation Due to Adverse Events	4% (5)	3% (4)	2% (4)	2% (1)

Lan = lansoprazole 30 mg; Amx = amoxicillin 1 gm
Studies included: M93-125, M93-130, and M93-131

Of the 137 patients who received lansoprazole TID/amoxicillin TID, four reported serious adverse events (cerebrovascular accident, abdominal pain [two patients], diarrhea, melena, pleural effusion, atrial arrhythmia). All but one adverse event of abdominal pain were considered unrelated to study medication.

Among the 137 patients treated with dual therapy lansoprazole TID/amoxicillin TID, three patients discontinued the study during the treatment period and two discontinued during the posttreatment period at least in part due to adverse events.

Events leading to discontinuation during the treatment period included cerebrovascular accident; rash; pruritus and maculopapular rash, all of which were considered possibly or probably treatment-related, except for cerebrovascular accident. Events leading to discontinuation during the posttreatment period included abdominal pain, carcinoma, diarrhea, and melena, all of which were considered unrelated to study medication, except for one report of a possibly related abdominal pain.

Among all lansoprazole TID/amoxicillin TID-treated patients, all treatment-emergent and all possibly or probably treatment-related adverse events leading to premature discontinuation during the treatment period were considered by the investigator to be mild or moderate in severity, except for one case of severe rash. For the two patients who discontinued the study during the posttreatment period, both had events (abdominal pain, carcinoma, diarrhea, and melena) that were considered by the investigator to be severe. One of the adverse events leading to discontinuation during the posttreatment period (abdominal pain) was considered possibly or probably treatment-related.

Lansoprazole/Amoxicillin Dual-Therapy: Adverse Events in the Supportive Studies

In the U.S. supportive lansoprazole/amoxicillin dual-therapy studies of 29 patients (M95-270 and M95-271), the most frequently reported adverse events during the treatment period were diarrhea (17%), abdominal pain (3%), constipation (3%), flatulence (3%), peripheral edema (3%), and rash (3%). No deaths or serious adverse events were reported in these studies. One patient in Study M95-270 prematurely discontinued due to rash, which was considered probably related to study medication.

Lansoprazole/Amoxicillin Dual-Therapy: Conclusions of Clinical Laboratory Determinations in the Principal Studies

Some statistically significant differences in mean and percent changes from baseline were observed between the lansoprazole TID/amoxicillin TID and other treatment groups analyzed and among demographic subsets, these changes were small and not considered clinically significant. No statistically significant differences were observed between the lansoprazole TID/amoxicillin TID and other treatment groups analyzed for the proportions of patients with laboratory values requiring further clinical review.

Although there were statistically significant differences between the lansoprazole TID/amoxicillin TID and other treatment groups analyzed in mean and percent changes for some hematology parameters (neutrophils, eosinophils, lymphocytes, monocytes, basophils, hematocrit, WBC count, and platelets), these changes were small and not considered clinically significant. No statistically significant differences were observed between the lansoprazole TID/amoxicillin TID and

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20876

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Lansoprazole delayed-release capsules
New Protocol

DATE of SUBMISSION
September 30, 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: TAP Holdings Inc
Bannockburn Lake Office Plaza,
2355 Waukegan Rd., Deerfield, IL 60015

Type of Submission New Indication
Code 1S

REVIEWER: He Sun, Ph.D.

I. SYNOPSIS

The pharmacokinetics of lansoprazole, administered in various daily dosing regimens were investigated (M93-006). Study results show that there were no statistically significant effects of dosing regimens on T_{max} in either group. When dose normalized AUC values of the morning doses for the entire study were collectively considered as total daily dose or dosing frequency, there was no indication of nonlinearity. There was no significant difference in either T_{max} or $t_{1/2}$ upon comparison of values resulting from the 8:00 am or 6:00 pm dose in any of the BID analyses.

The effect of concomitant administration of lansoprazole and clarithromycin on the steady state pharmacokinetics of both compounds, as well as the 14[R]-hydroxy metabolite of clarithromycin, were also evaluated (M93-063). Results indicate that concomitant administration of clarithromycin resulted in a statistically significant increase (19%) in the lansoprazole AUC for the evening dose. A statistically significant increase (28%) in the lansoprazole AUC values following the morning dose on Day 5 was also seen during concomitant administration of lansoprazole and clarithromycin. Lansoprazole had no significant effect on the C_{max}, T_{max} and AUC or half-life for clarithromycin in this study. AUC of 14[R]-hydroxy-clarithromycin after the third dose on Day 5 was significantly increased by 16%.

The effect of concomitant administration of lansoprazole and amoxicillin on the steady state pharmacokinetics of both compounds were evaluated (M94-168). Lansoprazole pharmacokinetic parameters were unaltered by coadministration of amoxicillin, with the single exception of a 14% reduction in AUC between the administration of the 1300 hour and 1800 hour doses. Small decreases in amoxicillin mean C_{max} following the 1300 hour and 1800 hour doses were observed upon concomitant lansoprazole administration along with a small increase in mean AUC following the 1800

hour dose associated with a longer $t_{1/2}$. Neither lansoprazole nor amoxicillin total AUC over the 24 hour period was significantly affected. None of these pharmacokinetic results preclude coadministration of lansoprazole and amoxicillin.

II. RECOMMENDATION

Studies #M93-063, #M93-006, and M94-168 are acceptable.

III. BACKGROUND

The sponsor, TAP Holdings Inc. submits this NDA for the use of PREVACID (lansoprazole) delayed-release capsules in combination with clarithromycin and/or amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer in the past year). Both the triple and dual therapy regimens will be available to patients by prescription only.

Three clinical pharmacokinetic studies were included. Study M93-006 is to investigate the pharmacokinetics of lansoprazole administered in various daily dosing regimen. Studies of M93-063 and M94-168 are pharmacokinetic drug interaction studies of lansoprazole with clarithromycin (M93-063) and amoxicillin (M94-168), respectively.

IV. STUDY SUMMARY

1. Study # *M93-006*

Title:

Dose response evaluation of multiple doses of lansoprazole using 24 hour determinations of pH. (The report below is the pharmacokinetic portion of the study only)

Investigator:

Study Design:

The pharmacokinetics of lansoprazole, administered in various daily dosing regimens were investigated in a randomized, double-blind, four-way crossover study. The study involves two groups of 16 healthy adult male subjects. A total of 33 subjects (one withdraw), aged from years (mean 25 years) in high from inches (mean 70 inches), and weight from pounds were enrolled in the study.

Dosage Forms:

Lansoprazole capsules, 15 mg, NPRO 6154, Bulk Lot 73-256-AR. Placebo was supplied as capsules identical in appearance to lansoprazole. Capsules were supplied by TAP Pharmaceuticals Inc., Deerfield, IL.

Dosing Regimen:

Within each group, the subjects were randomly assigned to receive the following regiments, according to one of four possible sequences:

Regimen	Group	Regimen	Time	Lansoprazole	Placebo
			0800	2	2
A	I and II	30 mg QD	1300	-	4
			1800	-	4
			0800	1	3
B	I	15 mg BID	1300	-	4
			1800	1	3
			0800	2	2
C	I	30 mg BID	1300	-	4
			1800	2	2
			0800	2	2
D	I	30 mg TID	1300	2	2
			1800	2	2
			0800	4	-
E	II	60 mg QD	1300	-	4
			1800	-	4
			0800	4	-
F	I	60 mg BID	1300	-	4
			1800	4	-
			0800	4	-
G	II	60 mg TID	1300	4	-
			1800	4	-

All medication was administered 30 minutes prior to meals.

Blood Sampling:

Blood samples were collected by venipuncture on Day 5 of each study period. Samples were taken at 0 hour (prior to 0800 dosing), 0.5, 1, 1.5, 2, 3, 4, 5 (prior to 1300 hour dose), 5.5, 6, 6.5, 7, 8, 9.0, 10 (prior to 1800 hour dose), 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 19 and 22 hours after dosing. The samples were centrifuged and the plasma collected and frozen at -10°C or lower until assayed.

Analytical Methodology:

Pharmacokinetic Analyses:

C_{max}, C_{min}, T_{max}, AUC_{0-24}, $AUC_{0-\infty}$ (the AUC due to a single dose) and $t_{1/2}$ were determined for lansoprazole by methods. The concentration of the hour sample reported in the tables was estimated by

Statistical Analyses:

The effects of various regimens of lansoprazole when administered daily for five consecutive days were compared with a cross-over analysis of variance (ANOVA) model which includes effects for regimens, period, sequence, and subjects within sequence. The two sample t-test was used to compare Group I and Group II on the basis of pharmacokinetic parameter data of the 30 mg QD regimens, the only regimen administered to both groups. Group I (15 mg BID and 30 mg BID) data were analyzed with an ANOVA model with effects for subjects, dose level (regimen), dose time, and the interaction of dose level and dose time. The 15 mg BID data of Group I and the 60 mg BID data of Group II were analyzed with an ANOVA with effects for regimen, subjects within regimen, dose time, and the interaction of regimen and dose time. The same model was used for analysis of the data of the 30 mg BID regimen.

Results:

Pharmacokinetic parameter means for lansoprazole following administration of the various regimens are given below. There were no statistically significant differences detected in any of the pharmacokientic parameters between the 30 mg QD Group I and Group II data when compared using the t-test. There were no statistically significant differences in the PK parameters of the 30mg BID (Group I) and the 60mg QD (Group II) regimens.

Mean lansoprazole AUC values for Day 5

Regimen	Group	AUC0-24 ng*hr/ml	AUC0-24/D ng*hr/ml/mg	AUCinf ng*hr/ml 8:00 am	AUCinf/ ng*hr/ml/mg 8:00am	AUCinf ng*hr/ml 1:00pm	AUCinf ng*hr/ml 6:00pm
30 mg QD	I	2432	81	2428	81	-	-
30 mg QD	II	1934	64	1963	65	-	-
60 mg QD	II	4743	79	4742	79	-	-
15 mg BID	I	2132	71	1188	79	-	1064
30 mg BID	I	4693	78	2504	83	-	2164
60 mg BID	II	8508	71	4602	77	-	3896
30 mg TID	I	8208	91	2893	96	2705	2573
60 mg TID	II	14083	78	4802	80	4709	4533
30 mg QD	I and II	2183	73	2182	73	-	-

QD=once daily, BID=twice daily, TID=three times daily.
AUCinf represents the total AUC due to only the dose administered at the specified time.
AUC0-24 represents the AUC from 8:00am on Day 5 to 8:00an on Day 6.
In the computation of AUC0-24/D, D represents the total dose per day; i.e. for 30 mg BID, D=60 mg
In the computation of AUCinf/D, D represents the magnitude of a single dose; i.e. for 30 mg BID, D=30mg.

Mean lansoprazole $t_{1/2}$ for Day 5

Regimen	Group	$t_{1/2}$ (hours) 8:00 am	$t_{1/2}$ (hours) 1:00 pm	$t_{1/2}$ (hours) 6:00 pm
30 mg QD	I	1.40	-	
30 mg QD	II	1.22		
60 mg QD	II	1.24		
15 mg BID	I	1.56	-	1.29
30 mg BID	I	1.40	-	1.34
60 mg BID	II	1.20	-	1.35
30 mg TID	I	1.44	1.48	1.46
60 mg TID	II	1.38	1.48	1.29
30 mg QD	I and II	1.31		

Mean Lansoprazole T_{max} and C_{max} for Day 5

Regimen	Group	Cmax (ng/mL) 8:00am	Tmax (hours) 8:00 am	Cmax (ng/mL) 1:00pm	Tmax (hours) 1:00 pm	Cmax (ng/mL) 6:00pm	Tmax (hours) 6:00 pm
30 mg QD	I	701	1.3				
30 mg QD	II	684	1.3				
60 mg QD	II	1556	1.4				
15 mg BID	I	377	1.2	-	-	384	1.3
30 mg BID	I	814	1.3	-	-	696	1.8
60 mg BID	II	1667	1.5	-	-	1537	1.4
30 mg TID	I	1037	1.0	1079	1.1	1052	1.2
60 mg TID	II	1581	1.5	2080	1.0	1884	1.3
30 mg QD	I and II	693	1.3				

The results of the one way analysis of variance for bioavailability for the two groups is summarized below. There were statistically significant differences in the PK parameters between the different dosing regimens.

Group I and Group II regimen effects

PK parameter	p-value for test on regimen Effects	
	Group I	Group II
T_{max}	0.2788	0.8531
Ln C_{max}/D (8:00am)	0.0001	0.0747
ln AUC0-00/D (8:00am)	0.0001	0.0001
ln AUC0-24/D	0.0003	0.0001
t1/2 (8:00am)	0.7921	0.0020

BID Regimen p-values

	Effect of Dose Magnitude	Effect of Dose Time 8am vs 6pm	Interaction Dose*time
PK parameter	15 mg BID group I combined with 30 mg BID group I		
T_{max}	0.1136	0.0764	0.2414
Ln C_{max}/D (8:00am)	0.6692	0.0487	0.2786
ln AUC0-00/D (8:00am)	0.7540	0.0053	0.3043
t1/2 (8:00am)	0.7753	0.1772	0.4355
PK parameter	15 mg BID group I combined with 30 mg BID group I		
T_{max}	0.2257	0.9852	0.5676
Ln C_{max}/D (8:00am)	0.3386	0.2459	0.4344
ln AUC0-00/D (8:00am)	0.2487	0.0094	0.7584
t1/2 (8:00am)	0.7314	0.7545	0.0930
PK parameter	15 mg BID group I combined with 30 mg BID group I		
T_{max}	1.000	0.3791	0.1936
Ln C_{max}/D (8:00am)	0.2473	0.0211	0.1676
ln AUC0-00/D (8:00am)	0.3222	0.0004	0.2526
t1/2 (8:00am)	0.7568	0.6143	0.2290

Conclusion:

There were no statistically significant effects of dosing regimen on T_{max} in either group, implying similarity in rates of absorption, irrespective of dose or time of dosing, and minimal influence of residual drug from previous doses on T_{max}. Within each group, there was an indication of a minor improvement in absorption with higher doses, possibly due to reduced acid mediated degradation. However, when the dose normalized AUC values of the morning doses for the entire study were collectively considered as a function of total daily dose or dosing frequency, there was no indication of nonlinearity since no consistent trend was apparent. There was no significant difference in either T_{max} or $t_{1/2}$ upon comparison of values resulting from the 8:00 am or 6:00 pm dose in any of the BID analyses. In contrast to once-daily PM dosing, the results of the current study indicate that the decrease in absorption is minimal when lansoprazole is dosed at 6:00 pm prior to the evening meal in the context of BID dosing.

2. Study # *M94-168*

Title:

The Effect of Concomitant Administration of Lansoprazole and Amoxicillin in Normal Subjects.

Investigator:

Study Design:

The pharmacokinetics of lansoprazole, administered in various daily dosing regimens were investigated in a randomized, double-blind, placebo-controlled, three-period crossover study (M94-168). A total of twenty-four (24) nonsmoking healthy male and female subjects were enrolled. The mean age of 17 male and 7 female subjects was 29.5 years (range years), the mean weight was 167.3 pounds (range: pounds) and the mean height was 68.6 inches (range inches).

Dosage Forms:

Lansoprazole capsules, 30 mg, NPRO 6089R, Lot 81-447-AR. Capsules were supplied by TAP Pharmaceuticals Inc., Deerfield IL.

Amoxicillin capsules, 250 mg amoxicillin as the trihydrate. Capsules were furnished by

Dosing Regimen:

Regimen A: One 30 mg lansoprazole capsule three times daily plus placebo for amoxicillin capsules three time daily on days 1-5.

Regimen B: One placebo for lansoprazole capsule three times daily plus four 250 mg amoxicillin capsules three time daily on days 1-5.

Regimen C: One 30 mg lansoprazole capsule three times daily plus four 250 mg amoxicillin capsules three time daily on days 1-5.

Doses were administered at 0800, 1300, and 1800 hours for all three regiments.

Blood Sampling:

Blood samples were collected by venipuncture on Day 5 of each study period. Samples were taken at 0 hour (prior to 0800 dosing), 0.5, 1, 1.5, 2, 3, 4, 5 (prior to 1300 hour dose), 5.5, 6, 6.5, 7, 8, 9.0, 10 (prior to 1800 hour dose), 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 19 and 22 hours after dosing. The samples were centrifuged and the plasma collected and frozen at -10°C or lower until assayed.

Analytical Methodology:

Pharmacokinetic Analyses:

C_{max}, C_{min}, T_{max}, AUC_{0-24}, $AUC_{0-\infty}$ (the AUC due to a single dose) and $t_{1/2}$ were determined for lansoprazole by methods. The concentration of the hour sample reported in the tables was estimated by

Statistical Analyses:

The effects of various regimens of lansoprazole when administered daily for five consecutive days were compared with a cross-over analysis of variance (ANOVA) model which includes effects for regimens, period, sequence, and subjects within sequence. For Cmax and AUC, a logarithmic transformation was employed. In addition, for C_{max} and AUC of lansoprazole and amoxicillin, a 95% CI was obtained for the combination of drugs (regimen C) relative to that of the single drugs.

Results:

A summary of the pharmacokinetic parameters for lansoprazole and amoxicillin is presented in the following table:

Lansoprazole Parameters

	dose 1		dose 2		dose 3	
Parameter	L	L+A	L	L+A	L	L+A
C_{max}(ng/ml)	769±318	817±371	909±515	887±627	671±399	721±417
T_{max}(hr)	1.5±0.5	1.3±0.7	1.3±0.8	1.6±1.2	1.5±0.6	1.5±0.8
C_{min}(ng/ml)	128±167	94±147	122±175	133±170	7.3±35.8	7.7±31.8
AUC_{inf}	1656±938	1609±937	1913±1398	1790±1563	1996±1872	2122±2019
$t_{1/2}$					1.21±0.41	1.17±0.44
AUC_{0-24}	5565±4138	5521±4381				

Amoxicillin Parameters

	dose 1		dose 2		dose 3	
Parameter	L	L+A	L	L+A	L	L+A
C_{max}	15.3±6.3	13.9±4.8	14.9±5.2	12.6±5.1	16.9±6.1	13.6±5.2
T_{max}	1.5±1.4	1.8±0.6	1.8±0.8	2.1±1.1	1.6±0.5	2.3±0.8
C_{min}	2.0±0.9	2.2±1.1	2.7±1.4	4.3±3.8	0.0±0.0	0.0±0.0
AUC	34.5±11.8	34.7±11.3	38.6±11.5	36.5±8.6	44.7±14.4	51.2±20.5
$T_{1/2}$					1.22±0.22	1.45±0.36
AUC_{0-24}	117.8±35.8	122.4±34.4				

P-Values for Regimen effects
Effect of Amoxicillin on Lansoprazole Parameters

Parameter	Dose 1	Dose 2	Dose 3
C_{max}	0.6008	0.4103	0.6644
C_{min}	0.1124	0.2968	
T_{max}	0.1106	0.0979	
β			0.0041
AUC_{int}	0.8564	0.3766	0.0063
AUC_{0-24}	0.0683		

For lansoprazole pharmacokinetic data, there was no statistically significant difference in mean parameters values due to amoxicillin with the exception of the AUC following the second dose (AUC_{int2}). For amoxicillin parameters T_{max} following the first dose, C_{max} and C_{min} following the second dose, and C_{max}, T_{max}, AUC_{int3}, and β after the third dose were statistically significantly different as a result of lansoprazole administration.

Conclusion:

Lansoprazole pharmacokinetic parameters were unaltered by coadministration of amoxicillin, with the single exception of a 14% reduction in the mean values of AUC between the administration of the 1300 hour and 1800 hour doses. Small decreases in amoxicillin mean C_{max} following the 1300 hour and 1800 hour doses were observed upon concomitant lansoprazole administration along with a small increase in mean AUC following the 1800 hour dose associated with a longer $t_{1/2}$. Neither lansoprazole nor amoxicillin total AUC over the 24 hour period was significantly affected. None of these pharmacokinetic results preclude coadministration of lansoprazole and amoxicillin.

3. Study *#M93-063*

Title:

The Effect of Lansoprazole (Abbott-65006) on Steady-State Clarithromycin Plasma Concentrations Following Concomitant Oral Administration of Both Drugs in Normal Subjects.

Objective:

The objectives of this study were two fold. The first objective was to determine the effect of lansoprazole on steady-state plasma concentrations of clarithromycin and 14-[R]-hydroxy-clarithromycin. The second objective was to determine the effect of clarithromycin on steady state lansoprazole pharmacokinetics and pharmacodynamics as measure by gastric pH. This report addresses the pharmacokinetics of lansoprazole, clarithromycin and 14[R]-hydroxy-clarithromycin.

Investigator:

Design:

Double-blind, randomized, placebo-controlled, three-period crossover study.

Twenty-four healthy male subjects were enrolled into, and 20 completed the study and were randomly assigned to receive the following treatment regimens according to one of six possible sequences:

Regimen A:	lansoprazole (30 mg, TID) + Placebo (TID)
Regimen B:	lansoprazole (30 mg, TID) + clarithromycin (500 mg, TID)
Regimen C:	Placebo (TID) + clarithromycin (500 mg, TID)

Lansoprazole or placebo was administered three times a day at approximately 8 am, 1pm and 6pm on days 1-6. Clarithromycin (500mg) or clarithromycin placebo was administered three times a day on days 1-5 at approximately one-half hour after administration of lansoprazole or lansoprazole placebo. Crossover periods were separated by at least 10-days washout interval.

Ambulatory 24-hour intra-gastric pH was monitored at screening period to the first period and beginning period to the morning dose of study drug(s) on day 5 of each crossover period. Venous blood samples for lansoprazole determinations were collected at 0, 1.0, 1.5, 2.0, 3.0 and 5.0 hours after the morning dose and again at 0, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0 9.0, and 12 hours following the third dose. Samples for clarithromycin and 14-[R]-hydroxy-clarithromycin were withdrawn on Day 5 at 0, 1, 1.5, 2.5, and 5 hours after the first (am) dose and at 1, 1.5, 2.5, 5, 6.5, 8.5, 11.5, 14, 18, 24, and 36 hours after the third dose on Day 5. A pre-regimen sample was drawn on Day -1 of all periods.

Doagesforms:

*Lansoprazole, 30mg capsules (NPRO 5605R, bulk lot 73-257-AR, TAP pharmaceuticals Inc., Deerfield, IL)
*Clarithromycin, 500mg tablets (NPRO 5916N, bulk lot 69-794-AR, Abbott Laboratories, Abbott Park, Illinois)
*Placebo was supplied as either a capsule or tablet identical in appearance to the lansoprazole or Clarithromycin.

Analysis:

Results:

Concomitant administration of clarithromycin resulted in a statistically significant increase in the lansoprazole AUC (3180 ng.h/ml) for the evening dose as compared to the lansoprazole + placebo regimen (2726 ng.h/ml). The average percent change in the AUC was about 19%, or 17% based on

the least square mean of the log transformed values. A statistically significant increase (32% or 28% based on least square means) in the lansoprazole AUC values (1911 vs 1712 ng.h/ml) following the morning dose on Day 5 was also seen during concomitant administration of lansoprazole and clarithromycin. However, there were no statistically significant differences between the placebo and clarithromycin regimens in the other pharmacokinetic parameters for lansoprazole, including C_{max}, T_{max} and terminal disposition rate constant (β).

Summary of pharmacokinetic parameters

Lansoprazole

Parameter	dose 1 L	dose 3 L	dose 1 L+C	dose 3 L+C	p(dose 1)	p(dose 3)
Cmax(ng/ml)	698	919	727	975	0.2648	0.0905
Tmax(hr)	1.48±0.62	1.17±0.29	1.78±0.82	1.26±0.50	0.1313	0.9077
AUCinf	1712±1171	2726±2465	1911±1463	3182±3638	0.0333	0.0289
t1/2	1.34±0.65	1.05±0.50	1.24±0.63	1.07±0.55	0.3037	0.5298

Clarithromycin

Parameter	dose 1 L	dose 3 L	dose 1 L+C	dose 3 L+C	p(dose 1)	p(dose 3)
Cmax(ng/ml)	3.78±1.19	4.60±1.37	3.64±0.94	4.56±0.9+7	0.9070	0.6049
Tmax(hr)	1.55±0.92	1.27±0.59	1.65±0.55	1.35±0.44	0.6998	0.7219
AUCinf	15.15±4.97	37.55±11.47	14.50±4.09	38.52±10.85	0.8139	0.1993
t1/2		6.60±1.66		6.72±1.53	0.3414	0.4969

14[R]-OH-Clarithromycin

Parameter	dose 1 L	dose 3 L	dose 1 L+C	dose 3 L+C	p(dose 1)	p(dose 3)
Cmax(ng/ml)	1.06±0.19	1.17±0.21	1.13±0.24	1.32±0.34	0.1669	0.0851
Tmax(hr)	1.82±1.19	1.45±0.77	1.65±0.61	1.52±0.91	0.4883	0.8266
AUCinf	4.68±0.81	12.22±2.18	5.02±1.18	13.89±3.52	0.1803	0.0222

On the other hand, lansoprazole had no significant effect on the C_{max}, T_{max} and AUC or half-life for clarithromycin in this study. The lack of a significant effect of lansoprazole on the C_{max} and AUC values indicate that the decrease in the intra-gastric H concentration caused by lansoprazole did not affect the oral bioavailability of clarithromycin, even though clarithromycin may be somewhat to degradation in an acidic medium.

AUC of 14[R]-hydroxy-clarithromycin after the third dose on Day 5 was significantly increased by 16% based on mathematical mean, or 14% based on the least square mean of the log transformed values.

V. SPECIFIC COMMENTS (need not to be sent to the sponsor)

1. All three studies are well conducted and are acceptable.

2. Study results show that there were no statistically significant effects of dosing regimens on pharmacokinetic properties of lansoprazole.

3. Clarithromycin dosing resulted a statistically significant increase (19%) in lansoprazole's AUC for the evening dose. A statistically significant increase (28%) in the lansoprazole AUC values following the morning dose on Day 5 was also seen.

   Lansoprazole has no significant effect on the C_{max}, T_{max} and AUC or half-life of clarithromycin. AUC of 14[R]-hydroxy-clarithromycin after the third dose on Day 5 was significantly increased by 16%.

4. Lansoprazole pharmacokinetic parameters were unaltered by coadministration of amoxicillin. Small decreases in amoxicillin mean C_{max} were observed upon concomitant lansoprazole administration along with a small increase in mean AUC following the 1800 hour dose associated with a longer $t_{1/2}$. Neither lansoprazole nor amoxicillin total AUC over the 24 hour period was significantly affected. None of these pharmacokinetic results preclude coadministration of lansoprazole and amoxicillin.

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. _____

cc:

HFD-520 (Clinical, CSO)
HFD-340 (Viswanathan)
HFD-880 (Pelsor, Sun)
HFD-880 Div. File NDA (Lansoprazole)
CDR (Att: Barbara Murphy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20876

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-876 Supplement # ____Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: 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.

Jose R. Cintron, R.Ph., M.A.
Signature of Preparer and Title

June 6, 1997
Date

cc: Orig NDA/PLA/PMA # 20-876
HFD-520/Div File
NDA/PLA Action Package
HFD-006/ SOImstead (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 6/6/97)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA #_ 20-877 Supplement # ____Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520__ Trade and generic names/dosage form:__PREVACID® (lansoprazole) Delayed-Release Capsules labeling for the use of lansoprazole in combination with 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.

Jose R. Cintron, R.Ph., M.A.
Signature of Preparer and Title

June 6, 1997
Date

cc: Orig NDA/PLA/PMA # 20-877
HFD-520/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 6/6/97)

13.0 PATENT INFORMATION

We, TAP Holdings Inc. (TAP), certify that the drug lansoprazole is claimed in U.S. Patents as listed below. Takeda Chemical Industries, Ltd., of Japan has licensed lansoprazole as covered by these patents to TAP.

U.S. Patent No.	Expiration Date	Coverage
4,628,098	07/29/05	Compound
4,689,333	07/29/05	Pharmaceutical formulations containing lansoprazole, and a method of treating gastritis
5,013,743	02/12/10	Use of lansoprazole for combatting diseases caused by the genus *Campylobacter*
5,026,560	06/25/08	Formulation (spherical granules)
5,045,321	09/03/08	Formulation (spherical granules or tablets stabilized with inorganic salt)
5,093,132	09/03/08	Formulation stabilized with inorganic salt

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.

5/23/97

Chair, CDER Labeling and Nomenclature Committee

Date: June 16, 1997

To: Jose Cintron, R.Ph., Project Manager, HFD-520

Subject: NDA [redacted] (Prevacid in combination with clarithromycin or amoxicillin)

From: Robert E. Osterberg, Ph.D., Pharmacology Team Leader, HFD-520

Both of the antibiotics, clarithromycin and amoxicillin, and the proton-pump inhibitors Prilosec and Prevacid are the subjects of approved NDAs. The pharmacology and toxicology data submitted with those applications are complete and, therefore, the pharmacology and toxicology group of this division has no need for additional data at this time, and no review of existing data is necessary.

cc:

NDA [redacted]

HFD-520 (Medical Officer)
HFD-520 (Osterberg)

Consult #796 (HFD-520)

PREVPAC
PREVPAC-Hp lansoprazole, clarithromycin and amoxicillin

There were no look-alike/sound-alike conflicts or misleading aspects found in the proposed proprietary name PREVPAC. However, the Committee recommends against the use of "Hp" with the brand name as an unwarranted profusion of abbreviations. The Committee also recommends the use of a term such as "kit" or equivalent with the brand name to identify the multiple component nature of the product.

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

_____, Chair
CDER Labeling and Nomenclature Committee

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20876

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 16 1996

TAP Holdings Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Rd
Deerfiled, IL 60015

Attention: Linda J. Peters, M.S.,
Regulatory Products Manager

Dear Ms. Peters:

Reference is made to your letters dated September 12, and October 10, 1996, in which you requested comments from FDA on the stability requirements for the proposed triple therapy compliance pack consisting of lansoprazole capsules, 30 mg, clarithromycin tablets, 500 mg, and amoxicillin capsules, 500 mg.

I have consulted with the CDER Stability Technical Committee regarding your proposal for the triple therapy compliance pack, and have the following comments:

In order for us to evaluate such a product for marketing, it is recommended that the following data and information be submitted as an amendment to the NDA as soon as possible:

(1) Data demonstrating that the blister package material for the compliance pack is as protective as, or more protective than, the original materials in which the three individual drug products are packaged.

(2) Three months of accelerated stability data on 1 batch of the product packaged in the compliance pack. The size of this stability batch should be at least 10% of the proposed commercial batch. If the accelerated stability data are satisfactory, the expiration date placed on a commercial batch of the compliance pack can be the same as, but should not exceed, the earliest expiration date of any of the three bulk product batches as shown on their corresponding shipping container labels. It is preferred that the individual product batches be purchased in bulk containers which will not be opened prior to repackaging.

(3) Provide a commitment to a) place the first three production batches, and one annual batch thereafter, on long-term stability study for a period of time equal to the shortest expiration dating period of the three products and report stability data in the

annual reports, and b) withdraw from the market any batches found to fall outside the approved specifications for the drug products.

To summarize, the expiration dating period established by TAP should not exceed the shortest for any of the three products when the long-term stability study is completed; i.e., the expiration date appearing on the compliance pack should never exceed the earliest expiration date used by the original manufacturers of the corresponding bulk product batches.

If you have any additional questions, please do not hesitate to contact me..

Sincerely yours,

Eric B. Sheinin, Ph.D.
Director,
Office of New Drug Chemistry, HFD-800
Center for Drug Evaluation and Research

Food and Drug Administration
Rockville MD 20857

OCT 8 1996

TAP Holdings Inc.
Attention: Ms. Linda J. Peters, M.S.
Regulatory Product Manager
2355 Waukegan Road
Deerfield, Il 60015

Dear Ms. Peters:

We have received your new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Prevacid (lansoprazole) Delayed-Released Capsules in combination with clarithromycin and/or amoxicillin..
Therapeutic Classification:	Standard
Date of Application:	September 30, 1996
Date of Receipt:	October 1, 1996
Our Reference Number:	

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act in accordance with 21 CFR 314.101(a).

Should you have any questions, please call: Mr.Jose R. Cintron, R.Ph., M.A., Project Manager at (301) 827-2125.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-743
HFD-520/Div. Files
HFD-520/PM/JCintron
DISTRICT OFFICE

drafted:jrc /October 7, 1996/
Final:

ACKNOWLEDGEMENT (AC)

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lannockburn Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

2

September 30, 1996

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

RE: Lansoprazole with Clarithromycin and/or Amoxicillin for the Eradication of *H. pylori*

New Drug Application

Ladies/Gentlemen:

The sponsor, TAP Holdings Inc., submits the following New Drug Application under the provisions of Section 505 (i) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50. TAP submits this NDA for the use of PREVACID® (lansoprazole) Delayed-Release Capsules in combination with clarithromycin and/or amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer in the past year). Both the triple and dual therapy regimens will be available to patients by prescription only.

This NDA submission consists of an FDA Form 356h, an Application Summary and all applicable technical sections (Chemistry, Manufacturing and Controls, Human Pharmacokinetics and Bioavailability, Microbiology, Clinical and Statistical). The Preclinical Pharmacology and Toxicology technical section as well as the Methods Validation and Samples portion of Section 4.0 are not applicable to this NDA because TAP will be offering patients with *H. pylori* the same 15 mg and 30 mg PREVACID Delayed-Release Capsules that are currently being marketed in the U.S. for other indications. In addition, information for Section 14.0 (Patent certification with respect to any patent which claims the drug) is included with Section 13.0 (Patent information on any patent which claims the drug). Therefore, Section 15.0 (Other) has been named Section 14.0 for this NDA.

The New Drug Application number assigned is and consists of 215 volumes numbered 1.1 to 1.215. Development of this NDA has been extensively discussed with the appropriate persons at both the Anti-Infective Drug Products Division (HFD-520) and the Gastrointestinal and Coagulation Drug Products Division (HFD-180).

TAP Holdings Inc., holds the IND and NDA for PREVACID. Both the IND and NDA for PREVACID reside in the Division of Gastrointestinal and Coagulation Drug Products. Letters of cross-reference to the PREVACID IND and NDA are contained in Volume 1.1. of this NDA. Clarithromycin is an antibiotic drug product sponsored by Abbott Laboratories which has several INDs and an NDA residing in the Anti-Infective Drug Products Division. Letters of cross-reference to the clarithromycin IND and NDA which supported TAP's clinical investigations are also contained in Volume 1.1. Amoxicillin is a widely prescribed antibiotic which has been commercially available for several decades. Currently, PREVACID, clarithromycin and branded/generic amoxicillin are commercially available in the U.S. by prescription. Upon marketing clearance for TAP's triple therapy and dual therapy regimens, physicians will have the ability to write separate prescriptions for PREVACID, clarithromycin and amoxicillin for their patients which can then be filled by a pharmacist. TAP is negotiating with a packaging vendor to produce a triple therapy compliance package in the near future. Supportive documentation will be provided to the Agency at a later date.

Also included separately to support this NDA is a Computer Assisted New Drug Application (CANDA). The CANDA contains a data portion which will allow the reviewer to query case report form data contained in TAP's five primary U.S. studies. The text portion of the CANDA contains the written reports from a majority of the primary and supportive U.S. studies. The NDA Table of Contents that is included in both the paper NDA and the CANDA footnotes which documents are provided in either the text and/or data portion of the CANDA. TAP plans to install the final version of the CANDA on three laptop computers which will be provided to the Anti-Infective Drug Products Division's Medical Review Officer, the Microbiology Review Officer and the Statistical Review Officer. Docking stations for the computers as well as printers will also be provided to the reviewers. The scheduled date to provide the reviewers with the CANDA is October 3, 1996. In addition, please note that the Table of Contents provided in the text portion of the CANDA contains the paper NDA pagination.

Furthermore, appended is a photocopy of the cover letter, FDA Form 3397 and check for check number representing the user fee for filing a new drug application with clinical data. The fee was submitted to the on August 28, 1996.

Please direct any questions you may have on this application to my attention.

Sincerely,

Linda J. Peters, M.S.
Regulatory Products Manager
Phone: (847) 374-5481
Fax: (847) 317-5795

enclosures LJP/pjp original.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1995
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
1 Oct 96	
DIVISION ASSIGNED	NDA/ANDA NO. ASS
520	

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
TAP Holdings Inc.

DATE OF SUBMISSION
September 30, 1996

ADDRESS *(Number, Street, City, State and ZIP Code)*
2355 Waukegan Road
Deerfield, IL 60015

TELEPHONE NO. *(Include Area Code)*
(847) 374-5481

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Lansoprazole with Clarithromycin and/or Amoxicillin for the Eradication of H. pylori

PROPRIETARY NAME *(If any)*
PREVACID® Delayed-Release Capsules

CODE NAME *(If any)*
AG-1749

CHEMICAL NAME
2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

DOSAGE FORM
Capsules

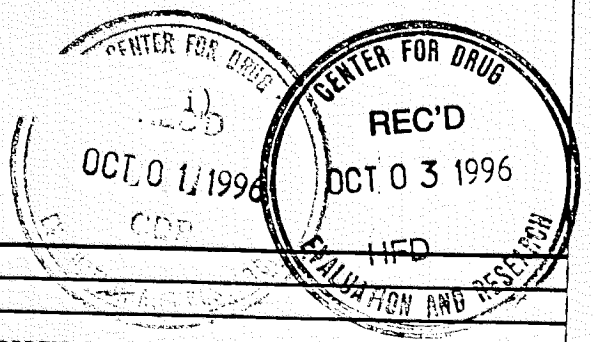
ROUTE OF ADMINISTRATION
Oral

STRENGTHS(S)
30 mg

PROPOSED INDICATIONS FOR USE
PREVACID® (lansoprazole) in combination with clarithromycin and/or amoxicillin for the eradication of Helicobacter pylori in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer in the past year)

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

20-406 (PREVACID NDA)
50-662 (Biaxin NDA)



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)*
☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))*

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Bannockburn Lake Office Plaza
1355 Waukegan Rd
Deerfield, IL 60015

August 28, 1996

Food and Drug Administration
c/o Mellon Bank
Mellon Bank Center
27th Floor (FDA-360909)
Pittsburgh, PA 15259-0001

RE: User Fee I.D.
User Fees for NDA

Dear Sirs:

Enclosed is a check in the amount of (Check No. from TAP Holdings Inc. This check represents half of the User Fee due for a New Drug Application for Lansoprazole *H. pylori* Triple Therapy. The sponsor anticipates submitting this application on or about September 30, 1996.

Should there be any questions, please direct them to my attention.

Thank you.

Linda J. Peters

Linda J. Peters, M.S.
Regulatory Products Manager
Phone: (847) 374-5481
Fax: (847) 317-5795

LJP/pjp

cc: Mr. Thomas Hassall
Consumer Safety Officer
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-5
5600 Fishers Lane
Rockville, MD 20857

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Barrington Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

September 5, 1996

Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attn: Stephen B. Fredd, M.D.

RE: PREVACID® (lansoprazole) Delayed-Release Capsules
NDA 20-406

General Correspondence

Dear Dr. Fredd:

This letter is to authorize you to release to HFD-520 any information contained in NDA 20-406 or in any of the amendments and/or supplements in support of NDA to be filed in approximately 30 to 60 days for the use of PREVACID (lansoprazole) plus clarithromycin and/or amoxicillin in the eradication of *Helicobacter pylori* and the prevention of recurrence of duodenal ulcer.

Sincerely,

Judy Decker Wargel

Judy Decker Wargel
Associate Director, Regulatory Affairs
Phone: (847) 317-5781
Fax: (847) 317-5795

JDW/pjp

cc: Linda Peters, TAP Holdings Inc.

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lincolnshire Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

September 5, 1996

Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attn: Stephen B. Fredd, M.D.

Name of Investigational Drug: Lansoprazole (PREVACID® Delayed-Release Capsules)
IND

General Correspondence

Dear Dr. Fredd:

The sponsor, TAP Holdings Inc., submits this amendment to an Investigational New Drug Application under the provisions of Section 505(i) of the Federal Food, Drug and Cosmetic Act and 21 CFR §312.30.

The purpose of this amendment is to authorize you to release information contained in IND held by TAP Holdings Inc. in support of NDA to be filed in approximately 30 to 60 days by TAP to HFD-520 for the use of PREVACID (lansoprazole) plus clarithromycin and/or amoxicillin for the eradication of *Helicobacter pylori* and the prevention of recurrence of duodenal ulcers.

Sincerely,

Judy Decker Wargel

Judy Decker Wargel
Associate Director, Regulatory Affairs
(847) 317-5781

JDW/pjp
Attachment

cc: Linda Peters, TAP Holdings Inc.

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

September 23, 1996

Ms. Linda Peters
Regulatory Affairs
TAP Pharmaceuticals
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Peters,

Enclosed you will find a copy of the authorization letters which were submitted to FDA today on your behalf. These submissions authorize your reference to Abbott's IND for Clarithromycin Tablets (IND and to Abbott's NDA for Clarithromycin Tablets (NDA 50,662) which reside in FDA's Division of Anti-Infective Drug Products, to support NDA for lansoprazole

Should you have any further questions, please feel free to contact me.

Sincerely,

Greg Bosco

Greg Bosco
Product Manager
PPD Regulatory Affairs
(847) 937-6970

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

September 23, 1996

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
1st Floor Document Control Room
Rockville, Maryland 20850

Re: BIAXIN® Filmtab® (clarithromycin tablets)
NDA 50-662

Dear Sir or Madam:

The sponsor, Abbott Laboratories, is hereby providing authorization to the Food and Drug Administration to make reference to information regarding clarithromycin tablets contained in NDA 50-662 by:

Tap Pharmaceuticals, Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Tap Pharmaceuticals plans to file their NDA for lansoprazole for the use of lansoprazole in combination with clarithromycin and amoxicillin for the treatment of patients with *Helicobacter pylori* infection.

This permission and authorization extends only to the above submission and shall not be construed to authorize the divulging of such information to anyone outside the Food and Drug Administration except in accordance with Section 301(j) of the Federal Food, Drug, and Cosmetic Act.

Sincerely,

Greg Bosco
Product Manager
PPD Regulatory Affairs
(847) 937-6970

CC: Linda Peters, TAP Pharmaceuticals

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

September 23, 1996

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
1st Floor Document Control Room
Rockville, Maryland 20850

Re: Clarithromycin (Abbott-56268)
IND

Dear Sir or Madam:

This correspondence provides authorization to the Food and Drug Administration to make reference to the information contained in Abbott Laboratories' Investigational New Drug Application (IND) for Clarithromycin Tablets (IND in support of NDA submitted by TAP Pharmaceuticals. This reference applies to chemistry, manufacturing and controls information regarding clarithromycin placebo tablets.

This permission and authorization extends only to the above submission and shall not be construed to authorize the divulging of such information to anyone outside the Food and Drug Administration except in accordance with Section 301(j) of the Federal Food, Drug, and Cosmetic Act.

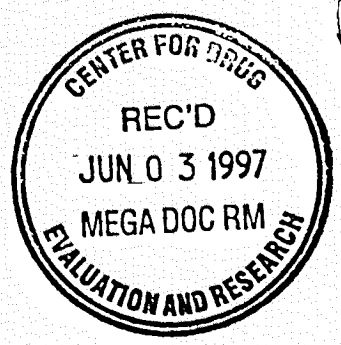
Sincerely,

Greg Bosco
Product Manager
PPD Regulatory Affairs
(847) 937-6970

CC: Linda Peters, TAP Pharmaceuticals

TAP HOLDINGS INC.

DUPLICATE



June 2, 1997

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Anti-Infective Drug Products (HFD-520)
9201 Corporate Blvd.
Room South 354
Rockville, MD 20850

Attn: Dr. Gino Girardi, Medical Officer

RE: **PREVACID® (lansoprazole) plus Clarithromycin and Amoxicillin for the Eradication of *Helicobacter pylori***

- Revised Draft Package Insert Labeling -

Dear Dr. Girardi

Per our phone conversation today, please find enclosed two copies of the revised PREVACID draft package insert labeling for the indication *H. pylori*. One copy has been shaded to highlight the changes made and the other copy is a clean copy of the draft labeling. Also included is a 3.5" diskette containing the two versions of the draft labeling. The files were saved in Microsoft Word for Windows, Version 6.0.

Please do not hesitate to call me if you require any additional information.

Sincerely,

Linda J. Peters

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

LJP:lp c:\winword\npylon\nomem129
attachments

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DUPLICATE

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

REVIEWS COMPLETED

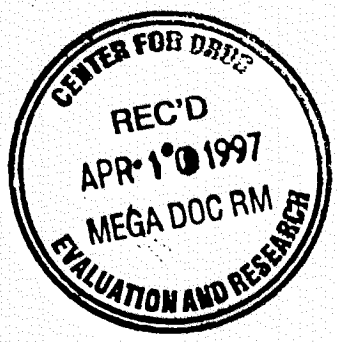
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

April 9, 1997

NEW CORRESPONDENCE

Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 1st Floor
9201 Corporate Boulevard
Rockville, MD 20850



Attn: David Feigal, MD, Division Director

RE: Lansoprazole with Clarithromycin and/or Amoxicillin for the Eradication of *H. pylori*

Amendment

RE: PROPOSED PRODUCT TRADENAME

Dear Dr. Feigal:

In accordance with Section 505(b) 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 lansoprazole with clarithromycin and/or amoxicillin for the eradication of *Helicobacter pylori*.

The purpose of this communication is to submit the following tradenames for TAP's triple therapy *H. pylori* patient compliance pack which will contain PREVACID® (lansoprazole), BIAXIN® (clarithromycin) and TRIMOX® (amoxicillin). We are currently working with Mr. Cintron and Mr. Timper regarding the forthcoming submission of the Chemistry, Manufacturing and Controls (CMC) documentation for the compliance pack.

We request that our first and second choices for tradenames be reviewed for acceptability by the Anti-Infective Division and the Nomenclature Committee:

First Choice for Compliance Pack Tradename: **PREVPAC Hp™**

Second Choice for Compliance Pack Tradename: **PREVPAC™**

Our Legal Department has conducted tradename searches on PREVPAC Hp and PREVPAC. These two names do not appear to infringe on any other currently marketed US prescription drug tradenames. In addition, we have filed the necessary trademark applications for PREVPAC Hp and PREVPAC with the United States Patent and Trademark Office.

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.
Regulatory Products Manager
(847) 374-5481
(847) 317-5795 FAX

LJP/ljp c:\winword\hpylori\NDA\amend03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1995
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASSIGNED

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*

NAME OF APPLICANT	DATE OF SUBMISSION
TAP Holdings Inc.	April 9, 1997
ADDRESS *(Number, Street, City, State and ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
2355 Waukegan Road Deerfield, IL 60015	(847) 374-5481
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*

DRUG PRODUCT

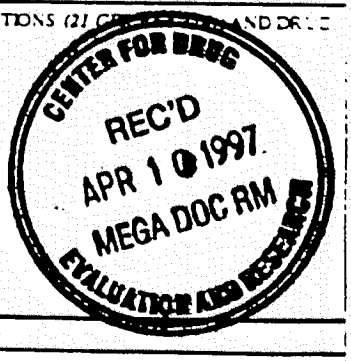
ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Lansoprazole with clarithromycin and/or Amoxicillin for the Eradication of H. pylori	PREVACID® Delayed-Release Capsules

CODE NAME *(If any)*	CHEMICAL NAME
AG-1749	2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS(S)
Capsules	Oral	30 mg

PROPOSED INDICATIONS FOR USE

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))*

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

TAP HOLDINGS INC.

DUPLICATE

NC
NEW CORRESP

April 25, 1997

Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, First Floor
9201 Corporate Boulevard
5600 Fishers Lane
Rockville, MD 20850

RE: Lansoprazole with Clarithromycin and/or Amoxicillin for the Eradication of *H. pylori*

Dear Sir or Madam:

The sponsor, TAP Holdings Inc., is hereby providing authorization to the Food and Drug Administration to make reference to information contained in New Drug Application in support of a supplemental application for BIAXIN® Filmtab® (clarithromycin tablets), NDA No. 50-662. The company which holds the NDA for BIAXIN Filmtab is:

Abbott Laboratories
Pharmaceutical Products Division
100 Abbott Park Road
Abbott Park, IL 60064-3500

Within the next 30 days, Abbott Laboratories will submit a labeling supplement for the dual therapy regimen of BIAXIN Filmtab and PREVACID® (lansoprazole) Delayed-Release Capsules for the eradication of *Helicobacter pylori* and the prevention of recurrence of duodenal ulcers.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

This permission and authorization extends only to the above submission and shall not be construed to authorize the divulging of such information to anyone outside the Food and Drug Administration except in accordance with Section 301(j) of the Federal Food, Drug and Cosmetic Act.

Please do not hesitate to call me if you have any further questions.

Sincerely,

Linda J. Peters

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

CC: Mr. Greg Bosco, Regulatory Affairs (Dept. 491), Abbott Laboratories

ljp word_doc\anso\h-pylori\hpmem102

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1997
See OMB Statement on Page 3

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASSIGNED

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
TAP Holdings Inc.	April 25, 1997
ADDRESS *(Number, Street, City, State and ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
2355 Waukegan Road Deerfield, IL 60015	(847) 374-5481
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*

DRUG PRODUCT

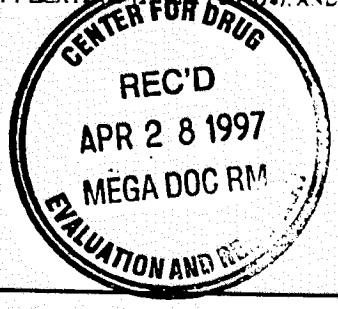
ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Lansoprazole with clarithromycin and/or Amoxicillin for the Eradication of H. pylori	PREVACID® Delayed-Release Capsules

CODE NAME *(If any)*	CHEMICAL NAME
AG-1749	2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS(S)
Capsules	Oral	30 mg

PROPOSED INDICATIONS FOR USE

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

DUPLICATE

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015

NEW CORRESPONDENCE

February 4, 1997

Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 1st Floor
9201 Corporate Boulevard
Rockville, MD 20850

Attn: Mr. James Timper, Chemistry Reviewer

RE: Lansoprazole with Clarithromycin and/or Amoxicillin for the Eradication of *H. pylori*

Amendment

REQUEST FOR FDA RESPONSE

Dear Mr. Timper:

The purpose of this communication is to respond to the Agency's letter dated December 16, 1996 (attached for your information). In that letter, Dr. Eric Sheinin, Director, Office of New Drugs (HFD-800), outlined the necessary accelerated stability data TAP would need to provide for the *H. pylori* patient compliance pack containing PREVACID® (lansoprazole), BIAXIN® (clarithromycin) and TRIMOX® (amoxicillin). For this compliance pack, commercially available product will be purchased in large count bottles or drums unpackaged and then be blister-packaged on a daily dosing card. Please refer to attached letter from TAP dated November 13, 1996 for further information on this compliance pack.

We appreciate the Agency's guidance with this daily compliance pack, and at the present time, we are moving ahead with preparing the dedicated penicillin facility for commercial production. However, due to some delays with acquiring the necessary tooling, it appears that we will not have the required 3-month accelerated stability data until the last 90 days of the User Fee "review clock" for NDA Since we do not want to jeopardize the overall review time for the NDA, we would like to request the Agency's concurrence on an alternate daily compliance pack.

TAP will provide the third-party packaging company with commercially available hospital unit-dose (HUD) blisters of PREVACID, BIAXIN and TRIMOX, and these individual blisters will be placed in an outer holding card. Each compliance card will accommodate one day's worth of dosing (two 30 mg PREVACID capsules, two 500 mg BIAXIN tablets and four 500 mg TRIMOX capsules). The outer card for the preblistered drugs will be shaped like a small billfold wallet. A group of daily cards will then be placed into a cardboard shipping box. Please note that the HUD blisters of PREVACID, BIAXIN and TRIMOX will not be reopened for the preblistered pack and packaging will still occur in a dedicated penicillin facility.

TAP plans to amend the NDA with the necessary documentation to support the preblistered pack as soon as possible. Since the unit-dose blisters of drug product already have stability data in their respective NDAs or AADAs, we do not believe up-front stability data are needed. However, we will provide a stability commitment letter describing that the first commercial batch, and one annual batch thereafter, will be placed on stability. Ongoing stability data will be provided in the Annual Report for NDA . As discussed earlier, expiry dating for the preblistered pack will be based on the shortest expiration period of the three products.

We would like to receive the Agency's concurrence on our plans for the preblistered pack before submitting the amendment to the NDA scheduled for March 31, 1997. After NDA receives marketing clearance by the Agency,

Please do not hesitate to contact me if you have any questions regarding this submission.

Sincerely,

Linda J. Peters

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

LJP/ljp c:\winword\hpylori\NDA\amend02
attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1997
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASSIGNED

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
TAP Holdings Inc.

DATE OF SUBMISSION
February 4, 1997

TELEPHONE NO. (Include Area Code)
(847) 374-6481

ADDRESS *(Number, Street, City, State and ZIP Code)*
2355 Waukegan Road
Deerfield, IL 60015

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 05 1997
MEGA DOC RM

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Lansoprazole with clarithromycin and/or Amoxicillin for the Eradication of H. pylori

PROPRIETARY NAME *(If any)*
PREVACID® Delayed-Release Capsules

CODE NAME *(If any)*
AG-1749

CHEMICAL NAME
2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS (S)
Capsules	Oral	30 mg

PROPOSED INDICATIONS FOR USE

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION

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NAME OF DRUG

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TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☒ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))*

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

November 8, 1996

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Scientific Investigations (HFD-344)
Metro Park North 1
Room 125
7520 Standish Place
Rockville, MD 20855

Attn: Dr. Matthew Thomas

PREVACID® (lansoprazole) with clarithromycin and/or amoxicillin for the eradication of *Helicobacter pylori*

RE: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Thomas:

The purpose of this communication is to respond to your November 7, 1996 request for information pertaining to NDA Please find enclosed the following information:

- List of primary US efficacy/safety studies (Study Nos. M93-131, M95-392, M93-130 and M93-125)
- Names and addresses of investigators who participated in the four primary US efficacy/safety studies.

Also per your request, the following information regarding investigators participating in the primary US efficacy/safety studies have been broken down by investigator site:

- Total number of patients enrolled
- Total number of patients who completed the studies
- Total number of evaluable patients

- Total number of patients who experienced adverse events
- Total number of adverse events.

Please note that all patients enrolled in Study Nos. M93-131, M95-392, M93-130 and M93-125 were randomized. In addition, the total number of evaluable patients were broken down further into two categories: number of patients evaluable for *H. pylori* eradication and number of patients evaluable for ulcer prevalence.

Please do not hesitate to contact me if your have any questions or require additional information.

Sincerely,

Linda J. Peters

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

enclosures
ljp lanso/h-pylori/thomas.doc

LIST OF PRIMARY US EFFICACY/SAFETY STUDIES FOR NDA

Triple Therapy (lansoprazole, clarithromycin and amoxicillin):

Study M93-131

A Study to Evaluate the Effects of Therapy with Lansoprazole and Clarithromycin and/or Amoxicillin on the Eradication of *Helicobacter pylori* and the Recurrence of Duodenal Ulcer

Study M95-392

A Study to Evaluate the Effects of Triple Therapy with Lansoprazole, Clarithromycin and Amoxicillin versus Dual Therapy with Clarithromycin and Amoxicillin on the Eradication of *Helicobacter pylori*

Dual Therapy (lansoprazole and clarithromycin):

Study M93-131

A Study to Evaluate the Effects of Therapy with Lansoprazole and Clarithromycin and/or Amoxicillin on the Eradication of *Helicobacter pylori* and the Recurrence of Duodenal Ulcer

Study M93-130

A Study to Evaluate the Effects of Dual Therapy with Lansoprazole and Clarithromycin on the Eradication of *Helicobacter pylori*

Dual Therapy (lansoprazole and amoxicillin):

Study M93-131

A Study to Evaluate the Effects of Therapy with Lansoprazole and Clarithromycin and/or Amoxicillin on the Eradication of *Helicobacter pylori* and the Recurrence of Duodenal Ulcer

Study M93-125

A Study to Evaluate the Effects of Dual Therapy with Lansoprazole and Amoxicillin on the Eradication of *Helicobacter pylori*

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT/DIED LOCATION
DONALD R. ABRAHM, M.D. 1525 SUPERIOR AVENUE SUITE 104 NEWPORT BEACH, CA 92663	M95-392	5		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
FIRAS H. AL-KAWAS, M.D. GEORGETOWN UNIVERSITY MEDICAL CENTER DIVISION OF GASTROENTEROLOGY, M2122 3800 RESERVOIR ROAD, N.W. WASHINGTON, DC 20007	M93-130	8		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, 1.194, P 002
AJIT S. ARORA, M.D. 5066 N. FRESNO SUITE 102 FRESNO, CA 93710	M93-125	14		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
BASHAR M. ATTAR, M.D., F.A.C.P., F.A.C.G. COOK COUNTY HOSPITAL 1835 WEST HARRISON CHICAGO, IL 60612	M93-130	7		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
DENNIS L. AVNER, M.D. 1220 EAST 3900, SOUTH, #3C SALT LAKE CITY, UT 84124	M93-131	7		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
CANAN AVUNDUK, M.D., PHD. BAYSTATE MEDICAL CENTER DIVISION OF GASTROENTEROLOGY 759 CHESTNUT STREET SPRINGFIELD, MA 01199	M93-131	4		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
CHARLES F. BARISH, M.D., F.A.C.P., FACG WAKE RESEARCH ASSOCIATES 3100 BLUE RIDGE ROAD SUITE 100 RALEIGH, NC 27612	M93-125	8		S 8.5.5, V 1.75 P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	5		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	2		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
MARCELO A. BARREIRO UNITED MEDICAL ASSOCIATES, PC 1159 VESTAL AVENUE BINGHAMTON, NY 13903	M93-130	6		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
ROBERT T. BASS, JR., M.D. 2380 THIRD STREET SOUTH JACKONSVILLE BEACH, FL 32250	M93-130	3		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
RICHARD K. BATH, M.D. HILLTOP RESEARCH 7720 MONTGOMERY ROAD CINCINNATI, OHIO 45236	M93-130	7		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
CHARLES K. BEDARD, M.D. ADVANCED RESEARCH MANAGMENT L.P. 600 BROADWAY SUITE 112 SEATTLE, WA 98122	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
RAYMOND L. BELL, M.D. 2261 COSTARIDES STREET MOBILE, AL 36617	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
ARNOLD BERLIN, M.D. INSTITUTE OF HEALTHCARE ASSESSMENT, INC. 6699 ALVARADO ROAD SUITE 2304 SAN DIEGO, CA 92120	M93-131	8		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
WILLIAM R. BERRY, M.D. LONGMONT CLINIC, P.C. 1925 WEST MOUNTAIN VIEW AVENUE LONGMONT, CO 80501	M93-125	1		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
THOMAS D. BIANCHI, M.D. COMMUNITY MEDICAL ARTS CENTER 875 FRIENDSHIP ROAD TALLASSEE, AL 36078	M93-130	24		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	7		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
CHARLES A. BIRBARA, M.D. CLINICAL PHARMACOLOGY STUDY GROUP 26 QUEEN STREET WORCESTER, MA 01610	M93-125	4		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 001	S 12.2, V 1.207, P 001
	M95-392	5		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152 , P 001	S 12.2, V 1.198, P 001
PHILIP C. BIRD, M.D. RESEARCH ASSOCIATES OF NORMAN, INC 1125 NORTH PORTER SUITE 302 NORMAN, OK 73071	M93-125	8		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	3		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	4		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
SCOTT R. BRAZER, M.D., M.H.S. DUKE UNIVERSITY MEDICAL CENTER 212 BELL BUILDING, BOX 3662 TRENT DRIVE DURHAM, NC 27710	M93-130	5		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
JEFFERY R. BREITER, M.D. 945 MAIN STREET, SUITE 203 MANCHESTER, CONNECTICUT 06040	M93-130	8		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	4		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
DONALD L. BRUNS, M.D. INTERSTATE MEDICAL CENTER 2835 SOUTH SERVICE DRIVE RED WING, MN 55066	M93-130	5		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	4		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
DONALD R. CAMPBELL, M.D. VETERANS ADMINISTRATION MEDICAL CENTER (111) 4801 EAST LINWOOD BOULEVARD KANSAS CITY, MO 64128	M93-130	21		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	3		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
DONALD O. CASTELL, M.D. THE GRADUATE HOSPITAL 1800 LOMBARD STREET SUITE 501, PEPPER PAVILION PHILADELPHIA, PA 19146	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
AN-YU CHEN, M.D. THE MONROE CLINIC 515 22ND AVENUE MONROE, WI 53566	M93-125	11		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001

Takeda F = Takeda of France

V = VOLUME
S = SECTION
P = PAGE

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
EDWARD H. CHENG, M.D. NORTHPORT VA MEDICAL CENTER MEDICAL SERVICE GI SECTION BUILDING 200, BI-38 79 MIDDLEVILLE ROAD (111E) NORTHPORT, NY 11768	M93-125	7		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M95-392	5		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
ROLAND B. CHRISTIAN, M.D. PREVEA CLINIC 1726 SHAWAND AVENUE GREEN BAY, WI 54303	M93-125	4		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 001	S 12.2, V 1.207, P 001
RICHARD G. CLINE, M.D. TENNESSEE ENDOSCOPY CENTER 1706 EAST LAMAR ALEXANDER PARKWAY MARYVILLE, TN 37804	M93-130	10		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	2		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
CHARLES L. COLIP, M.D. ADVENTIST HEALTH 10201 SOUTHEAST MAIN SUITE 29 PORTLAND, OR 97216	M93-130	14		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
ALAN F. CUTLER, M.D. SINAI HOSPITAL 6767 WEST OUTER DRIVE DETROIT, MI 48235	M93-125	10		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
GARY W. FALK, M.D. THE CLEVELAND CLINIC FOUNDATION HEALTH SCIENCE CENTER OF THE OHIO STATE UNIVERSITY 9500 EUCLID AVENUE, DESK 540 CLEVELAND, OH 44195	M93-130	9		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
BRIAN FENNERTY, M.D. OREGON HEALTH SCIENCES UNIVERSITY 3181 SW SAM JACKSON PARK ROAD, PV-310 PORTLAND, OR 97201-3098	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
ROBERT S. FISHER, M.D. TEMPLE UNIVERSITY HEALTH SCIENCES CENTER DEPARTMENT OF GASTROENTEROLOGY 3401 NORTH BROAD STREET 8TH FLOOR PARKINSON PAVILION PHILADELPHIA, PA 19140	M93-125	3		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
DUANE D. FITCH, M.D. TRIANGLE EAST GASTROENTEROLOGY, P.A. 1704 SOUTH TARBORO STREET WILSON, NC 27893	M93-125	6		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
RONALD P. FOGEL, M.D. HENRY FORD HOSPITAL DIVISION OF GASTROENTEROLOGY 2799 WEST GRAND BLVD DETROIT, MI 48202	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
STEPHEN R. FREEMAN, M.D. RESEARCH DEPT. MIDTOWN MEDICAL CENTER I, SUITE 210 2005 FRANKLIN STREET DENVER, CO 80205	M93-130	7		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	6		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
ANDREW P. FRIDBERG, M.D. CLINICAL RESEARCH GROUP OF MARYLAND, INC 111 WEST HIGH STREET, SUITE 315 ELKTON, MD 21921	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
WALTER N. GAMAN, M.D. 4301 NORTH MACARTHUR BLVD SUITE 200 IRVING, TX 75038	M93-131	13		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
RONALD D. GASKINS, M.D. WEST VIRGINIA MEDICAL CENTER WEST VIRGINIA UNIVERSITY HEALTH SCIENCE CENTER SECTION OF GASTROENTEROLOGY P.O. BOX 9161 MORGANTOWN, WV 26506	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
KEVIN T. GERACI, M.D., F.A.C.P. UNIVERSITY HOSPITAL DIVISION OF GASTROENTEROLOGY 11100 EUCLID AVENUE WEARN BUILDING ROOM 244 CLEVELAND, OH 44106	M93-130	1		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
HOWARD K. GOGEL, M.D. SOUTHWEST GASTRO 201 CEDAR STREET, SOUTHEAST, SUITE 702SI ALBUQUERQUE, NM 87106	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
DAVID Y. GRAHAM, M.D. VETERANS ADMINISTRATION MEDICAL CENTER 2002 HOLCOMBE BOULEVARD (111D) ROOM 3A-352 HOUSTON, TX 77030	M93-125	7		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	9		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
JON D. GREEN, M.D. FUTURE HEALTHCARE RESEARCH CENTER 193 FAIRFIELD ROAD FAIRFIELD, NJ 07004	M93-125	2		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
MILES E. GRESHAM, M.D. HILLTOP RESEARCH 516 BROOKWOOD BOULEVARD HOMEWOOD, AL 35209	M93-125	7		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
ROBERT A. HAMMER, M.D. TULANE UNIVERSITY SCHOOL OF MEDICINE SECTION OF GASTROENTEROLOGY, SL-35 1430 TULANE AVENUE NEW ORLEANS, LA 70112	M93-125	2		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
WILLIAM V. HARFORD, M.D. VETERANS AFFAIRS MEDICAL CENTER (111B1) 4500 SOUTH LANCASTER ROAD DALLAS, TX 75216	M93-125	15		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
VERNON G. HEE, M.D. THE VANCOUVER CLINIC, INC. 700 NORTH EAST 87TH AVENUE VANCOUVER, WA 98664	M93-130	8		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
EDWARD F. HERLIHY, M.D. HILLTOP RESEARCH 823 ROCKDALE AVENUE NEW BEDFORD, MA 02740	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
BASIL I. HIRSCHOWITZ, M.D. UNIVERSITY OF ALABAMA AT BIRMINGHAM DIVISION OF GASTROENTEROLOGY 701 SOUTH 19TH STREET UAB STATION LHR 440 BIRMINGHAM, AL 35294	M93-125	9		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
SAMUEL B. HO, M.D. GASTROENTEROLOGY SECTION (111D) VA MEDICAL CENTER ONE VETERANS DRIVE MINNEAPOLIS, MN 55417	M93-130	17		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	4		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
COLIN W. HOWDEN, M.D. DEPARTMENT OF INTERNAL MEDICINE 2 RICHLAND MEDICAL PARK, SUITE 506 COLUMBIA, SOUTH CAROLINA 29203-6808	M93-131	4		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
KEITH P. HUSSEY, M.D. CLINICAL PHARMACOLOGY INVESTIGATIONS DIAGNOSTIC SERVICES, INC 340 GOODLETTE ROAD SOUTH NAPLES, FL 33940	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	1		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
M. MAZEN JAMAL, M.D. UNIVERSITY OF NEW MEXICO HOSPITAL CLINICAL TRIALS CENTER 2211 LOMAS BOULEVARD NORTH EAST, ACC-5 5TH FLOOR NORTH ALBUQUERQUE, NM 87106	M93-131	5		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
DAVID S. JAMES, D.O., F.A.C.G., F.A.A.O.S 3345 SOUTH HARVARD SUITE 301 TULSA, OK 74135	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	5		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
JAMES V. JONES, M.D. THE GREEN CLINIC 1200 SOUTH FARMERVILLE STREET RUSTON, LA 71270	M93-130	9		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
PETER J. KAHRILAS, M.D. NORTHWESTERN MEMORIAL HOSPITAL 250 EAST SUPERIOR 1526 WESLEY TOWERS CHICAGO, IL 60611	M93-125	3		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
NEIL M. KASSMAN, M.D. STATESVILLE MEDICAL GROUP, P.A. OLD MOCKSVILLE ROAD P.O. BOX 1821 STATESVILLE, NC 28687-1821	M93-131	6		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
MILTON S. KHANDELWAL, M.D. HERSHEY MEDICAL CENTER 500 UNIVERSITY DRIVE, ROOM C5800 P.O. BOX 850 HERSHEY, PA 17033	M93-131	6		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
JONG K. KIM, M.D. EDGEWATER HOSPITAL PROFESSIONAL BUILDING 5720 NORTH ASHLAND AVENUE SUITE C-47 4TH FLOOR CHICAGO, IL 60660	M93-130 M95-392	18 8		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002 S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002 S 12.2, V 1.198, P 001
KERRY H. KING, M.D. 575 PROFESSIONAL DRIVE SUITE 150 LAWRENCEVILLE, GA 30245	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
PHILLIP K. KIYASU, M.D. THE PORTLAND CLINIC 800 SW 13TH AVENUE PORTLAND, OR 97205	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
LINAS M. KLYGIS, M.D. MACNEAL CENTER FOR CLINICAL RESEARCH 3231 SOUTH EUCLID AVENUE, SUITE 200 BERWYN, IL 60402	M93-130	3		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
DAVID G. KOGUT, M.D. PIEDMONT GASTROENTEROLOGY CLINIC 1835 DAVIE AVENUE STATESVILLE, NC 28677	M93-125	7		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M95-392	5		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
KENNETH R. KOHAGEN, M.D. RALEIGH INTERNAL MEDICINE 3320 WAKE FOREST ROAD RALEIGH, NC 27609	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
ROBERT N. KORNFIELD, M.D. 1401 STONE ROAD SUITE 302 ROCHESTER, NEW YORK 14615	M93-130	3		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
PHILIP M. KOSZYK, M.D. SOUTHERN ILLINOIS UNIVERSITY SCHOOL OF MEDICINE, DIVISION OF GI/DEPTARMENT OF IMM/C/1311 800 NORTH RUTLEDGE, ROOM D-123 SPRINGFIELD, IL 62781	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
THOMAS KOVACS, M.D. CENTER FOR ULCER RESEARCH AND EDUCATION V.A. MEDICAL CENTER WEST LOS ANGELES 11301 WILSHIRE BOULEVARD BUILDING 115, ROOM 212 LOS ANGELES, CA 90073	M93-130	20		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	4		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
GEORGE KOVAL, M.D. WEST HILLS GASTROENTEROLOGY ASSOCIATES 9155 SOUTH WEST BARNES ROAD SUITE 636 PORTLAND, OR 97225	M93-125	6		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
KENNETH R. KRANZ, M.D. INTERNAL MEDICINE GROUP, P.C. 1200 EAST 20TH STREET CHEYENNE, WY 82001	M93-130	7		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
RICHARD A. KRAUSE, M.D. PARKRIDGE MEDICAL CENTER 2333 MCCALLIE AVENUE, SUITE 400 CHATTANOOGA, TN 37404	M93-131	21		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
DANIEL M. KRUSS, M.D., F.A.C.P. DIGESTIVE DISEASE CENTER OAK PARK HOSPITAL 520 SOUTH MAPLE AVENUE OAK PARK, IL 60304	M93-130	6		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	2		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
FRANK T. KUCER, M.D. UPPER BUCKS MEDICAL ARTS BUILDING 817 LAWN AVENUE SELLERSVILLE, PA 18960	M93-125	2		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
MICHAEL D. KURTZ, M.D. NORTH COUNTY GASTROENTEROLOGY GROUP 3520 COLLEGE BOULEVARD, SUITE 203 OCEANSIDE, CA 92056	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
MARK LAMET, M.D., F.A.C.G. THE CENTER FOR GASTROINTESTINAL DISORDERS 2740 HOLLYWOOD BOULEVARD HOLLYWOOD, FLORIDA 33020	M93-131	15		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
FRANK L. LANZA, M.D. HOUSTON INSTITUTE FOR CLINICAL RESEARCH 7777 SOUTH WEST FREEWAY SUITE 700 HOUSTON, TX 77074	M93-125	14		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	4		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

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INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
DAVID H. LEBIODA, M.D. FUTURE HEALTHCARE RESEARCH CENTER 393 WHOOPING LOOP SUITE 1461 ALTAMONTE SPRINGS, FL 32701	M93-125	9		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
MICHAEL S. LEVINE, M.D. 2520 WINDY HILL ROAD SUITE 102 MARIETTA, GA 30067	M93-131	8		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
THOMAS R. LIEBERMAN, M.D. AUSTIN DIAGNOSTIC CLINIC CENTER FOR CLINICAL RESEARCH 12221 MOPAC EXPRESSWAY NORTH, THIRD FLOOR AUSTIN, TX 78758	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
IRA F. LOBIS, M.D., F.A.C.G. MEDICAL RESEARCH INSTITUTE OF DELAWARE 4745 OGLETOWN-STANTON ROAD SUITE 134 NEWARK, DELAWARE 19713	M93-131	5		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
THOMAS A. LOIUDICE, D.O. AKRON GASTROENTEROLOGY ASSOCIATES, INC. 224 WEST EXCHANGE STREET SUITE 410 AKRON, OH 44302	M93-130 M95-392	10 3		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002 S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002 S 12.2, V 1.198, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
FREDRICH C. LOURA, M.D. 3216 NORTON AVENUE SUITE 102 EVERETT, WA 98201	M93-125	3		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
RALPH T. LYERLY, M.D. NORWOOD CLINIC RESEARCH CENTER 1528 CARRAWAY BOULEVARD BIRMINGHAM, AL 35234	M93-131	7		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
DAVID M. MACCINI, M.D. HOLY FAMILY HOSPITAL NORTH 1212 WASHINGTON, SUITE 10 SPOKANE, WA 99201	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
HENRY N. MAIMON, M.D. HILLTOP RESEARCH 580 LINCOLN PARK BOULEVARD SUITE 266 DAYTON, OH 45429	M93-130	4		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
RANJIT C. MATHEW, M.D., PHD. ATHENS REGIONAL MEDICAL CENTER 3400 MCCLURE BRIDGE ROAD BUILDING F, SUITE C DULUTH, GA 30136	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
ARTHUR J. MCCULLOUGH, M.D. METROHEALTH MEDICAL CENTER GI DIVISION, W603 2500 METROHEALTH DRIVE CLEVELAND, OH 44109-1998	M93-130	11		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
DAVID C. METZ, M.D. HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA 3400 SPRUCE STREET CLINICAL RESEARCH CENTER PHILADELPHIA, PA 19104	M93-130	9		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	2		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P001
BARRY A. MILLS, M.D. ASSOCIATED MEDICAL RESEARCH 2202 SOUTH BABCOCK STREET SUITE 101 MELBOURNE, FL 32901	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P001
TIMOTHY R. MORGAN, M.D. VA MEDICAL CENTER GASTROENTEROLOGY-111G 5901 EAST SEVENTH STREET LONG BEACH, CA 90822	M93-125	4		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P001
SEYED N. MOUSSAVIAN, M.D. 9200 MONTGOMERY ROAD BUILDING E, SUITE 18A CINCINNATI, OH 45242	M93-131	7		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
RAO V. MOVVA, M.D. 615 35TH AVENUE MOLINE, IL 61265	M93-125	5		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
UMA K. MURTHY, M.D. VETERANS ADMINISTRATION MEDICAL CENTER 800 IRVING AVENUE SYRACUSE, NEW YORK 13210	M93-130	7		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	3		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
JAMES S. NOVICK, M.D. PARTNERS IN MEDICAL RESEARCH 1122 KENILWORTH DRIVE, #200 BALTIMORE, MD 21204	M93-130	5		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
JACK NUDEL, M.D. NUDEL AND GLUCK, M.D., P.A. 2245 NORTH UNIVERSITY DRIVE PEMBROKE PINES, FL 33024	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
DANIEL J. PAMBIANCO, M.D. CHARLOTTESVILLE GASTROENTEROLOGY ASSOCIATES 1139 EAST HIGH STREET SUITE 203 CHARLOTTESVILLE, VIRGINIA 22902	M93-131	11		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
NORMAN M. PANITCH, M.D. WESTERN CLINICAL RESEARCH 23441 MADISON STREET SUITE 130 TORRANCE, CA 90505	M93-131	7		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
STEVEN R. PEIKEN, M.D. COOPER HOSPITAL UNIVERSITY MEDICAL CENTER 401 HADDON AVENUE, 2ND FLOOR CAMDEN, NJ 08103	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
ROBERT L. PINTOZZI, M.D. CEDARWOOD MEDICAL CENTER 820 LESTER AVENUE ST. JOSEPH, MI 49085	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
ALAN POSNER, M.D. HARRIMAN JONES MEDICAL GROUP 2600 REDONDO AVENUE LONG BEACH, CA 90806	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
DAVID C. POUND, M.D. INDIANAPOLIS GASTROENTEROLOGY AND HEPATOLOGY INC 8051 S. EMERSON AVENUE SUITE 200 INDIANAPOLIS, IN 46237	M93-130	4		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	4		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
J. MARK PROVENZA, M.D. SHREVEPORT ENDOSCOPY CENTER, A.M.C. 3217 MABEL STREET SHREVEPORT, LA 71103	M93-131	10		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
RONALD E. PRUITT, M.D. NASHVILLE MEDICAL RESEARCH INSTITUTE 4230 HARDING ROAD SUITE 309W NASHVILLE, TN 37205	M93-125	12		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	4		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	6		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
ADISESHA B. REDDY, M.D. GASTROENTEROLOGY CONSULTANTS, P.C. TUSCALOOSA ENDOSCOPY CENTER 100 RICE MINE ROAD SUITE E TUSCALOOSA, AL 35406	M93-131	12		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
ROBERT W. RHAME, M.D. CAROLINA RESEARCH 511 CAROLINA AVENUE ORANGEBURG, SC 29115	M93-131	5		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
LEEK. RICHMAN, M.D. ROCKY MOUNTAIN GASTROENTEROLOGY 8550 WEST 38TH AVENUE, SUTIE 300 WHEATRIDGE, CO 80033	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
DENNIS S. RIFF, M.D. ASSOCIATED GASTROENTEROLOGY MEDICAL GROUP 1211 WEST LAPALMA SUITE 408 ANAHEIM, CA 92801	M93-125	12		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	5		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
MALCOLM ROBINSON, M.D. OKLAHOMA FOUNDATION FOR DIGESTIVE RESEARCH HCA PRESBYTERIAN HOSPITAL 700 NORTHEAST 13TH STREET, 6TH FLOOR OKLAHOMA CITY, OK 73104	M93-131	13		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
WALTER M. ROUFAIL, M.D. PIEDMONT RESEARCH ASSOCIATES 1901 SOUTH HAWTHORNE ROAD SUITE 306 WINSTON-SALEM, NC 27103	M93-130	5		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
J. DAVID. ROWEKAMP, M.D. WINONA CLINIC LTD. 420 EAST SARNIA STREET WINONA, MN 55987	M93-130	6		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
HERBERT A. RUBIN, M.D. BEVERLY HILLS GASTROENTEROLOGY INSTITUTE 465 NORTH ROXBURY DRIVE, SUITE 711 BEVERLY HILLS, CA 90210	M93-125	12		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	1		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	11		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
SEYMOUR M. SABESIN, M.D. RUSH-PRESBYTERIAN ST. LUKE'S MEDICAL CENTER DIRECTOR, DIGESTIVE DISEASES UNIVERSITY GASTROENTEROLOGISTS 1725 WEST HARRISON STREET SUITE 339 CHICAGO, IL 60612-3864	M93-125	8		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
MICHAEL A. SAFDI, M.D. CONSULTANTS FOR CLINICAL RESEARCH INC. 2925 VERNON PLACE SUITE 100 CINCINNATI, OH 45219	M93-130	12		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	7		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
BRUCE SAHBA, M.D. CALIFORNIA RESEARCH FOUNDATION 2800 THIRD AVENUE SAN DIEGO, CA 92103-6204	M93-131	20		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
LOUIS A. SALAS, M.D. CLINICAL RESEARCH GROUP OF MARYLAND INC. 3449 WILKENS AVENUE SUITE 310 BALTIMORE, MD 21229	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
RICHARD E. SAMPLINER, M.D., F.A.C.P. VA MEDICAL CENTER GI SECTION, 111G 3601 SOUTH 6TH AVENUE TUSCON, AZ 85723	M93-125	2		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
TIMOTHY T. SCHUBERT, M.D. ALLENMORE MEDICAL CENTER, B-4006 1901 SOUTH UNION AVENUE TACOMA, WA 98405	M93-125	2		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V1.207, P 001
HOWARD I. SCHWARTZ, M.D. SOUTH FLORIDA CENTER FOR DIGESTIVE DISEASE 8950 NORTH KENDALL DRIVE SUITE 508 MIAMI, FL 33176	M93-131	38		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
JERROLD L. SCHWARTZ, M.D. NORTHWEST GASTROENTEROLOGISTS, S.C. 1215 S. ARLINGTON HEIGHTS ROAD ARLINGTON HEIGHTS, IL 60005	M93-125	11		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	1		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
MICHAEL E. SCHWARTZ, D.O. SOUTH FLORIDA CENTER OF GASTROENTEROLOGY 2051 45TH STREET SUITE 301 WEST PALM BEACH, FL 33407	M95-392	6		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
RONALD P. SCHWARZ, M.D. RALEIGH MEDICAL GROUP 3521 HAWORTH DRIVE RALEIGH, NC 27609	M93-125	4		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
CHARLES SCOWCROFT, M.D. 505 EAST CALHOUN STREET ANDERSON, SC 29621	M93-125	9		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M95-392	5		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
NAYAN R. SHAH, M.D., F.A.C.G. SHAH ASSOCIATES, M.D., P.A. SHANTI MEDICAL CENTER ROUTE 5 LEONARDTOWN, MD 20650	M93-130	23		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
UMEDCHANDRA K. SHAH, M.D., F.A.C.G. SHAH ASSOCIATES, M.D., P.A. SHANTI MEDICAL CENTER ROUTE 5 LEONARDTOWN, MD 20650	M95-392	8		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
LOUIS I. SHANE, M.D. PHYSICIANS CLINICAL RESEARCH ASSOCIATES 47 DAVIS AVENUE WHITE PLAINS, NY 10505	M93-131	1		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
BAVIKATTE N. SHIVAKUMAR, M.D. GASTROINTESTINAL CLINIC OF QUAD CITIES 3400 DEXTER COURT SUITE 105 DAVENPORT, IA 52807	M93-125	11		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M95-392	8		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
HOWARD I. SIEGEL, M.D. EASTSIDE COMPREHENSIVE MEDICAL SERVICES 133 EAST 73RD STREET SUITE 209 NEW YORK, NY 10021	M93-131	21		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
ANN L. SILVERMAN, M.D. WILLIAM BEAUMONT HOSPITAL 3601 WEST THIRTEEN MILE ROAD ROYAL OAK, MICHIGAN 48073-6769	M93-130	4		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
DAVID R. SILVERS, M.D. DRUG RESEARCH SERVICES 4720 SOUTH I-10 SERVICE ROAD SUITE 501 METAIRIE, LA 70001	M93-130	11		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	2		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
ROBERT A. SIMMONS, M.D. CONSULTANTS IN GI DISEASES 1212 EAST ELIZABETH STREET FORT COLLINS, CO 80524	M93-130	1		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
DOUGLAS M. SIMON, M.D. JACOBI HOSPITAL ROOM 303 ENDOSCOPY UNIT 1400 PELHAM PARKWAY SOUTH BRONX, NY 10461	M93-131	17		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
JOHN W. SINGLETON, M.D. UNIVERSITY HOSPITAL 4200 EAST 9TH AVENUE, BOX B-158 DENVER, CO 80262	M93-130	2		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
KURTIS SMITH, M.D. VA MEDICAL CENTER DIVISION OF GASTROENTEROLOGY SOUTHFIELD AND OUTER DRIVE ALLEN PARK, MI 48101	M93-130	3		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
WILLIAM B. SMITH, M.D. LOUISIANA CARDIOVASCULAR RESEARCH CENTER 2820 CANAL STREET NEW ORLEANS, LA 70119	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
WILLIAM J. SNAPE, JR., M.D. LONG BEACH GASTROENTEROLOGY ASSOCIATES 2650 ELM AVENUE SUITE 201 LONG BEACH, CA 90806	M93-125	8		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M95-392	9		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
THOMAS J. SOBIESKI, M.D. MCGUIRE MEDICAL GROUP 7702 PARHAM ROAD, SUITE 303 RICHMOND, VA 23294	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
STEVEN C. SOLIK, M.D. DURHAM INTERNAL MEDICINE ASSOCIATION 4205 BEN FRANKLIN BOULEVARD DURHAN, NC 27704	M93-130	9		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
ROGER D. SOLOWAY, M.D. UNIVERSITY OF TEXAS MEDICAL BRANCH 301 UNIVERSITY BOULEVARD GALVESTON, TEXAS 77555	M93-131	10		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
STEPHEN J. SONTAG, M.D. HINES VETERANS ADMINISTRATION HOSPITAL BUILDING 200, ROOM A148 (11C3) HINES, IL 60141	M93-125	4		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT/DIED LOCATION
MALCOLM J. SPERLING, M.D. EDINGER MEDICAL GROUP INC. 11180 WARNER AVENUE SUITE 365 FOUNTAIN VALLEY, CA 92708	M93-131	12		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
LEWIS R. STRONG, M.D. ASPEN MEDICAL CENTER BIG THOMPSON MEDICAL GROUP, P.C. 1808 NORTH BOISE AVENUE LOVELAND, CO 80538	M93-131	4		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
JOHN A. THESING, M.D. HEART OF AMERICA RESEARCH INSTITUTE 5799 BROADMOOR, SUITE 338 MISSION, MO 66202	M93-131	3		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
RAYMOND TIDMAN, M.D. BURNS PROFESSIONAL BUILDING SUITE 101 BLUE RIDGE, GA 30513	M93-131	2		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
THOMAS G. TIETJEN, M.D. INTERNAL MEDICINE GROUP, P.C. 1200 EAST 20TH STREET CHEYENNE, WY 82001	M95-392	1		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001

Takeda F = Takeda of France

V = VOLUME
S = SECTION
P = PAGE

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
ESTHER A. TORRES, M.D., F.A.C.P. GASTROENTEROLOGY SECTION UNIVERSITY OF PUERTO RICO SCHOOL OF MEDICINE PUERTO RICO MEDICAL CENTER SANJUAN, PUERTO RICO 00936-5067	M93-131	7		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
AMY M. TSUCHIDA, M.D., F.A.C.G. MADIGAN ARMY MEDICAL CENTER 3315 SOUTH 23RD STREET, #108-PC3 TACOMA, WA 98405	M93-131	10		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
PATRICK R. VOLAK, M.D. MIDWEST FOUNDATION FOR DIGESTIVE HEALTH 6465 SOUTH YALE SUITE 715 TULSA, OK 74136	M93-125	3		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
STEVEN J. WEGLEY, M.D. SEATTLE GASTROENTEROLOGY ASSOCIATES, P.S. 1560 NORTH 115TH SUITE 207 SEATTLE, WA 98133	M93-125	4		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
STUART M. WEISMAN, M.D. 2900 WHIPPLE AVENUE SUITE 245 REDWOOD CITY, CA 94062	M93-131	8		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
SANDRA L. WILBORN, M.D. METROPOLITAN CLINIC P.C. 265 NORTHBROADWAY PORTLAND, OR 97227	M93-131	1		S 8.5.1, V 1.26 P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
BARRY D. WINSTON, M.D. NORTH HOUSTON GASTROENTEROLOGY CLINIC, P.A. 800 PEAKWOOD DRIVE SUITE 5-D HOUSTON, TX 77090-2903	M93-130	10		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002
	M95-392	6		S 8.5.1, V 1.40, P 001 S 10.4.1, V 1.152, P 001	S 12.2, V 1.198, P 001
PETER C. WITT, M.D. GREELEY MEDICAL CLINIC, P.C. 1900 16TH STREET GREELEY, CO 80631	M93-131	4		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
ROBERT A. WOHLMAN, M.D. NORTHWEST GASTROENTEROLOGY ASSOCIATES 1700 116TH AVENUE NORTHEAST SUITE 200 BELLEVUE, WA 98004	M93-131	9		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001
LAWRENCE D. WRUBLE, M.D. MEMPHIS GASTROENTEROLOGY GROUP 80 HUMPHREYS CENTER SUITE 220 MEMPHIS, TN 38120	M93-125	7		S 8.5.5, V 1.75, P 002 S 10.4.3, V 1.172, P 002	S 12.2, V 1.207, P 001
	M93-130	1		S 8.5.3, V 1.54, P 002 S 10.4.2, V 1.159, P 002	S 12.2, V 1.201, P 001 S 12.1, V 1.194, P 002

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8.2.1 List of Investigators (U.S. and Puerto Rico) Who Participated in the Primary Efficacy/Safety Studies (Study Nos. M93-131, M95-392, M93-130 and M93-125) (Continued)

INVESTIGATOR NAME/ADDRESS	STUDY NO.	NO. PATIENTS	CONTRACT RESEARCH ORGANIZ.	REPORT LOCATION	CR FORMS DISCONT./DIED LOCATION
SALAM F. ZAKKO, M.D. THE UNIVERSITY OF CONNECTICUT HEALTH CENTER, MC-1845 GI DIVISION 263 FARMINGTON AVENUE FARMINGTON, CT 06030	M93-131	15		S 8.5.1, V 1.26, P 001 S 10.4.1, V 1.138, P 001	S 12.2, V 1.195, P 001

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SUMMARY OF PATIENT ACCOUNTABILITY BY INVESTIGATIVE SITE

STUDY	INVESTIGATOR NAME (NUMBER)	NUMBER OF PATIENTS ENROLLED	NUMBER OF PATIENTS WHO COMPLETED STUDY	NO. PTS EVALUABLE FOR HP ERADICATION	NO. PTS EVALUABLE FOR ULCER PREVALENCE	NUMBER OF PATIENTS WITH AES	TOTAL NUMBER OF AES
M93-125	ARORA (9118)	14	13	10	10	11	22
	BARISH (8417)	8	7	8	6	5	12
	BERRY (2927)	1	1	0	0	1	1
	BIRBARA (8586)	4	4	3	3	3	3
	BIRD (9194)	8	8	8	7	4	7
	CHEN (7565)	11	9	9	9	1	2
	CHENG (5585)	7	6	5	5	5	6
	CHRISTIAN (8911)	6	6	3	3	3	11
	CUTLER (9197)	10	10	10	10	0	0
	FISHER (4444)	3	1	1	1	3	5
	FITCH (2936)	6	5	5	5	0	0
	GRAHAM (5526)	7	4	4	3	1	1
	GREEN (9121)	2	2	2	2	1	3
	GRESHAM (9122)	7	7	4	4	3	3
	HAGGER (8536)	2	1	1	1	1	3
	HARFORD (7192)	15	15	14	9	13	48
	HIRSCHOWITZ (4468)	9	7	6	5	7	14
	KAHRILAS (7193)	3	3	3	3	1	1
	KOGUT (4257)	7	7	6	6	2	3
	KOVAL (2965)	6	3	4	4	3	5
	KUCER (8517)	2	2	1	1	1	2
	LANZA (4265)	14	12	10	10	4	6
	LEBIUDA (9124)	9	8	8	8	5	6
	LOURA (9614)	3	3	2	2	2	5
	MORGAN (8918)	4	4	4	2	1	1
	MOVVA (2942)	5	5	3	3	1	3
	PRUITT (7123)	12	11	11	12	3	3
	RIPP (9172)	12	10	9	9	2	3
	RUBIN (9303)	12	10	11	9	3	5
	SABESIN (3510)	8	8	8	8	1	2
	SAMPLINER (4000)	2	2	2	2	0	0
	SCHUBERT (9217)	2	2	2	2	0	0
	SCHWARTZ (2953)	11	10	10	8	8	14
	SCHWARZ (9781)	4	3	3	3	3	4
	SCOWCROFT (2954)	9	8	8	8	1	1
	SHIVAKUMAR (2955)	11	10	10	9	1	1
	SHAPE (9026)	8	8	7	7	3	4
	SONTAG (3511)	4	3	2	2	3	4
	VOLAK (9835)	3	2	1	1	1	3
	WEGLEY (9125)	4	4	4	3	0	0
	WRUBLE (6562)	7	7	7	7	0	0

SUMMARY OF PATIENT ACCOUNTABILITY BY INVESTIGATIVE SITE

STUDY	INVESTIGATOR NAME (NUMBER)	NUMBER OF PATIENTS ENROLLED	NUMBER OF PATIENTS WHO COMPLETED STUDY	NO. PTS EVALUABLE FOR HP ERADICATION	NO. PTS EVALUABLE FOR ULCER PREVALENCE	NUMBER OF PATIENTS WITH AES	TOTAL NUMBER OF AES
M93-130	AL-KAWAS (8585)	8	6	6	4	8	24
	ATTAR (5872)	7	7	6	5	2	5
	BARISH (8417)	5	4	4	3	5	10
	BARREIRO (8568)	6	5	4	4	3	6
	BASS (9126)	3	3	3	2	1	1
	BATH (9373)	7	6	7	6	4	5
	BELL (8179)	2	1	1	1	0	0
	BIANCHI (8920)	24	23	23	21	14	21
	BIRD (9194)	3	3	3	3	3	4
	BRAZER (7190)	5	5	5	3	2	11
	BREITER (8647)	8	3	5	3	7	19
	BRUNS (2928)	5	3	3	2	4	7
	CAMPBELL (3508)	21	19	19	16	17	39
	CASTELL (4338)	2	2	2	2	0	0
	CLINE (9141)	10	9	9	9	1	3
	COLIP (8923)	14	13	11	12	5	9
	FALK (8924)	9	8	8	7	5	9
	FRIEDMAN (9027)	7	6	5	5	4	14
	GASKINS (7191)	2	2	1	2	2	6
	GERACI (5862)	1	0	0	0	0	0
	GRAHAM (5526)	9	8	6	6	4	6
	HEE (4233)	8	7	7	6	4	9
	HERLIHY (9894)	2	2	2	2	1	2
	HO (8926)	17	14	12	7	8	13
	HUSSEY (8451)	2	2	2	2	1	3
	JAMES (8460)	2	2	1	1	0	0
	JONES (2940)	9	9	9	7	5	8
	KIM (9930)	18	17	13	14	6	10
	KLYGIS (8936)	3	3	3	3	1	2
	KOHAGEN (9095)	2	2	2	2	2	4
	KORNFIELD (8576)	3	2	1	1	0	0
	KOVACS (4445)	20	17	17	17	7	10
	KRANZ (8929)	7	6	7	7	5	11
	KRUSS (9158)	6	5	5	4	1	1
	LANZA (4265)	4	4	4	4	1	1
	LOIUDICE (9163)	10	7	6	6	3	6
	MAIMON (9129)	4	4	4	4	4	10
	MCCULLOUGH (8930)	11	10	11	10	7	17
	METZ (8931)	9	9	8	8	6	11
	MURTHY (9210)	7	6	4	4	5	10
	MOVICK (8932)	5	5	4	4	5	6
	POUND (9214)	4	4	4	3	2	5
	PRUITT (7123)	4	4	4	4	2	8
	RIFF (9172)	5	4	4	4	2	2
	ROUFAIL (4543)	5	5	5	5	3	4
	ROWEKAMP (2950)	6	6	6	5	4	7

SUMMARY OF PATIENT ACCOUNTABILITY BY INVESTIGATIVE SITE

STUDY	INVESTIGATOR NAME (NUMBER)	NUMBER OF PATIENTS ENROLLED	NUMBER OF PATIENTS WHO COMPLETED STUDY	NO. PTS EVALUABLE FOR HP ERADICATION	NO. PTS EVALUABLE FOR ULCER PREVALENCE	NUMBER OF PATIENTS WITH AES	TOTAL NUMBER OF AES
M93-130	RUBIN (9300)	1	0	0	0	0	0
	SAFDI (8515)	12	10	9	8	9	18
	SCHWARTZ (2953)	1	1	1	1	1	2
	SEAR (8937)	23	19	19	18	19	29
	SILVERMAN (9219)	4	2	2	3	1	5
	SILVERS (4261)	11	8	8	7	6	8
	SIMMONS (9178)	1	1	1	1	1	2
	SINGLETON (8463)	2	2	1	1	1	2
	SMITH (8933)	3	2	2	2	0	0
	SOLIK (8934)	9	8	8	6	5	12
	WINSTON (9615)	10	10	9	9	8	14
	WRUBLE (6562)	1	1	0	1	1	1

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STUDY	INVESTIGATOR NAME (NUMBER)	NUMBER OF PATIENTS ENROLLED	NUMBER OF PATIENTS WHO COMPLETED STUDY	NO. PTS EVALUABLE FOR HP ERADICATION	NO. PTS EVALUABLE FOR ULCER PREVALENCE	NUMBER OF PATIENTS WITH AES	TOTAL NUMBER OF AES
X93-131	AVNER (3094)	7	7	7	7	4	10
	AVUNDUX (9287)	4	4	2	2	0	0
	BEDARD (9819)	2	1	0	0	2	6
	BERLIN (11334)	8	6	7	6	2	2
	FENOVERTY (9648)	1	1	1	1	0	0
	FOGEL (8572)	2	2	0	2	0	0
	FRIDBERG (9820)	1	1	1	1	0	0
	GAMAN (11335)	13	8	6	6	5	8
	GOGEL (9740)	1	1	1	1	1	2
	HOWDEN (9742)	4	2	2	1	2	2
	JAMAL (9348)	5	3	2	1	4	6
	KASHMAN (9660)	6	4	4	4	3	6
	KHANDELWAL (9743)	6	5	4	3	4	4
	KING (11330)	1	1	1	1	0	0
	KIYASU (11375)	3	3	3	3	2	3
	KOSEYK (9746)	1	1	1	1	1	2
	KRAUSE (9747)	21	15	18	13	17	39
	KURTZ (9748)	3	3	3	3	0	0
	LAMET (7462)	15	13	9	9	6	10
	LEVINE (4267)	8	5	2	4	2	2
	LIEBERMANN (9749)	2	1	0	0	1	3
	LOBIS (9750)	5	5	5	5	3	6
	LYERLY (9751)	7	7	7	7	4	7
	MACCINI (9923)	2	2	2	2	0	0
	MATHEW (11323)	1	0	0	0	0	0
	MILLS (9821)	3	3	2	2	2	2
	MOUSSAVIAN (9822)	7	1	2	2	1	1
	MUDEL (11337)	3	3	3	3	0	0
	PAMBIANCO (7315)	11	11	10	10	6	15
	PANITCH (9753)	7	5	6	3	3	6
	PRIKEM (9212)	2	1	1	1	1	1
	PINTOZZI (9754)	3	3	2	2	3	3
	POSNER (9783)	1	1	1	1	1	1
	PROVENZA (9755)	10	8	7	6	6	14
	REDDY (9756)	12	10	8	7	5	11
	REAME (9931)	5	5	5	5	0	0
	RICHMAN (9758)	2	1	2	2	2	4
	ROBINSON (3509)	13	11	12	11	7	19
	SAHBA (2951)	20	16	17	17	7	10
	SALAS (9759)	1	0	0	1	0	0
	SCHWARTZ (8570)	38	34	33	31	11	13
	SEANE (11338)	1	0	0	0	1	1
	SIEGEL (9760)	21	18	15	15	2	2
	SIMON (9922)	17	11	13	10	3	3
	SMITH (6653)	2	2	2	2	2	5
	SOBIESKI (8462)	3	3	2	1	3	10

SUMMARY OF PATIENT ACCOUNTABILITY BY INVESTIGATIVE SITE

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M93-131	SOLOWAY (9221)	10	6	7	7	7	22
	SPERLING (9319)	12	11	11	9	5	8
	STRONG (11339)	4	4	4	3	2	2
	THESING (8452)	3	3	3	2	2	5
	TIDMAN (11281)	2	2	0	0	0	0
	TORRES (7143)	7	4	5	5	5	13
	TSUCHIDA (9761)	10	6	7	6	6	13
	WEISMAN (9859)	8	7	6	6	7	13
	WILBORN (9762)	1	1	1	1	0	0
	WITT (11340)	4	4	4	4	2	5
	WOHLMAN (9644)	9	7	4	5	3	5
	ZARKO (9763)	15	13	14	14	6	10

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M95-392	ABRAHM (11380)	5	5	5	5	4	7
	BARISH (8417)	2	2	2	2	0	0
	BIANCHI (8920)	7	7	7	7	1	1
	BIRBARA (8586)	5	5	3	4	3	3
	BIRD (9194)	4	3	3	2	3	7
	BREITER (8647)	4	3	3	3	2	2
	BRUNS (2928)	4	4	4	4	4	14
	CAMPBELL (3508)	3	3	3	2	2	2
	CHENG (5585)	5	5	4	4	3	6
	CLINE (9141)	2	2	2	2	0	0
	FREEDMAN (9027)	6	6	5	5	6	11
	HO (8926)	4	4	4	4	3	6
	HUSSEY (8451)	1	1	1	1	1	1
	JAMES (8460)	5	4	2	2	4	5
	KIM (9930)	8	7	7	7	4	4
	KOGUT (4257)	5	5	4	4	1	1
	KOVACS (4445)	4	3	3	3	0	0
	KRUSS (9158)	2	2	2	2	0	0
	LOIUDICE (9163)	3	3	1	1	1	1
	METZ (8931)	2	2	2	2	1	1
	MURTHY (9210)	3	3	3	3	2	2
	POUND (9214)	4	2	2	2	3	5
	PRUITT (7123)	6	6	6	6	0	0
	RUBIN (9303)	11	10	10	10	4	4
	SAFDI (8515)	7	6	6	6	6	15
	SCHWARTZ (11382)	6	4	4	4	4	5
	SCOWCROFT (2954)	5	5	5	5	0	0
	SHAH (8097)	8	8	6	6	3	6
	SHIVAKUMAR (2955)	8	8	7	6	6	6
	SILVERS (4261)	2	2	2	2	0	0
	SMAPE (9026)	9	8	8	7	2	3
	TIETJEN (11383)	1	1	1	1	0	0
	WINSTON (8615)	6	6	6	6	2	3

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lakeburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015

October 10, 1996

Food and Drug Administration
Center for Drug Evaluation & Research
Office of New Drug Chemistry (HFD-830)
Central Document Room
5600 Fishers Lane
Rockville, MD 20857

Attn: Eric Sheinin, Ph.D., Office Director

RE: PREVACID® (lansoprazole) plus Clarithromycin and Amoxicillin for the Eradication of *Helicobacter pylori*

REQUEST FOR FDA RESPONSE

Dear Dr. Sheinin:

The purpose of this communication is to follow-up on our September 19, 1996, telephone conversation regarding TAP Holding's Inc.'s New Drug Application, PREVACID® (lansoprazole) with clarithromycin and amoxicillin for the eradication of *H. pylori*. As you may be aware, TAP submitted the NDA to the Anti-Infective Drug Products Division (HFD-520) on September 30, 1996. In earlier communications with the Agency, we expressed an interest in offering patients our triple therapy regimen of lansoprazole/clarithromycin/amoxicillin in a "compliance pack" that would contain all of the doses for one day of treatment on a single blister card rather than the patient having to fill three prescriptions separately by their pharmacist. As mentioned in a previous correspondence to your attention dated September 12, 1996, each capsule or tablet in the compliance pack will be contained in its own individual well of polyvinylchloride/polyethylene/aclar material which is heat seal coated to an aluminum/paper backing material. Drug product will be purchased commercially and provided to the vendor for packaging in a dedicated penicillin facility.

Per our telephone conversation on September 19th, you stated that it would not be possible to get an answer back quickly from Dr. Chi Wan Chen and members of the Stability Committee regarding TAP's request to submit a stability commitment letter in lieu of real-time stability data in the NDA for the compliance pack. Due to time constraints, a decision was made to submit the NDA without the compliance pack with plans to submit the necessary

Chemistry, Manufacturing and Controls documentation for the pack at a later date. The NDA that was submitted on September 30th to HFD-520 currently only allows the physician the ability to write three separate prescriptions for the lansoprazole, clarithromycin and amoxicillin which can be later filled by the patient's pharmacist. As discussed earlier, the patient will need to consume eight capsules/tablets per day for the *H. pylori* treatment, which may cause difficulty with compliance.

Based on the fact that the materials in our compliance pack will have the same product contact surface that PREVACID, BIAXIN® Filmtab® (clarithromycin tablets) and TRIMOX® (amoxicillin USP) currently have in their commercially marketed hospital unit-doses, we believe a stability commitment letter per the February, 1987 Guidelines would be sufficient in lieu of real-time stability data prior to approval. In addition, the PVC/PE/aclar blister material that will be used in the compliance pack will be the same as, or more conservative than, the material in which the three drug products are currently packaged.

Therefore, we kindly request Dr. Chen and the Stability Committee's comments on the proposed packaging procedures and stability plan described in our September 12th letter (copy attached). If deemed acceptable by the Agency, the current NDA would be amended with the proper documentation to support the triple therapy compliance pack. If a conference call or direct meeting is necessary, please do not hesitate to contact me for scheduling. As the NDA is currently under review at this time, your prompt assistance in this matter is greatly appreciated.

Sincerely,

Linda J. Peters

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

cc: J. Cintron, HFD-520 (desk copy)
J. Timper, HFD-520 (desk copy)

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TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Bannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015

September 12, 1996

Food and Drug Administration
Center for Drug Evaluation & Research
Office of New Drug Chemistry (HFD-830)
Central Document Room
5600 Fishers Lane
Rockville, MD 20857

Attn: Eric Sheinin, Ph.D., Office Director

RE: Lansoprazole Plus Clarithromycin and Amoxicillin
for the Eradication of *Helicobacter pylori*

REQUEST FOR FDA RESPONSE

Dear Dr. Sheinin:

The purpose of this communication is to request your input on a drug product stability issue that arose during a September 9, 1996 telephone conversation between TAP Holdings Inc. and the Anti-Infective Drug Products Division (HFD-520). During this conversation, Mr. Jim Timper, Chemistry Reviewer, HFD-520, recommended that we pursue our request with you further.

TAP is currently in the process of preparing a NDA for the eradication of *H. pylori* with a triple therapy regimen of PREVACID® (lansoprazole) 30 mg BID plus BIAXIN® (clarithromycin) 500 mg BID and TRIMOX® (amoxicillin) 1 gm BID. Currently, these three drugs are approved by the Agency for other indications. The NDA is will be submitted to the Anti-Infective Division on or about September 30, 1996

The triple therapy regimen of lansoprazole/clarithromycin/amoxicillin requires the patient to consume a series of eight tablets/capsules daily (four in the morning and four in the evening) for 14 days. This high number of pills the patient has to take has raised concerns regarding compliance. Therefore, TAP has expressed an interest in offering patients this triple therapy regimen in a "compliance pack" that would contain all of the doses for one day of treatment on a single card rather than the patient having to fill three separate prescriptions for the drugs and then take the medications from three containers. Each capsule or tablet will be contained in its own individual well

of aclar/polyethylene/vinyl material which is heat seal coated to an aluminum/paper backing material. The AM and PM dose will be clearly indicated on the card. Additionally, the compliance pack has passed child-proof testing by an independent research facility.

Since TAP does not have the facilities to package this type of product, , will be responsible for packaging these three drugs together in the compliance pack. is currently in the process of leasing a penicillin-dedicated facility for our packaging needs. Drug product will be purchased commercially and provided to the vendor for packaging.

During the September 9th phone conversation, we informed Mr. Timper that the packaging materials used in the compliance pack will have the same product contact as what is currently approved for the three products individually. In addition, these materials in the compliance pack will be more conservative in regards to moisture impermeability (0.01" PVC versus 0.0075" PVC). Stability for these products have already been proven in the blister materials contained in their respective NDAs and AADAs. The material contents are as follows:

PREVACID® **(lansoprazole, TAP)** **30 mg capsule** **NDA 20-406**	**Biaxin®** **(clarithromycin, Abbott)** **500 mg tablet** **NDA 50-662**	**TRIMOX®** **(amoxicillin, Apothecon)** **500 mg capsule** **AADA**	*TAP's Compliance Blister Pack for NDA*
0.0075" (7.5 mil) PVC (Mirrex 1025-CL-06 vinyl) bonded to 0.002" (2.0 mil) PE bonded to 0.0015" (1.5 mil) Aclar 22A	0.01" PVC (10 mil) throughout	0.0075" (7.5 mil) PVC (VPA 711) bonded to 0.002" (2.0 mil) LDPE bonded to 0.0015" (1.5 mil) Aclar 22A	

Note: The foil backing material for all products is which consists of

The blister packaging CMC documentation to support PREVACID, Biaxin and TRIMOX are contained in their respective NDAs and AADAs.

Based on the fact that TAP will be using the same type of blister materials in the compliance pack as already approved for the three products, we do not believe that additional real time stability data are needed on the compliance pack at NDA submission time. We stated to Mr. Timper that a stability commitment letter for upcoming stability testing will be provided in the NDA, along with the other necessary supportive CMC documentation. Mr. Timper said that it is his understanding that packaging and blister seal coating these three drugs together at the same time would be considered a significant CMC change and would therefore require real-time stability data at the time of NDA submission. We explained that due to the extra needed time to have the new penicillin-dedicated facility and equipment validated and producing commercial supply, real-time and challenge stability data on the compliance pack would not be available until mid-1997.

In addition, TAP proposes that the initial expiry dating for the compliance package be based on the earliest expiration date given for the three lots of drugs used in the package. Again, expiry dating has already been proven for these drugs in their respective blister materials. Mr. Timper stated that expiry dating can only be based on real time stability data for the product and that expiry dating can be extended with accelerated stability testing.

Mr. Timper also raised some concerns that there could be the possibility that the different drug products could somehow touch each other during the blistering process and cause an unknown interaction between the products. Based on discussions with about this issue, they do not believe that their current packaging procedures would allow the different drugs to touch each other in any way during the packaging process. Two capsules or tablets of any combination will not fit into a single blister well. If two tablets or capsules should drop into a single position, it would be immediately apparent and culled during the quality control check. We believe this scenario is acceptable to ensure the integrity of the drug products and seek your concurrence.

There may be an alternative packaging option which TAP could possibly pursue if the current scenario is not acceptable to the Agency. The second option would allow to separately package the drugs using the same materials as previously described for the compliance pack. This packaging scenario would eliminate the theoretical chance of the individual drug products touching each other in any way. Please note, though, that this process will be less efficient, limit the layout of the package and may be cost prohibitive.

Mr. Timper stated that he understood TAP's reasoning for only providing a stability commitment at submission time and, therefore, suggested that we pursue this issue with you further for clarification. He also agreed that compliance could be an issue if the patient has to rely on three separate drug prescriptions filled by their pharmacist.

In closing, we kindly request the Agency's comments on the proposed packaging procedures and stability plan described herein. If a conference call is necessary, please do not hesitate to contact me for scheduling. As the NDA is scheduled to be submitted September 30th, your prompt assistance in this matter is greatly appreciated.

Sincerely,

Linda J. Peters

Linda J. Peters, M.S.
Regulatory Products Manager
(847) 374-5481
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cc: J. Cintron, HFD-520 (desk copy)
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