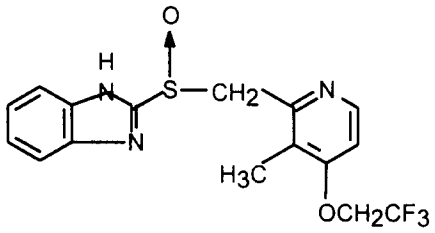
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020406/S016

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW 1	1. Organization: HFD-180	2. NDA Number: 20-406
3. Name and Address of Applicant (City & State): TAP Holdings, Inc. 2355 Waukegan Road Deerfield, IL 60015		4. AF Number: MAY - 1 1997 5. Supplement(s)
6. Name of Drug: Prevacid®	7. Nonproprietary Name: lansoprazole	Numbers: SE1-016 Dates: December 20, 1996
8. Supplement Provides for: addition of new indication - treatment of non-erosive gastroesophagel reflux disease		9. Amendments and Other (Reports, etc.) Dates:
10. Pharmacological Category: anti-ulcer	11. How Dispensed: RX X OTC __	12. Related IND/NDA/DMF(s):
13. Dosage Form: Delayed-Release Capsules	14. Potency: 15 and 30 mg	
15. Chemical Name and Structure: 2-[[[3-methyl-4-(2,2,-trifluoroethoxy)-2-pyridyl-]methyl]-sulfinyl]benzimidazole 		16. Records and Reports: Current Yes X No __ Reviewed Yes X No __

17. Comments: No CMC information provided. See EA Review
cc: NDA 20-406/SE1-016
HFD-180/Div File
HFD-181/CSO
HFD-180/SFredd
HFD-180/AShaw
R/D init by:EDuffy 4-30-97
ABS/dob **F/T 4-30-97**/WP: c:\wpfiles\chem\S\20406016.1AS

/S/ 5/1/97

18. Conclusions and Recommendations: The submitted EA is acceptable. No new CMC information is presented. The supplement may be approved. (AP)

19. Reviewer

Name:	Signature	Date Completed:
Arthur B. Shaw, Ph. D.	/S/ 5/1/97	April 22, 1997

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020406/S016

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

MAY - 9 1997

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PREVACID® Delayed Release Capsules (30 mg) (lansoprazole)

NDA 20-406/S-016

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS (HFD-180)

LT 5-19-97

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-406/S-165
PREVACID® (lansoprazole) Delayed Release Capsules (30 mg)

Indicated for treatment of non-erosive gastroesophagel reflux disease

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center of Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for PREVACID® (lansoprazole) Delayed Release Capsules (30 mg) TAP Holdings, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

In support of their supplemental new drug application (S-016), TAP Holdings, Inc. has submitted an environmental assessment (EA). The new EA information does not present new information on the manufacture of lansoprazole and PREVACID® (lansoprazole) Delayed Release Capsules (30 mg).. The manufacturing aspect of the EA remains the same with respect to manufacturing at the approved facilities, and the drug product formulation remains the same.

Approval of the supplemental application will make PREVACID® (lansoprazole) Delayed Release Capsules (30 mg) available to a larger group of patients as reflected in the additional indication. The drug product will be used for treatment of non-erosive gastroesophagel reflux disease. The fate and effects of lansoprazole remain unchanged from the original EA.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY
ON ORIGINAL

5/1/97
DATE

/S/

PREPARED BY:
Arthur B. Shaw, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of New Drug Chemistry

5/1/97
DATE

/S/

DIVISION CONCURRENCE:
ERIC P. DUFFY, PH.D.
Chemistry Team Leader
Office of New Drug Chemistry, HFD-820

APPEARS THIS WAY
ON ORIGINAL

5/9/97
DATE

/S/

APPROVED:
NANCY B. SAGER
Environmental Scientist, HFD-353
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: Original NDA 20-406/S-016(mailed)
357 HFD-~~004~~/FONSI File 20-406/S-016
357 HFD-~~004~~/Docket File
205 HFD-~~019~~/FOI Copy
HFD-180/AShaw
R/D init.: EDuffy/4-30-97
ABS/dob **F/T 4-30-97**/WP: c:\wpfiles\chem\S\20406016.2AS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020406/S016

STATISTICAL REVIEW(S)

Maria Walsh

STATISTICAL REVIEW AND EVALUATION

NDA: 20-406, S-016 **Date:** NOV 13 1997

Pharmacologic Category of the Drug: proton pump inhibitor; 1S

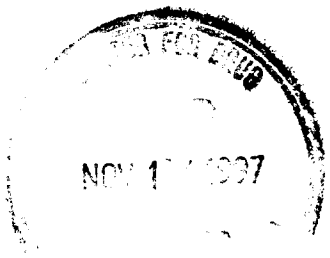
Name of Drug: Lansoprazole (Prevacid®) delayed-release capsules

Date Received in Branch: HFD-180 received 12mo/23/1996

Date of 45 Day Meeting: 2mo/3/1997

Sponsor: Tap Holdings Inc.

Indication: Symptomatic GERD



Number and Type of Controlled Clinical Studies: 3
M87-092: U.S. reanalyzed for subset
M95-300: U.S. prospective
D57p501: U.K. supportive

Statistical Reviewer: Ferrin Harrison

Clinical Reviewer: John Senior

Project Manager: Maria Walsh

Documents Surveyed: Volumes 1, 27 to 45, dated 12/20/1996; three responses to requests for information 10/1997

I. INTRODUCTION

The sponsor seeks to expand the labeling from lesions detected by endoscopy to symptomatic GERD.

In addition to the three studies completed and submitted, there is one ongoing study, M96-519, *A study to Evaluate the Effects of Lansoprazole 15mg and 30mg Versus Ranitidine or Placebo on Non-Erosive Gastroesophageal Reflux Disease* (GERD). The number of patients is about 420 and the indication is symptomatic GERD; otherwise the ongoing trial is similar to M87-092 and M95-300, covered in this review.

II. SPONSOR'S SUBMISSION AND ANALYSIS

The sponsor included a diskette with demographic and diary datasets for the two primary studies, M87-092 and M95-300. The original endpoints for M97-092 were ulcer healing validated by endoscopy, submitted years ago for its respective indication. The original endpoints for M95-300 were symptomatic relief.

The sponsor seems to favor analyzing the diary data based endpoints over clinical assessment based endpoints, for heartburn and gelusil use. The diary assessments are "daily" patient assessments, versus one clinical assessment by the investigator per two weeks or less often. In this reviewer's assessment, the diaries give more data, more information, and thus generate more power. The sponsor appears focussed on using diary assessments in this submission (both pivotal studies).

II.a Study M87-092, U.S., reanalyzed for subset

This study was named *Effects of lansoprazole on acute gastroesophageal reflux disease*, on both erosive and non-erosive patients. This was a 34 center, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study comparing three doses of lansoprazole (15, 30, and 60mg QD) with placebo for 8 weeks. The original final report for this study summarized the demographic, efficacy, and safety data for all patients (with and without erosive esophagitis) and was submitted in the original NDA. The severity of day and night heartburn endpoints were scored 0=none, 1=mild, 2=moderate, and 3=severe.

In this supplement, the sponsor focussed on the 106 patients with non-erosive GERD for analysis. Of these 106, 105 were included in symptom data intent-to-treat analysis, 104 in the diary intent-to-treat analysis, and 102 in at least one evaluable analysis. There were 26 placebo patients and 23, 24 and 31 patients in the lansoprazole 15mg, 30mg and 60 mg groups, respectively.

Baseline variables and demographics were not significantly unbalanced between treatment arms. Both genders were reasonably well represented. Non-Caucasian races were scarce. The number of elderly and the number of post-menopausal women is addressed in this reviewer's comments.

Table A
Study M87-092 (Non-Erosive)
from a SAS Run Similar to Sponsor's Table 8.1.4, V27 pp. 33-34
8 Week Diary Data for Intent-to-treat Patients
Placebo N=26, 15mg N=23, 30mg N=24

	15mg vs. PLA	30mg vs. PLA
% Days with Heartburn	-23%, p=.031	-44%, p=.001
Mean Day Pain Severity	-0.4, p=.041	-0.6, p=.001
% Nights with Heartburn	-17%, p=.109	-27%, p=.012
Mean Night Pain Severity	-0.3, p=.155	-0.5, p=.008
% Days Gelusil Used	-25%, p=.014	-28%, p=.004
Mean Gelusil per Day	-1.3, p=.005	-1.3, p=.001

These p-values are based on the Wilcoxon two-sample test for a difference between indicated groups.

The efficacy results are summarized in the preceding **Table A** and appendix **Table 1**.

II.b Study M95-300, U.S., prospective

This study was named *A study to evaluate the effects of lansoprazole 15mg and 30mg QD versus placebo on non-erosive gastroesophageal disease*. This was an 18 center, randomized, placebo-controlled fixed-dose study, comparing two doses of lansoprazole (15mg and 30mg QD) with placebo for 8 weeks.

There was one demographic or baseline difference in H. Pylori status, with disproportionately more in placebo. The H. Pylori rates for placebo were 18/37(49%) positive, and 17/37(46%) negative. For lansoprazole 15mg, 18/68(27%) positive, 50/68(74%) negative, and for 30mg, 18/74(24%) positive, 55/74(74%) negative. This reviewer found the p-value by exact test including equivocal status (H. Pylori status unknown) to be p=.010; excluding equivocal status, p=.012. This reviewer addresses the potential for bias arising from H. Pylori imbalance in his comments. The imbalance in the dropout rate for placebo could be due to the imbalance in the H. Pylori rate for placebo.

Both genders were well represented. The Caucasian race was well represented. In the evaluable subset, there were 9 placebo, 11 lanso 15mg, and 10 lanso 30mg blacks. This sample size is adequate so that a side effect with a mean rate of 30% in this sub-population is likely to produce at least one case in the study. Races other than black or Caucasian were scarce. The number of elderly, and the number of post-menopausal women, is addressed in this reviewer's comments.

Of the 214 patients enrolled, 211 were included in the intent-to-treat analysis, and 185 in at least one efficacy analysis. Premature withdrawals totaled 20/214, with 10 attributed to treatment failure. In Vol. 1 pg. 291, 6/44 placebo, 0/82 lanso 15mg, and 4/88 lanso 30mg withdrawals were attributed to treatment failure. This reviewer finds the overall imbalance in treatment withdrawals significant at p=.002. Of the three pairwise unadjusted p-values, only one is below 0.05, Placebo vs. 15mg, p=.001. In this reviewer's assessment, the dropout rate in placebo could be adequately addressed by addressing the imbalance in H. Pylori.

Table B below summarizes the efficacy results for U.S. Study M95-300.

Table B
Study M95-300
From a SAS Run Similar to Sponsor's Table 8.1.4, V27 pp. 37-38
8 Week Diary Data for Intent-to-treat Patients

	15mg vs. PLA	30mg vs. PLA	30mg vs. 15mg
% Days with Heartburn	-47%, p<.001	-44%, p<.001	5%, p=.281
Day Pain Severity	-0.8, p<.001	-0.6, p<.001	0.2, p=.336
% Nights with Heartburn	-37%, p<.001	-26%, p<.001	11%, p=.027
Night Pain Severity	-0.7, p<.001	-0.4, p=.001	0.3, p=.027
% Days Gelusil Used	-37%, p<.001	-31%, p<.001	6%, p=.279
Mean Gelusil per Day	-1.6, p<.001	-1.3, p<.001	0.3, p=.395

These p-values are based on the Wilcoxon two-sample test for a difference between indicated arms.

II.c Trial D57p501, U.K., supportive

This trial was named *A controlled clinical trial of lansoprazole against ranitidine in reflux oesophagitis: A dose comparison study.* This was a multicenter, randomized, double-blind, stratified, comparative, parallel-group study, comparing two doses of lansoprazole (30mg and 60mg QD) with ranitidine 150mg bid for 4-8 weeks.

In this supplement, the sponsor focussed on the 57 patients with non-erosive GERD (erythema/edema and friability of mucosa with contact bleeding, Grade 1.)

Baseline demographics show good representation and balance with respect to gender, but the sample size is small, around 9 per treatment arm for each gender. Age averaged 47.3 years and was similar across treatment arms, but the range did not exceed 70 years, so there is probably not much clinical experience in the more than 65 year old group, in this portion of this supporting trial.

The mean change from baseline gave p-values below 0.05 for lansoprazole 30mg at both 4 and 8 weeks. Lansoprazole 60mg showed improvement from baseline at 8 weeks. No effect from baseline was shown for ranitidine 150mg bid.

III. REVIEWER'S COMMENTS AND ANALYSES FOR 30mg

The sponsor is seeking approval for this 30mg dose.

III.a M87-092, U.S., pivotal analysis for the 30mg dose

Granting the focus on these six endpoints, all the endpoints and their correlations are shown in appendix **Table 4**. As with supplement 003, the correlation between frequency and severity of heartburn exceeds 0.9, with none of these correlation estimates smaller than 0.5. Bonferroni and independence assumption adjustments are therefore going to give adjusted p-values which are substantially far from maximizing power. Given the correlations, the Tukey-Ciminera-Heyse (TCH) method should yield reasonable results. The TCH adjusted p is `1-(1-p)**sqrt(k)`, where k is the number of endpoints. The source is (1985), "Testing the statistical certainty of a response to increasing doses of a drug", *Biometrics* **41**, 295-301.

The p-values are given in **Table A** and appendix **Table 1**. The largest p-value for the 30mg dose is p=.012 for % of nights with night heartburn pain, which by the TCH method adjusts to p=.029, which is significant at the 0.05 level.

III.b M95-300, U.S., pivotal analysis for the 30mg dose

The p-values from the Wilcoxon method are all 0.001 or smaller for both 15mg and 30mg, so multiple endponts are not a major issue in this study. With van Elteren covariate adjustment for H. Pylori status, the weakest case is 30mg night heartburn frequency at p=.016, for a TCH adjusted p=.039 for six endpoints.

The central issue is the imbalance in H. Pylori status. Adjusting for H. Pylori status as a covariate yields each p≤.001 for 15mg, as shown in the following **Table C**. However, the subset analysis means summarized in appendix **Tables 5** to **7** imply that among lansoprazole 15mg patients, patients with H. Pylori have a better outcome than patients without, for day heartburn, night heartburn frequency, and gelusil. The numerical advantage of having H. Pylori is not corroborated by lansoprazole 30mg patients. The final appendix **Table 8** corroborates and addresses this concern, showing that the numerical advantage for H. Pylori status among 15mg patients, although consistent across the six endpoints, is not statistically significant for any of the six endpoints, each p≥.16.

the six endpoints, is not statistically significant for any of the six endpoints, each p≥.16.

Table C
Study M95-300
from SAS run Similar to Sponsor's Appendix D.2.4.2
8 Week Lansoprazole Diary Data for Intent-to-treat Patients
Controlling for H. Pylori Status by van Elteren's method

	15mg vs. PLA	30mg vs. PLA
% Days with Pain	p<.001	p<.001
Mean Day Pain Severity	p<.001	p<.001
% Nights with Pain	p<.001	p=.009
Mean Night Pain Severity	p<.001	p=.016
% Days Gelusil Used	p<.001	p=.001
Mean Gelusil per Day	p<.001	p<.001

Effect sizes by H. Pylori status and other details are in appendix **Tables 5-7.**

III.c Age and Gender Representation in both pivotal studies

Table D below summarizes patient disposition by age. More details including gender are provided in appendix **Table 3.**

Table D
Reviewer Generated
Pivotal Studies M87-092 non-erosive, M95-300
Intent-to-Treat Patient Frequencies by Age and Treatment Arm

Age in years	Treatment Arm Pla	15mg	30mg	60mg	Total
<=50	47	75	78	28	228(73%)
51-65	17	17	23	2	59(19%)
66+	5	11	9	1	26(8%)
Total	69	103	110	31	313(100%)

Treatment Arms: Pla=Placebo,
15mg, 30mg, 60mg are doses for Lansoprazole arms.

The number of elderly 66 years or older randomized to drug was 21/244(9%). Post-

menopausal women (age 51 or higher) randomized to drug were 30/244(12%); see appendix **Table 3**. With such small numbers of patients randomized to lansoprazole, the extent to which the efficacy and safety results can be generalized to post-menopausal women and to the elderly is unclear. There may be some safety or efficacy concerns within subsets, to be addressed by further inquiries.

IV. REVIEWER'S COMMENTS AND ANALYSES FOR 15mg

This dose was reviewed before this reviewer was informed that approval is not being sought for it. In study M95-300, the 15mg dose has a consistent numerical advantage over 30mg, which sometimes achieves statistical significance, per appendix **Table 2**. The conclusions may be of use in the future.

IV.a M87-092, U.S., reanalyzed for subset analysis for the 15mg dose

The central issues are multiple endpoints and weakness in the p-values. As shown in the preceding **Table A** or appendix **Table 1**, there is no statistically significant result for night heartburn for the 15mg dose. It should be noted that the prospectively defined primary endpoints are ulcer healing. The analysis for symptomatic GERD is a retrospective analysis in a study not designed to show a result for the symptomatic GERD subset, or for these formerly secondary efficacy endpoints. The study appears underpowered at about 25 patients per arm.

Based on the TCH (Tukey-Ciminera-Heyse) method, there is a statistically significant result for the 15mg dose for both Gelusil endpoints, but no statistically significant result for any of the four heartburn endpoints.

IV.b M95-300, U.S., prospective analysis for the 15mg dose

The Wilcoxon method in appendix Table 2 gives all 6 $p<.001$ for the 15mg dose in this trial. The van Elteren method of appendix Tables 7 to 9 also give all 6 $p<.001$ after making a covariate adjustment for H. Pylori status. These p-values are highly significant after adjustment for 6 endpoints.

IV.c Summary Comments/Conclusion for the 15mg dose

There is a prospective placebo-controlled trial in progress, M96-519. The efficacy of 15mg versus placebo might be addressed in a year or two by M96-519.

V. SUMMARY COMMENTS/CONCLUSION

The sponsor submitted two studies (M87-092, M95-300) supporting the efficacy of the 30mg dose in symptomatic GERD for reduction of day heartburn, night heartburn, and gelusil use. The analysis method for Study M87-092 was not prospectively planned. The analysis method for Study M95-300 was prospectively planned.

Both studies have multiple endpoint issues, and M95-300 has imbalance issues in H. Pylori status and dropouts. Both issues were addressed before reaching these conclusions.

The number of post-menopausal women (30, 12%) and the number of elderly of either gender (21, 9%) randomized to treatment in these studies (M87-092 non-erosive, M95-300) was small. Supporting study D57p501, U.K. offers little additional support for these groups. Generalizing the overall results to these groups may be problematic.

/S/ 11mo/13/1997

Ferrin Harrison, Ph.D. Mathematical Statistician

This review consists of 8 pages of text and 8 pages of tables.

/S/ 11/13/97

Concur: Abdul Sankoh, Ph.D. Team Leader Nov 1997-Feb 1998

/S/ 11/13/97

Nancy Smith Ph.D. Division Director

cc: Archival NDA 20-406
HFD-180/ Division Files
HFD-180/ Dr. Talarico
HFD-180/ Dr. Senior
HFD-180/ Ms. Maria Walsh
HFD-344/ Barton
HFD-720/ Dr. Smith
HFD-720/ Dr. Sankoh
HFD-720/ Dr. Harrison
HFD-720/ File Copy
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Table 1
Study M87-092 (Non-erosive)
from SAS run Similar to Sponsor's Table 8.1.4, V27 pp. 33-34
8 Week Diary Data for Intent-To-Treat Non-erosive Patients

	N	Mean(SD)	—Quantiles— 25% Median 75%	Lanso. vs PLA
Day Abdominal Pain in % Days with Pain				
Placebo	26	56%(35%)	69%	
Lansoprazole 15 mg	23	33%(32%)	19%	p=.031
Lansoprazole 30 mg	24	22%(23%)	10%	p=.001
Lansoprazole 60 mg	31	30%(29%)	19%	p=.006
Day Abdominal Pain in Mean Pain Severity/Day				
Placebo	26	0.9(0.7)	0.75	
Lansoprazole 15 mg	23	0.5(0.5)	0.33	p=.041
Lansoprazole 30 mg	24	0.3(0.3)	0.13	p=.001
Lansoprazole 60 mg	31	0.4(0.5)	0.24	p=.014
Night Abdominal Pain in % Nights with Pain				
Placebo	26	48%(36%)	50%	
Lansoprazole 15 mg	23	31%(30%)	17%	p=.109
Lansoprazole 30 mg	24	21%(21%)	14%	p=.012
Lansoprazole 60 mg	31	27%(28%)	17%	p=.031
Night Abdominal Pain in Mean Pain Severity/Night				
Placebo	26	0.8(0.7)	0.62	
Lansoprazole 15 mg	23	0.5(0.5)	0.20	p=.155
Lansoprazole 30 mg	24	0.3(0.3)	0.18	p=.008
Lansoprazole 60 mg	31	0.4(0.4)	0.22	p=.037
Gelusil % Days Used				
Placebo	26	50%(35%)	49%	
Lansoprazole 15 mg	23	25%(29%)	13%	p=.014
Lansoprazole 30 mg	24	22%(24%)	14%	p=.004
Lansoprazole 60 mg	31	25%(29%)	10%	p=.008
Mean Gelusil/Day				
Placebo	26	2.0(1.8)	1.57	
Lansoprazole 15 mg	23	0.7(0.9)	0.32	p=.005
Lansoprazole 30 mg	24	0.7(1.5)	0.32	p=.001
Lansoprazole 60 mg	31	0.7(1.0)	0.27	p=.003

The p-values are based on the Wilcoxon two-sample test for difference between indicated groups.
Patient #3317 in the lansoprazole 60 mg group did not have any diary record during the study and was not included in the analysis.
Severity is scored as 0=none 1=mild 2=moderate 3=severe.

Table 2
STUDY M95-300
from SAS run Similar to Sponsor's TABLE 8.1.4, V27 pg 37
8 Week Diary Data for Intent-To-Treat Non-erosive Patients

Day Heartburn	N	Mean(SD)	—Quantiles— 25% Median 75%	P-values vs PLA, 15
Day Heartburn in % Days with Pain				
Placebo	43	76%(27%)	87%	
Lansoprazole 15 mg QD	80	29%(32%)	16%	p<.001
Lansoprazole 30 mg QD	86	34%(36%)	18%	p<.001,.281
Day Heartburn in Mean Pain Severity/Day				
Placebo	43	1.2(0.6)	1.3	
Lansoprazole 15 mg QD	80	0.4(0.5)	0.2	p<.001
Lansoprazole 30 mg QD	86	0.6(0.7)	0.2	p<.001,.336

Night Heartburn	N	Mean(SD)	—Quantiles— 25% Median 75%	P-values vs PLA, 15
Night Heartburn in % Nights with Pain				
Placebo	43	59%(37%)	64%	
Lansoprazole 15 mg QD	80	22%(29%)	8%	p<0.001
Lansoprazole 30 mg QD	86	33%(35%)	20%	p<0.001,0.027
Night Heartburn in Mean Pain Severity/Night				
Placebo	43	1.0(0.8)	0.9	
Lansoprazole 15 mg QD	80	0.3(0.5)	0.1	p<0.001
Lansoprazole 30 mg QD	86	0.6(0.8)	0.3	p=0.001,0.027

Gelusil usage	N	Mean(SD)	—Quantiles— 25% Median 75%	P-values vs PLA, 15
Gelusil % Days Used				
Placebo	43	63%(32%)	72%	
Lansoprazole 15 mg QD	80	26%(29%)	13%	p<0.001
Lansoprazole 30 mg QD	86	32%(34%)	21%	p<0.001,.279
Mean Gelusil/Day				
Placebo	43	2.4(1.9)	2.25	
Lansoprazole 15 mg QD	80	0.8(1.1)	0.36	p<0.001
Lansoprazole 30 mg QD	86	1.1(1.6)	0.39	p<0.001,.395

The p-values are based on the Wilcoxon two-sample test for a difference between indicated arms.

Severity is scored as 0=none 1=mild 2=moderate 3=severe.

Table 3
Pivotal Studies M87-092 and M95-300
Intent-to-Treat Patient Frequencies
by Gender, Age, Study and Treatment Arm

Female <=50 years

STUDY	Treatment Arm PLA	15	30	60	Total
M87-092	9	10	1	14	34
M95-300	15	28	38	0	81
Total	24	38	39	14	115

Male <50 years

Treatment Arm PLA	15	30	60	Total
9	11	13	14	47
14	26	26	0	66
23	37	39	14	113

Female 51-65 years

STUDY	Treatment Arm PLA	15	30	60	Total
M87-092	5	2	4	1	12
M95-300	8	7	9	0	24
Total	13	9	13	1	36

Male 51-65 years

Treatment Arm PLA	15	30	60	Total
1	0	3	1	5
3	8	7	0	18
4	8	10	1	23

Female 66+ years

STUDY	Treatment Arm PLA	15	30	60	Total
M87-092	1	0	1	0	2
M95-300	2	6	0	0	8
Total	3	6	1	0	10

Male 66+ years

Treatment Arm PLA	15	30	60	Total
1	0	2	1	4
1	5	6	0	12
2	5	8	1	16

Treatment Arms:
PLA=Placebo
15 =Lansoprazole 15mg
30 =Lansoprazole 30mg
60 =Lansoprazole 60mg

Table 4
Correlations between Diary Data Efficacy Endpoints
provided by sponsor on 10mo/21/1997

Study M87-092 (Non-Erosive)

	DAYNO8	DAYSC8	NIGHTNO8	NIGHTSC8	GELDAY8	GELUSIL8
DAYNO8 =% of Days with Heartburn	1	.92932	.89003	.83545	.73450	.65603
DAYSC8 =Mean Day Heartburn Severity	.92932	1	.87692	.93779	.64484	.60853
NIGHTNO8=% of Nights with Heartburn	.89003	.87692	1	.93053	.68088	.60207
NIGHTSC8=Mean Night Heartburn Severity	.83545	.93779	.93053	1	.58959	.57368
GELDAY8 =% of Days Gelusil Used	.73450	.64484	.68088	.58959	1	.86510
GELUSIL8=Mean Gelusil/Day	.65603	.60853	.60207	.57368	.86510	1

Study M95-300

	DAYNO8	DAYSC8	NIGHTNO8	NIGHTSC8	GELDAY8	GELUSIL8
DAYNO8 =% of Days with Heartburn	1	.94511	.73964	.69625	.79467	.72690
DAYSC8 =Mean Day Heartburn Severity	.94511	1	.71561	.75077	.77941	.73222
NIGHTNO8=% of Nights with Heartburn	.73964	.71561	1	.94564	.71707	.62636
NIGHTSC8=Mean Night Heartburn Severity	.69625	.75077	.94564	1	.70417	.63507
GELDAY8 =% of Days Gelusil Used	.79467	.77941	.71707	.70417	1	.89472
GELUSIL8=Mean Gelusil/Day	.72690	.73222	.62636	.63507	.89472	1

Table 5
Study M95-300
From a Sas Run Similar to Sponsor's Appendix D.2.4.2
8 Week Diary Data for Intent-To-Treat Patients
Controlling for H. Pylori Status by van Elteren's method

Variables/ H. Pylori Status	N	Mean(SD)	—Quantiles— 25% Median 75%	Lanso. vs PLA
Heartburn in % of Days with Pain				
H.Pylori Negative				
Placebo	20	73%(29%)	80%	
Lansoprazole 15 mg QD	56	32%(35%)	18%	p<.001
Lansoprazole 30 mg QD	60	32%(34%)	18%	p<.001
H.Pylori Positive				
Placebo	19	77%(27%)	83%	
Lansoprazole 15 mg QD	23	21%(24%)	15%	
Lansoprazole 30 mg QD	22	42%(42%)	30%	

Variables/ H. Pylori Status	N	Mean(SD)	—Quantiles— 25% Median 75%	Lanso. vs PLA
Heartburn in Mean Day Pain Severity				
H.Pylori Negative				
Placebo	20	1.1(0.5)	1.17	
Lansoprazole 15 mg QD	56	0.5(0.6)	0.21	p<.001
Lansoprazole 30 mg QD	60	0.5(0.6)	0.21	p<.001
H.Pylori Positive				
Placebo	19	1.3(0.6)	1.27	
Lansoprazole 15 mg QD	23	0.3(0.4)	0.19	
Lansoprazole 30 mg QD	22	0.8(0.9)	0.41	

H. Pylori status was obtained during the pre-treatment period by Serology test.

The p-values are based on van Elteran's method for a difference between indicated groups with H. Pylori status as stratum, and are not particular to H. Pylori status.

Severity is scored as 0=none 1=mild 2=moderate 3=severe

Table 6
Study M95-300
From Sas Run Similar to Sponsor's Appendix D.2.4.2
8 Week Diary Data for Intent-To-Treat Patients
Controlling for H. Pylori Status by van Elteren's method

Variables/ H. Pylori Status	N	Mean(SD)	—Quantiles— 25% Median 75%	Lanso. vs PLA
Heartburn in % Nights with Pain				
H.Pylori Negative				
Placebo	20	55%(39%)	61%	
Lansoprazole 15 mg QD	56	22%(31%)	6%	p<.001
Lansoprazole 30 mg QD	60	30%(32%)	20%	p=.009
H.Pylori Positive				
Placebo	19	61%(35%)	70%	
Lansoprazole 15 mg QD	23	19%(23%)	11%	
Lansoprazole 30 mg QD	22	45%(43%)	33%	

Variables/ H. Pylori Status	N	Mean(SD)	—Quantiles— 25% Median 75%	Lanso. vs PLA
Heartburn in Mean Night Pain Severity				
H.Pylori Negative				
Placebo	20	0.8(0.6)	0.76	
Lansoprazole 15 mg QD	56	0.3(0.5)	0.11	p<.001
Lansoprazole 30 mg QD	60	0.5(0.7)	0.27	p=.016
H.Pylori Positive				
Placebo	19	1.1(0.8)	0.94	
Lansoprazole 15 mg QD	23	0.3(0.3)	0.13	
Lansoprazole 30 mg QD	22	0.9(1.0)	0.49	

The H. Pylori status was obtained during the pre-treatment period by Serology test.

These p-values are based on van Elteran's method for a difference between indicated groups with H. Pylori status as stratum and are not particular to H. Pylori status.

Severity is scored as 0=none 1=mild 2=moderate 3=severe.

Table 7
Study M95-300
from a Sas Run Similar to Sponsor's Appendix D.2.4.2
8 Week Diary Data for Intent-To-Treat Patients
Controlling for H. Pylori Status by van Elteren's method

Variables/ H. Pylori Status	N	Mean(SD)	—Quantiles— 25%	Median	75%	Lanso. vs PLA
Gelusil Use in % of Days						
H.Pylori Negative						
Placebo	20	55%(35%)		54%		
Lansoprazole 15 mg QD	56	27%(32%)		12%		p<.001
Lansoprazole 30 mg QD	60	29%(30%)		19%		p=.001
H.Pylori Positive						
Placebo	19	67%(29%)		72%		
Lansoprazole 15 mg QD	23	23%(23%)		20%		
Lansoprazole 30 mg QD	22	40%(41%)		22%		

Variables/ H. Pylori Status	N	Mean(SD)	—Quantiles— 25%	Median	75%	Lanso. vs PLA
Mean Gelusil per Day						
H.Pylori Negative						
Placebo	20	1.9(1.5)		1.89		
Lansoprazole 15 mg QD	56	0.9(1.3)		0.29		p<.001
Lansoprazole 30 mg QD	60	1.0(1.5)		0.39		p<.001
H.Pylori Positive						
Placebo	19	2.5(2.0)		2.25		
Lansoprazole 15 mg QD	23	0.6(0.7)		0.45		
Lansoprazole 30 mg QD	22	1.4(1.8)		0.41		

The H. Pylori status was obtained during the pre-treatment period by Serology test.

These p-values are based on van Elteran's method for a difference between indicated groups with H. Pylori status as stratum and are not particular to H. Pylori status.

Severity is scored as 0=none 1=mild 2=moderate 3=severe.

Table 8
Study M95-300
from the SAS code supplied by the sponsor, 10mo/27/1997
Analysis of Variance Controlling for H. Pylori Status
Means and Standard Errors of All Effects in the Model
for Groups of Known Treatment and H. Pylori Status

% Days with Pain	Mean(StandardError)		Differ-	Pooled	Z-
Treatment Arm	Negative	Positive	ence	StdErr	score
Placebo	73.3(7.4)	76.7(7.6)			
Lansopra. 15mg QD	32.2(4.4)	20.6(6.9)	11.579	8.213	1.41 p=.16
Lansopra. 30mg QD	32.1(4.3)	42.1(7.1)			
Day Pain Severity	Mean(StandardError)		Differ-	Pooled	Z-
Treatment Arm	Negative	Positive	ence	StdErr	score
Placebo	1.10(.14)	1.26(.14)			
Lansopra. 15mg QD	0.48(.08)	0.30(.13)	0.18449	0.1518	1.22 p=.22
Lansopra. 30mg QD	0.50(.08)	0.78(.13)			
% Nights with Pain	Mean(StandardError)		Differ-	Pooled	Z-
Treatment Arm	Negative	Positive	ence	StdErr	score
Placebo	54.5(7.5)	61.3(7.7)			
Lansopra. 15mg QD	21.6(4.5)	19.3(7.0)	2.3502	8.3080	0.28 p=.78
Lansopra. 30mg QD	29.5(4.3)	44.5(7.2)			
Night Pain Severity	Mean(StandardError)		Differ-	Pooled	Z-
Treatment Arm	Negative	Positive	ence	StdErr	score
Placebo	0.80(.15)	1.11(.15)			
Lansopra. 15mg QD	0.32(.09)	0.28(.14)	0.04409	0.161	0.27 p=.78
Lansopra. 30mg QD	0.50(.08)	0.88(.14)			
% Days Gelusil Used	Mean(StandardError)		Differ-	Pooled	Z-
Treatment Arm	Negative	Positive	ence	StdErr	score
Placebo	54.9(7.1)	66.5(7.3)			
Lansopra. 15mg QD	26.8(4.2)	23.4(6.6)	3.4082	7.836	0.43 p=.66
Lansopra. 30mg QD	28.9(4.1)	40.2(6.7)			
Mean Gelusil/Day	Mean(StandardError)		Differ-	Pooled	Z-
Treatment Arm	Negative	Positive	ence	StdErr	score
Placebo	1.91(.33)	2.52(.33)			
Lansopra. 15mg QD	0.86(.19)	0.63(.30)	0.2332	0.3606	0.65 p=.52
Lansopra. 30mg QD	0.98(.19)	1.40(.31)			

The H. Pylori status was obtained during the pre-treatment period by Serology test.
Severity is scored as 0=none 1=mild 2=moderate 3=severe.
Differences, Pooled StdErr and Z-scores and p-values were computed by this reviewer.