

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20406/S021**

**COMBINED MEDICAL-STATISTICAL REVIEW(S)**

Medical/Statistical Review  
sNDA  
20-406/s-021

Medical/Statistical Review of Supplemental NDA

1. General Information

Submission Number: 20-406/S-021

Indication: Eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence.

Applicant Identification

Name: Tap Holdings, Inc.  
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Contact Person: Linda J. Peters, M.S. Regulatory Products Manager

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Submission/Review Dates

Date of Submission: June 25, 1997  
CDER Stamp Date: June 26, 1997  
Date Review Begun: October 14, 1997  
Date Review Completed: November 30, 1997  
Revised: December 9, 1997

Drug Identification

Generic Name: Lansoprazole, Clarithromycin, and Amoxicillin  
Current Trade Names of the Components: PREVACID, Biaxin Filmtab, and Amoxil

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)

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Route of Administration: oral

*Reviewer note: This combination therapy was approved on June 17, 1997. The sponsor seeks a reduction in duration of therapy from 14 to 10 days as stated in the proposed DOSAGE AND ADMINISTRATION section below.*

Proposed DOSAGE AND ADMINISTRATION section

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Triple Therapy: PREVACID/amoxicillin/clarithromycin

The recommended adult oral dose is 30 mg PREVACID, 1 gram amoxicillin, and 500 mg clarithromycin, all given twice daily (q 12h) for 10- or 14 days. (See INDICATIONS AND USAGE.)

*MO Note: The bolded numbers and words represent the proposed additions to the labeling.*

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2. Commercial Marketing History

Lansoprazole, used in combination with two antibiotics, has been approved for a 7-day duration of therapy for the eradication of *H. pylori* in the United Kingdom, France, Austria, and Denmark.

3. Microbiology

Please see the Microbiology review by Dr. Linda Utrup.

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4. Clinical Studies

A single U.S. study consisting of 284 enrolled patients was performed comparing the *H. pylori* eradication rates of 10 versus 14 days of Lansoprazole/clarithromycin/amoxicillin. The list of investigators follows.

*MO Note: A meeting held on March 4, 1996, between representatives of TAP Holdings, Inc. and representatives of FDA concluded that a single study was needed to demonstrate equivalence between 10 and 14 days of therapy employing a triple-therapy regimen. If the sponsor wished to pursue a reduction in duration of therapy for a dual-therapy regimen, then two studies would have been necessary.*

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20-406/s-021

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4

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5

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Study Design:

Study M95-399 was a stratified, randomized, double-blind, parallel-group, active-controlled, multicenter study comparing the effectiveness of triple therapy with lansoprazole 30 mg BID, clarithromycin 500 mg BID, and amoxicillin 1 gm BID administered for either 10 or 14 days in patients with documented presence of *H. pylori* and either active duodenal ulcer disease or an endoscopically-documented history of duodenal ulcer disease within the past year. 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). This last visit served as the test of cure.

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*Statistical Reviewer's Note: Patients were stratified at the time of randomization according to whether they had active DU disease or a recent history of DU disease. The sponsor did not specify how 95% confidence intervals for differences in rates such as eradication rates were calculated; however, the intervals do not appear to adjust for active vs. historical DU status. The sponsor did examine homogeneity of results across DU status using the Breslow-Day test. In addition, treatment group comparisons were performed adjusting for DU status using the Cochran-Mantel-Haenszel test.*

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The presence of *H. pylori* was confirmed at screening by rapid urease test (CLOtest®) and/or histological detection from gastric biopsy specimens. Positive culture or histology for *H. pylori* were required for the patient to remain 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.

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The endpoint of *H. pylori* was analyzed for three subsets of patients. These subsets included the evaluable patient subset, the intent-to-treat (all available data) subset, and the modified intent-to-treat (worst case) subset.

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*MO Note: This review will present results from the evaluable and modified intent-to-treat analyses as described in the Division's Guidance Document on Evaluability Criteria.*

Efficacy analyses (evaluable, intent-to-treat [all available data], and modified intent-to-treat [worst case]) excluded patients who did not have confirmed evidence of *H. pylori* at baseline or who had no duodenal ulcer present and no history of duodenal ulcer endoscopically documented within the past year. Evaluable analyses included all patients' data who met the evaluability criteria. Intent-to-treat (all available data) analyses excluded patients who did not

sNDA

20-406/s-021

return for the Week-6 Visit or did not have an endoscopy performed at the Week-6 Visit. Modified intent-to-treat (worst case) analysis included patients who did not return for the Week-6 Visit or did not have an endoscopy performed at the Week-6 Visit as treatment failures.

Overall, 284 patients were enrolled in Study M95-399; 136 patients received the 14-day triple-therapy regimen and 148 patients received the 10-day triple-therapy regimen.

### 5. *Evaluability Criteria/Efficacy Analysis*

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Patients could have been excluded from the *H. pylori* eradication analysis for more than one reason. If patients were prematurely discontinued due to adverse event(s) considered at least possibly related to study medication, were a therapeutic failure, or required anti-ulcer or anti-reflux medication(s) due to gastrointestinal disease, they were included in the evaluable analysis of *H. pylori* eradication regardless of protocol deviations. Patients prematurely discontinuing due to one of the above reasons and missing their endoscopy or *H. pylori* eradication assessment at the Week-6 Visit were included in the respective analyses as failures. *MO note: This was the review strategy for the NDA approved on June 17, 1997.*

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#### Reasons for 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, at least one of which was from either culture or histology (this was also applicable for exclusion from the intent-to-treat analysis)
- 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 analysis)
- Underwent therapeutic procedures or regimens which interfered with patient evaluation, including administration of antimicrobial agents or bismuth
- Less than 70% of prescribed active study medication was taken during the 14-day treatment period, and/or less than 7 days of active treatment were received for patients randomized to 10-day therapy and/or less than 10 days of active treatment were received for patients randomized to 14-day therapy
- Study blind was broken prior to the Week-6 Visit
- Culture and histology evaluation was not performed at the Week-6 Visit (25-60 days posttreatment), and there was no posttreatment documentation of the presence of *H. pylori* prior to this window (i.e., 0-24 days posttreatment). If only culture or histology was performed, patients were considered evaluable if the test indicated the presence of *H. pylori*

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**Patient Accountability:**

A total of 284 patients were enrolled in the study. The numbers of patients included in each of the analyses are presented below:

	Lan/Cla/Amx 10 Days	Lan/Cla/Amx 14 Days
Total Enrolled	148	136
Evaluable	123 (83%)	113 (83%)
MITT	135 (91%)	126 (93%)

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**Patients Excluded from the Evaluable Analysis:**

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Twenty-five patients were excluded from the 10-day arm for the following reasons:

(A single patient could have had more than one reason for exclusion.)

Negative for *H. pylori* at baseline: 13

No *H. pylori* assessment at week-six: 5

Concomitant antibiotic use: 3

*H. pylori* negative status at week-six documented by only one test: 3

Study Blind Broken: 1

Antibiotic used pre-study: 1

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Twenty-three patients were excluded from the 14-day arm for the following reasons:

(A single patient could have had more than one reason for exclusion.)

Negative for *H. pylori* at baseline: 9

No *H. pylori* assessment at week-six: 9

Received < 70% of study medicines: 7

Concomitant antibiotic use: 1

*H. pylori* negative status at week-six documented by only one test: 1

Received insufficient number of days of active study medication: 4

No documentation of DU history: 2

No evidence of DU: 1

Ulcer size not documented: 1

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In the MITT analysis, patients with a negative baseline *H. pylori* status (n=22) or no evidence of duodenal ulcer (n=1) were excluded. No other patient groups were excluded. The number of patients in each arm follows:

10-day therapy: 135

14-day therapy: 126

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### Sponsor's Results

#### H. pylori Eradication Rates at the Week-6 Visit

Dataset	Lan/Cla/Amx 10 days	Lan/Cla/Amx 14 days	95% C.I.
Evaluable	84% (103/123)	85% (96/113)	-10.5, 8.1
MITT	81% (110/135)	82% (103/126)	-9.7, 9.1

*Statistical Reviewer's Note: The sponsor did not specify how their 95% confidence intervals are calculated. This reviewer calculated confidence intervals using the normal approximation to the binomial distribution incorporating the continuity correction. Using this method, the 95% confidence interval for the difference in eradication rates, 10-day minus 14-day, is (-11.3, 8.9) in the evaluable patient analysis and (-10.4, 9.9) in the MITT analysis. Note that qualitative conclusions remain the same, i.e., 10-day therapy may be considered therapeutically equivalent to 14-day therapy in either analysis.*

*The 95% confidence interval around the point estimate of the eradication rate for 10-day therapy is (75.8, 89.6) in the evaluable patient analysis and (73.7, 87.4) in the MITT analysis.*

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### 6. Medical Officer Analysis

The review strategy employed by this reviewing Medical Officer was a patient-by-patient review of line-listing data presented in computerized format. As done in the review of NDA 50-876 and NDA 50-877, patients who dropped-out of the study because of an adverse event were considered evaluable failures. The sponsor analyzed these patients similarly. Therefore, the results of the evaluable analysis are the same as generated by the sponsor.

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In reviewing the data for the MITT analysis, the medical officer noted that patients who had been excluded from the evaluable analysis because of the use of concomitant antibiotics were included in the sponsor's MITT analysis. Three patients from the 10-day arm, and 1 patient from the 14-day arm received concomitant antibiotics. All were considered cures in the MITT analysis since

they all had documented eradication of *H. pylori* by the appropriate number of tests and at the appropriate time-point. Below is a listing of these patients and what concomitant antibiotics were given over what period of time during the study:

Patient #	Concomitant Antibiotic	Day Started	Day Ended
8097 3546	Isoniazid	-39	-1
8515 3168	Keftab	11	17
	Gentamicin	24	Ongoing
	Floxin	31	40
8570 3270	Cipro	36	41
1140 3273	Ancef	6	6
	Cephalexin	6	14

The reasons for the concomitant antibiotics were as follows:

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8097 3546: Isoniazid was taken for tuberculosis prophylaxis.

8515 3168: Antibiotics were taken for toe infection.

8570 3270: The reason listed for cipro use was "infection."

1140 3273: Antibiotics were given for a hand infection.

If these patients are excluded from the MITT analysis since it is not known what the effect, if any, on eradication these other antibiotics may have had, the rates are as follows:

	<u>10-DAY</u>	<u>14-DAY</u>
MITT	80.6% (107/132)	81.6% (102/125)

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This has no effect on the overall eradication rates or the difference in eradication rates. The corresponding 95% confidence interval for the difference in eradication rates, 10-day minus 14-day, becomes (-10.8, 9.8). The 95% confidence interval around the point estimate of the eradication rate in the 10-day arm becomes (73.1, 87.1).

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*Statistical Reviewer's Note: The above confidence intervals are calculated using the normal approximation to the binomial distribution incorporating the continuity correction.*

The next patient group to be analyzed was the group identified as having taken < 70% of their study medication. Among these patients, 3 took less than 70% because they actually experienced

sNDA

20-406/s-021

an adverse event. One patient (8097 3431) in the 10-day arm was considered a failure in the MITT analysis by the sponsor. One patient (8515 3166) in the 14-day arm was also considered a failure in the MITT analysis by the sponsor. One patient (7462 3013) in the 14-day arm took 45.8% of the study meds. This patient stopped taking the medications because of nausea, but did not drop out of the study. At the 6-week visit, endoscopy was performed and showed that *H. pylori* was eradicated. The patient was included in the MITT analysis as a cure.

#### Demographic Eradication Analysis

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The following tables display the eradication rates (MITT) based on duodenal ulcer status (active versus history) and demographic variables: Age, Gender, Race.

*MO Note: In all instances, the 14-day data are given first, followed by the 10-day data. POSITIVE refers to failures, while NEGATIVE refers to those eradicated of infection based on the requisite number of tests.*

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*Statistical Reviewer's Note: There were no significant differences between treatment groups for the demographic by DU status subgroups shown below. Overall, 92/113=81% of patients with active DU and 11/13=85% of patients with a history of DU were eradicated in the 14-day arm. In the 10-day arm, 97/117=83% of patients with active DU and 13/18=72% of patients with a history of DU were eradicated. These differences were also not statistically significant.*

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sNDA

20-406/s-021

AGE

TX_GROUP	LAN BID/CLA BID/AMX BID - 14 DAY				
DU_BASE	AGE_GRP	Data	POSITIVE	NEGATIVE	Grand Total
ACTIVE DU	<45	%	20.83%	79.17%	100.00%
		N	10	38	48
	45-65	%	14.58%	85.42%	100.00%
		N	7	41	48
	>65	%	23.53%	76.47%	100.00%
		N	4	13	17
DU HISTORY	45-65	%	18.18%	81.82%	100.00%
		N	2	9	11
	>65	%	0.00%	100.00%	100.00%
		N	0	2	2
Total %			18.25%	81.75%	100.00%
Total N			23	103	126

TX_GROUP	LAN BID/CLA BID/AMX BID -10 DAY				
DU_BASE	AGE_GRP	Data	POSITIVE	NEGATIVE	Grand Total
ACTIVE DU	<45	%	19.05%	80.95%	100.00%
		N	8	34	42
	45-65	%	17.74%	82.26%	100.00%
		N	11	51	62
	>65	%	7.69%	92.31%	100.00%
		N	1	12	13
DU HISTORY	<45	%	50.00%	50.00%	100.00%
		N	1	1	2
	45-65	%	23.08%	76.92%	100.00%
		N	3	10	13
	>65	%	33.33%	66.67%	100.00%
		N	1	2	3
Total %			18.52%	81.48%	100.00%
Total N			25	110	135

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sNDA

20-406/s-021

GENDER

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TX_GROUP	LAN BID/CLA BID/AMX BID - 14 DAY				
DU_BASE	GENDER	Data	POSITIVE	NEGATIVE	Grand Total
ACTIVE DU	FEMALE	%	17.24%	82.76%	100.00%
		N	5	24	29
	MALE	%	19.05%	80.95%	100.00%
		N	16	68	84
DU HISTORY	FEMALE	%	14.29%	85.71%	100.00%
		N	1	6	7
	MALE	%	16.67%	83.33%	100.00%
		N	1	5	6
Total %			18.25%	81.75%	100.00%
Total N			23	103	126

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TX_GROUP	LAN BID/CLA BID/AMX BID -10 DAY				
DU_BASE	GENDER	Data	POSITIVE	NEGATIVE	Grand Total
ACTIVE DU	FEMALE	%	21.28%	78.72%	100.00%
		N	10	37	47
	MALE	%	14.29%	85.71%	100.00%
		N	10	60	70
DU HISTORY	FEMALE	%	16.67%	83.33%	100.00%
		N	1	5	6
	MALE	%	33.33%	66.67%	100.00%
		N	4	8	12
Total %			18.52%	81.48%	100.00%
Total N			25	110	135

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sNDA

20-406/s-021

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TX_GROUP	LAN BID/CLA BID/AMX BID - 14 DAY				
DU_BASE	RACE_GRP	Data	POSITIVE	NEGATIVE	Grand Total
ACTIVE DU	BLACK	%	38.46%	61.54%	100.00%
		N	5	8	13
	CAUCASIAN	%	17.86%	82.14%	100.00%
		N	10	46	56
	OTHER	%	13.64%	86.36%	100.00%
		N	6	38	44
DU HISTORY	BLACK	%	0.00%	100.00%	100.00%
		N	0	5	5
	CAUCASIAN	%	33.33%	66.67%	100.00%
		N	2	4	6
	OTHER	%	0.00%	100.00%	100.00%
		N	0	2	2
Total %			18.25%	81.75%	100.00%
Total N			23	103	126

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TX_GROUP	LAN BID/CLA BID/AMX BID -10 DAY				
DU_BASE	RACE_GRP	Data	POSITIVE	NEGATIVE	Grand Total
ACTIVE DU	BLACK	%	25.00%	75.00%	100.00%
		N	5	15	20
	CAUCASIAN	%	15.94%	84.06%	100.00%
		N	11	58	69
	OTHER	%	14.29%	85.71%	100.00%
		N	4	24	28
DU HISTORY	BLACK	%	0.00%	100.00%	100.00%
		N	0	3	3
	CAUCASIAN	%	38.46%	61.54%	100.00%
		N	5	8	13
	OTHER	%	0.00%	100.00%	100.00%
		N	0	2	2
Total %			18.52%	81.48%	100.00%
Total N			25	110	135

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7. Safety Analysis

The following Table is a listing of all the available demographic data within the sNDA.

MO Note: The demographic data for the 14-day arm include data from NDA 50-876 and NDA 50-877.

This was done by the sponsor to include all safety data available for the 14-day arm.

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Demographics for Patients Who Received 10 or 14 Days of Triple Therapy		
Demographic Characteristics	Lan/Cla/Amx 10 days <sup>a</sup>	Lan/Cla/Amx 14 days <sup>b</sup>
Gender:		
Female	39% (57)	30% (82)
Male	61% (91)	70% (192)
Race:		
Black	18% (26)	18% (50)
Caucasian	61% (91)	54% (149)
Hispanic	18% (26)	19% (53)
Other	3% (5)	8% (22)
Age (years): <sup>c</sup>		
<45	31% (46)	41% (113)
45-65	54% (80)	45% (124)
>65	15% (22)	14% (37)
Mean (SD)	50.7 (13.2)	48.8 (14.4)
Range		
Weight - Females (lbs): <sup>c</sup>	(N = 57)	(N = 82)
<150	47% (27)	49% (40)
≥150	53% (30)	51% (42)
Mean (SD)	153.0 (37.8)	157.4 (37.3)
Range		
Weight - Males (lbs): <sup>c</sup>	(N = 91)	(N = 192)
<150	12% (11)	14% (27)
≥150	88% (80)	86% (165)
Mean (SD)	182.7 (31.6)	181.9 (32.3)
Range		
Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm		
<sup>a</sup> Included Study M95-399		
<sup>b</sup> Included Studies M93-131, M95-392, and M95-399		
<sup>c</sup> At baseline.		

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**Adverse Event Comparisons Between the 10- and 14-Day Triple Therapy Treatment Groups**

*Treatment Period*

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The overall incidence of treatment-emergent adverse events in the combined analysis was statistically significantly ( $p \leq 0.05$ ) lower for patients who received 14 days of therapy (39%, 107/274) compared with patients who received 10 days of therapy (49%, 73/148); however, no statistically significant differences were observed between the treatment groups for any specific adverse event.

*MO Note: -The reasons for this observation are outlined in the subsequent paragraphs.*

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Similarly, a statistically significantly lower percentage of patients reporting possibly or probably treatment-related adverse events was observed for patients who received the 14-day therapy (27%, 75/274) compared with the 10-day therapy (38%, 56/148). In addition, a statistically significantly lower incidence of possibly or probably treatment-related diarrhea was observed for 14-day therapy (9%) compared with 10-day therapy (17%). No other statistically significant differences were observed for any other specific adverse events.

A summary of treatment-emergent and possibly or probably treatment-related adverse events occurring during the treatment period in  $\geq 3\%$  of patients who received 10 or 14 days of therapy is presented.

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<b>Most Frequently Reported<sup>@</sup> Adverse Events During the Treatment Period for Patients Who Received 10 or 14 Days of Triple Therapy</b>		
<b>COSTART Term</b>	<b>Treatment Group % (n)</b>	
	<b>Lan/Cla/Amx 10 days<sup>a</sup> (N = 148)</b>	<b>Lan/Cla/Amx 14 days<sup>b</sup> (N = 274)</b>
<b>Treatment-Emergent Adverse Events</b>		
Any Event	49% (73)*	39% (107)
Diarrhea	17% (25)	11% (31)
Taste Perversion	15% (22)	11% (29)
Headache	3% (5)	5% (14)
Pharyngitis	3% (5)	3% (7)
<b>Possibly or Probably Treatment-Related Adverse Events</b>		
Any Event	38% (56)*	27% (75)
Diarrhea	17% (25)*	9% (26)
Taste Perversion	15% (22)	11% (29)
Headache	1% (2)	3% (9)
Lan = lansoprazole 30 mg; Cla = clarithromycin 500 mg; Amx = amoxicillin 1 gm		
<sup>@</sup> Reported by ≥3% of patients in any treatment group.		
<sup>a</sup> Included Study M95-399		
<sup>b</sup> Included Studies M93-131, M95-392, and M95-399		
* Statistically significant difference versus the 14-day therapy group (p≤0.05).		

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The overall incidence of treatment-emergent adverse events reported in Study M95-399 was not statistically significantly different between patients who received either 10 (49%, 73/148) or 14 (46%, 62/136) days of therapy. However, combining adverse events from the 14-day treatment arms of Studies M95-392 (34%, 25/74) and M93-131 (31%, 20/64), which had much lower overall incidences of adverse events, with the 14-day data from Study M95-399, resulted in a lower overall adverse event rate for the 14-day treatment regimen.

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Similar to the analysis of treatment-emergent adverse events, in Study M95-399, the overall incidence of possibly or probably treatment-related adverse events and the incidence of treatment-related diarrhea were not statistically significantly different between the 10 day (38% [56/148]; 17% [25/148], respectively) and 14 day (34% [46/136]; 13% [17/136], respectively) treatment groups. The statistically significant differences observed in the combined analyses of possibly or probably treatment-related adverse events are directly related to the lower incidences of possibly or probably treatment-related adverse events and diarrhea observed in Studies M95-392 (19% [14/74]; 7% [5/74], respectively) and M93-131 (23% [15/64]; 6% [4/64], respectively) compared with Study M95-399. The statistically significant difference observed between

the 10- and 14-day therapy groups for diarrhea in the combined analysis justified a comparison of incidence rates by study. The incidence of treatment-emergent and possibly or probably treatment-related adverse events, as well as the incidence of treatment-emergent and possibly or probably treatment-related diarrhea for patients who received 10 or 14 days of therapy, is presented by study.

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<b>Incidence of Treatment-Emergent and Possibly or Probably Treatment-Related Adverse Events and Diarrhea for Patients Who Received 10 or 14 Days of Triple Therapy by Study</b>				
<b>COSTART Term</b>	<b>Study % (n)</b>			
	<b>M95-399</b>		<b>M93-131</b>	<b>M95-392</b>
	<b>Lan/Cla/Amx 10 days (N = 148)</b>	<b>Lan/Cla/Amx 14 days (N = 136)</b>	<b>Lan/Cla/Amx 14 days (N = 64)</b>	<b>Lan/Cla/Amx 14 days (N = 74)</b>
<b>Treatment-Emergent Adverse Events</b>				
Any Event	49% (73)	46% (62)	31% (20)	34% (25)
Diarrhea	17% (25)	15% (21)	6% (4)	8% (6)
<b>Possibly or Probably Treatment-Related Adverse Events</b>				
Any Event	38% (56)	34% (46)	23% (15)	19% (14)
Diarrhea	17% (25)	13% (17)	6% (4)	7% (5)

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

Similar to the events of diarrhea reported by patients receiving 14-day therapy in Studies M93-131 and M95-392, the events of diarrhea reported for the 10- and 14-day therapies in Study M95-399 were mild to moderate in severity and self-limiting.

The differences between the results of the "combined analysis" and Study M95-399 alone are directly related to the lower incidence of adverse events reported in Studies M93-131 and M95-392.

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**8. Comments on Labeling**

Draft labeling was submitted as part of this NDA. There are five changes in the proposed labeling that reflect additions to the approved labeling of June 17, 1997. **APPEARS THIS WAY ON ORIGINAL**

1. In the **CLINICAL PHARMACOLOGY** section, the following sentence has been added: "Higher levels of acid suppression have been predicted to potentiate the activity of antibiotics in eradicating *Helicobacter pylori* (*H. pylori*)."  
This sentence had been deleted from the label approved June 17, 1997 because, at the time, it was felt that adequate data were not submitted to support this statement. The applicant has submitted 9 literature references to provide data with regard to the potential increased efficacy of antibiotics when used in combination with an acid-suppressing agent. One of the references ( Peterson W. The role of antisecretory drugs in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1997;(Suppl. 1)11:21-25) provides the most detail regarding this issue. There are few studies in which direct comparisons have been made between antibiotics alone and antibiotics plus an antisecretory drug. This article discusses the compilation of data accumulated among different studies each with a different design. The following table is taken from the article which displays eradication rates of various antibiotics with and without an antisecretory agent. Caution in interpreting these data is advised because methods of diagnosing *H. pylori* or information on how eradication was defined are not available.

Antibiotic(s)	Cure Rate (%)		
	Alone	+H2RA	+PPI
Amoxicillin	20	35	60
Clarithromycin	40	55	70
Amoxicillin + nitroimidazole	60	70	80
Clarithromycin + nitroimidazole	60	80	90
Bismuth Triple therapy	80	90	95

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As stated within the article, "Recognizing the limitations of the above data, it nevertheless appears clear that addition of an antisecretory agent enhances the *H. pylori* eradication rates of whichever antibiotic regimen it is added to. Less clear are the mechanisms by which antisecretory agents accomplish these results."

*MO Note: Based on the above data and a review of the publications submitted, this reviewer recommends the following wording to replace the sponsor's proposed statement: "Acid suppression may enhance the effect of antibiotics in eradicating Helicobacter pylori (H. pylori)."*

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2. In the **CLINICAL STUDIES** section, the following paragraph has been added:

"A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or a history of an ulcer within one year) compared the efficacy of PREVACID triple therapy for 10 and 14 days in combination with amoxicillin capsules and clarithromycin tablets. The study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori*."

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*MO Note: A table showing the data from the evaluable and MITT analyses should also be included in this section.*

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3. In the **INDICATIONS AND USAGE** section, the following wording has been added under the section for dual therapy: "Resistance to amoxicillin has not been demonstrated in clinical studies with PREVACID and amoxicillin."

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ON ORIGINAL

*MO Note: The reader is referred to the Microbiology review for recommendations regarding this addition.*

APPEARS THIS WAY  
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4. In the **ADVERSE REACTIONS** section, the following has been added under triple therapy: "There were no statistically significant differences in the frequency of reported adverse events between the 10- and 14-day triple therapy regimens."

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*MO Note: This addition is acceptable.*

5. In the **DOSAGE AND ADMINISTRATION** section the following has been added under triple therapy: "The recommended adult oral dose is 30 mg PREVACID, 1 gram amoxicillin, and 500 mg clarithromycin, all given twice daily (q 12h) for 10- or 14 days.(See INDICATIONS AND USAGE.)"

*MO Note: This addition is acceptable.*

**8. Medical Officer and Statistician's Conclusions and Recommendations**

The data presented in this sNDA support the efficacy and safety of the combination of lansoprazole, clarithromycin, and amoxicillin when given for 10 days to eradicate *H. pylori* in patients with either an active duodenal ulcer or a history of a duodenal ulcer within one year. An approval letter should be sent to the applicant upon agreement of final labeling.

Luigi S. Girardi, M.D.

/S/

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Nancy Silliman, PhD

/S/

Ph.D.

cc:

Original sNDA 20-406/S071  
HFD-590/Dr. Goldberger /S/ 12/12/97  
HFD-590/Dr. Hopkins  
HFD-520/Dr. Girardi  
HFD-520/Dr. Albuern /S/ 12/8/97  
HFD-520/Dr. Sun  
HFD-520/Mr. Cintron  
HFD-520/Dr. Sheldon  
HFD-725/Dr. Silliman  
HFD-725/Dr. Chakravarty  
HFD-725/Dr. Huque  
HFD-725/Ms. Shores  
HFD-590/Dr. Albrecht  
HFD-590/Dr. Utrup  
HFD-590/Ms. Anderson

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