DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS
DIVISION OF BIOMETRICS II

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA:	21281/SE8-014, 21428/SE8-004, 20406/SE5-057
Name of drug:	Prevacid (lansoprazole) for Delayed-Release Oral Suspension
Applicant:	Tap Pharmaceutical Products Inc.
Indication:	Lansoprazole is intended for use in the treatment of GERD in children 12 to 17 years of age.
Project manager:	Ms. Melissa Furness
Clinical reviewer:	Eric Brodsky, MD.
Dates:	Received 12/19/03; user fee 6/23/04.
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Keywords: NDA review, clinical studies, pediatric exclusivity.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

- ✓ Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the efficacy of lansoprazole, assessed from the statistical perspective, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.
- ✓ If from the clinical perspective, the concern for not recruiting sufficient patients with severe esophagitis and GERD symptoms is not critical for the use of the drug in the pediatric population, then the efficacy of lansoprazole, assessed from the statistical perspective based upon the sponsor's study data, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA pediatric supplement (SNDA) submission, two studies, Study M00-158 and Study M97-640, were submitted to support the use of lansoprazole in the treatment of GERD in children with ages 12 to 17.

Study M00-158 was an open-label study in adolescents with GERD, ages 12 to 17 years at 20 investigative sites. The study comprised two periods: a 7 to 14 day pre-treatment and an 8 to 12 week treatment periods. According to disease status (non-erosive GERD or erosive esophgitis), of the 87 enrolled children, 64 with non-erosive GERD were assigned to receive lansoprazole 15mg QD dose for 8 weeks and 23 with erosive esophagitis were assigned to receive lansoprazole 30mg QD dose for 8 to 12 weeks to assess efficacy and safety of lansoprazole. The primary efficacy endpoint was the change in frequency and severity (grading scale: none, mild, moderate, severe, and very severe) of GERD symptoms based on subject diary data from the pretreatment period to the Week 8 treatment period.

Study M97-640 was a randomized, double blind study conducted in the United States with ten sites enrolled 63 children. Of theses, 32 were randomized to receive lansoprazole 15mg QD dose and 31 subjects were randomized to receive lansoprazole 30mg QD dose for 5 days. Efficacy variables included symptom relief based on investigator interview and the percentage of days/nights with heartburn or other predominant symptom, severity of the heartburn or other predominant symptom, and Gelusil use recorded on subject diaries.

In addition, the objective of Study M00-158 was designed to assess the safety and efficacy of lansoprazole in adolescents, ages 12 to 17 years, with GERD while that of Study M97-640 was to assess the safety, pharmacokinetics, and pharmacodynamics of lansoprazole in pediatrics patients. Consequently, to evaluate the clinical efficacy of lansoprazole in adolescents subjects (ages 12 to 17 years) with GERD, in this review, Study M00-158 is considered as a pivotal study while Study M97-640 is a supportive study.

1.3 STATISTICAL ISSUES AND FINDINGS

1.3.1 Pivotal Study M00-158

The applicant found that for all subjects (87), non-erosive GERD subjects (64), and erosive esophagitis subjects (23), statistically significant ($p < 0.001$) reductions from the pretreatment period to the Final Visit Period were observed in the percentage of days the subjects had GERD symptoms, and the average daily severity of GERD symptoms. This reviewer's analyses did not contradict these results. However, there were the following issues:

- ✓ It is noted that less than 30% (26%; 23/87) of enrolled subjects had erosive esophagitis at baseline and only 3.4% (3/87) of subjects had esophagitis grade greater than 2. Therefore, due to lack of sufficient more severe esophagitis subjects enrolled, the efficacy of lansoprazole is not clear for the use in the treatment of more severe esophagitis disease in children of ages 12 to 17 years old.
- ✓ Similarly, most of the enrolled patients (90%; 78/87) were not with the severe GERD symptoms. Due to lack of sufficient subjects enrolled with severe GERD symptoms, the study did not provide sufficient evidence to demonstrate the efficacy of lansoprazole to treat children with more severe GERRD symptoms.

1.3.2 Supportive Study M97-640

Due to the following facts, the sponsor's efficacy analysis on the GERD symptoms assessed by investigators and patient diary data did not demonstrate significant evidence to support the efficacy of lansoprazole in the use of treatment of GERD in children of ages 12 to 17:

- ✓ Instead of assessing the drug efficacy, the objectives of this 5-day study were to evaluate the safety, pharmacokinetics, and pharmacodynamics of once daily (QD) administration of lansoprazole 15 mg or 30 mg in pediatric subjects, ages 12 to 17 with symptomatic GERD.
- ✓ Of 20 types of GERD symptoms assessed by the investigators, at 5% significance level, only 5 and 2 of them respectively for lansoprazole 15 mg and 30 mg showed significantly improved from baseline to Final Visit. In addition, the percentages of enrolled subjects with severe symptoms at baseline were small (less than 17%).
- ✓ Although the enrolled subjects underwent endoscopy exam during Screening Visit, due to short study time period (5-day study), the results of endoscopy analyses at end of the study may not provide meaningful information.

2.0 INTRODUCTION

2.1 OVERVIEW

In Volume 1 of this NDA submission, the sponsor made the following observations with regard to lansoprazole:

Lansoprazole is a compound of the substituted benzimidazole class which inhibits gastric acid secretion. Some lansoprazole-approved indications for adults in the United States include the short-term treatment of symptomatic, non-erosive gastroesophageal reflux disease (GERD), the short-term treatment of erosive esophagitis, and the long-term maintenance treatment of erosive esophagitis.

Lansoprazole, when administered orally to adults, is well absorbed with a reported absolute bioavailability of approximately 80% and a Tmax of less than 2 hours. The terminal elimination half-life is approximately 1.2 hours with no accumulation during multiple, once daily dosing. Lansoprazole is metabolized extensively in the liver, by CYP3A4 to the sulfone metabolite and by CYP2C19 to the hydroxylated sulfinyl metabolite. In addition, TAP has conducted 2 studies (Study M97-640 and M97-808) using lansoprazole in a pediatric population. Both studies showed that the pharmacokinetics of lansoprazole in the adolescents was similar to that previously observed in healthy adult subjects.

In this NDA pediatric supplement (SNDA) submission, two studies, Study M00-158 and Study M97-640, were submitted to support the use of lansoprazole in the treatment of GERD in children with ages 12 to 17.

Study M00-158 was an open-label study in adolescents with GERD, ages 12 to 17 years at 20 investigative sites. The study comprised two periods: a 7 to 14 day pre-treatment and an 8 to 12 week treatment periods. According to disease status (non-erosive GERD or erosive esophgitis), of the 87 enrolled children, 64 with non-erosive GERD were assigned to receive lansoprazole 15mg QD dose for 8 weeks and 23 with erosive esophagitis were assigned to receive lansoprazole 30mg QD dose for 8 to 12 weeks to assess efficacy and safety of lansoprazole. The primary efficacy endpoint was the change in frequency and severity (grading scale: none, mild, moderate, severe, and very severe) of GERD symptoms based on subject diary data from the pretreatment period to the Week 8 treatment period.

Study M97-640 was a randomized, double blind study conducted in the United States with ten sites enrolled 63 children. Of theses, 32 were randomized to receive lansoprazole 15mg QD dose and 31 subjects were randomized to receive lansoprazole 30mg QD dose for 5 days. Efficacy variables included symptom relief based on investigator interview and the percentage of days/nights with heartburn or other predominant symptom, severity of the heartburn or other predominant symptom, and Gelusil use recorded on subject diaries.

In addition, the objective of Study M00-158 was designed to assess the safety and efficacy of lansoprazole in adolescents, ages 12 to 17 years, with GERD while that of Study M97-640 was to assess the safety, pharmacokinetics, and pharmacodynamics of lansoprazole in pediatrics patients. Consequently, to evaluate the clinical efficacy of lansoprazole in adolescent subjects (ages 12 to 17 years) with GERD, in this review, Study M00-158 is considered as a pivotal study while Study M97-640 is a supportive study.

2.2 DATA SOURCES

To assess the clinical efficacy of lansoprazole in adolescent patients (ages 12 to 17) with GERD, this reviewer reviewed NDA Volumes 1 to 19, dated December 19, 2003. Data used by this

reviewer's statistical analysis was submitted by the sponsor on February 24, 2004, located at "\\Cdsesub1\n20406\S_057\2004-24-04\crt\datasets\".

3.0 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Study M00-158

Study Design and Endpoints

This open-label study was designed to assess the safety and efficacy of once daily administration of lansoprazole 15 mg and 30 mg in adolescents, ages 12 to 17 years, with GERD including non-erosive GERD and erosive esophagitis.

Eighty subjects were planed to be enrolled in the study. Of the 80 subjects, a minimum of 20 subjects respectively with non-erosive GERD (assigned to Treatment Group I defined below) and erosive esophagitis (Treatment Group II) were to be enrolled. The remaining subjects were to be enrolled in the appropriate treatment group based on endoscopic findings. The study comprised two periods: a 7 to 14 day pre-treatment and an 8 to 12 week treatment periods. During the pretreatment period, a pretreatment diary and antacid were dispensed; subjects/parents/caregivers, as necessary, were to record the severity of their GERD symptoms and the frequency of antacid use in the diary. Symptoms also were assessed by investigator interview. In addition, all subjects had endoscopies during the pretreatment period. Subjects with erosive esophagitis (esophagitis Grade ≥2 per TAP Grading Scale) at the Pretreatment Visit had follow-up endoscopies at the Week 8 Visit. Subjects with unhealed erosive esophagitis at the Week 8 Visit were treated for an additional 4 weeks with endoscopies repeated at Week 12 Visit.

Subjects who had completed all pretreatment procedures and met all eligibility requirements were assigned to one of the following two treatment groups based upon the disease status (non-erosive GERD or erosive esophagitis):

- Treatment group I - subjects with non-erosive GERD at the pretreatment visit (esophagitis Grade ≤ l per TAP grading scale) were to be treated with lansoprazole 15 mg, administered orally, once daily for 8 weeks.
- Treatment group II - subjects with erosive esophagitis at the pretreatment visit (esophagitis Grade ≥2 per TAP grading scale) were to be treated with lansoprazole 30 mg, administered orally, once daily for 8 weeks. In addition, subjects with unhealed erosive esophagitis at the Week 8 Visit were to be treated for another 4 weeks.

Antacid was provided during the treatment period for relief of discomfort as needed. Throughout the treatment period, subjects maintained a daily diary, in which they recorded severity of GERD symptom(s), the frequency and amount of antacid usage, and study drug dosing. In addition, at Weeks 4, 8, and 12 (if applicable), the subject answered a questionnaire regarding overall GERD

symptom relief during the preceding week as compared with before treatment. At the Week 4, 8, and 12 Visits, the following procedures were completed: a physical examination, adverse event assessment, concomitant medication assessment, laboratory evaluations, and overall GERD symptom assessment based on investigator interview.

All efficacy analyses were carried out using intent-to-treat population comprising subjects who received at least one dose of study drug and had efficacy measurements within the defined evaluated time period. Data from all subjects who entered the treatment period and received at least one dose of study drug were included in the safety analyses.

The sponsor indicated that due to few subjects expected to have treatment beyond Week 8, efficacy analyses at Week 12 (for subjects whose treatment was extended) per protocol for diary and investigator interview symptom assessment were not carried out.

The primary efficacy endpoint was the change in frequency and severity (grading scale: none, mild, moderate, severe, and very severe) of GERD symptoms based on subject diary data from the pretreatment period to the Week 8 treatment period. The percentage (frequency) of days with GERD symptoms and the average GERD symptom severity score based on 0 for none, 1 for mild, 2 for moderate, 3 for severe, and 4 for very severe was calculated by treatment group during the pretreatment period and during the first 8 weeks of treatment using diary data recorded on or prior to Day 1 and Days 2-57, respectively.

The secondary efficacy endpoints were 1) the percentage of subjects with pretreatment endoscopically-proven erosive esophagitis who had complete healing; 2) the change in antacid use from the pretreatment period to the Week 4, Week 8, and Final Visit Periods based on subject diary data; 3) the change in frequency and severity of GERD symptoms from the pretreatment period to during the first 4-week treatment period and over the entire treatment period based on subject diary; 4) and the change from the pretreatment period to the Week 4, Week 8, and Final Visits in overall GERD symptom severity (grading scale: none, mild, moderate, and severe) based on investigator interview.

For the sample size determination, 80 adolescents, aged 12 to 17 years, were to be enrolled in this study (approximately 6 subjects per investigative site). The sponsor indicated that given this sample size, if the incidence rate for an adverse event was 10%, the probability of observing an adverse event in four or more subjects is 0.96.

Statistical Methodologies

The change from the pretreatment period to each evaluated time interval during the treatment period in the frequency and severity of GERD symptoms and the change in antacid use based on subject diary data were analyzed using the sign test. The change from the pretreatment period to each evaluated time point in overall GERD symptom severity based on investigator interview was also analyzed using the sign test.

In addition, the percentage of subjects with pretreatment endoscopically-proven erosive esophagitis who had complete healing was tabulated.

Patient Disposition

Table 3.1.1.1 presents the number of subjects planned and analyzed by treatment group.

Table 3.1.1.1 (Sponsor's) Number of subjects planed and analyzed by treatment group

	All Lansoprazole-Treated Subjects	Lansoprazole 15 mg QD	Lansoprazole 30 mg QD
Number of subjects planned	80	Minimum 20	Minimum 20
Number of subjects enrolled	87	64	23
Number of subjects received study drug (analyzed)	87	64	23

Table 3.1.1.1 indicates that eighty-seven adolescent subjects were enrolled in the study and treated with lansoprazole. Subjects were assigned to receive either lansoprazole 15 mg or 30 mg based on the results of their pretreatment endoscopies. Sixty-four subjects with non-erosive GERD (esophagitis Grade ≤1 per TAP grading scale) were assigned to receive lansoprazole 15 mg and 23 subjects with erosive esophagitis (esophagitis Grade ≥ 2 per TAP grading scale) were assigned to receive lansoprazole 30 mg.

In addition, five subjects in the lansoprazole 15 mg treatment group were prematurely discontinued from the study: 3 for symptomatic therapeutic failure, 1 due to an adverse event, and 1 for poor compliance. No subjects were prematurely discontinued from the lansoprazole 30 mg treatment group.

Demographics and Baseline Characteristics

All subjects enrolled were considered by the investigators to have symptomatic GERD (including erosive and nonerosive esophagitis subjects). Table 3.1.1.2 (extracted from Table 11.2a at page 63 of the sponsor's electric submission for Clinical/Statistical Study Report) presents the demographic information for all lansoprazole-treated subjects, and separately, for lansoprazole 15 mg and 30 mg dose groups.

Table 3.1.1.2 (Sponsor's) Baseline Subject Demographics

Demographic Characteristic	All Subjects	Non-erosive GERD Lansoprazole 15 mg QD	Erosive Esophagitis Lansoprazole 30 mg QD
Gender			
N	87	64	23
Female	60.9% (53)	64.1% (41)	52.2% (12)
Male	39.1% (34)	35.9% (23)	47.8% (11)
Race			
N	87	64	23
Caucasian	80.5% (70)	79.7% (51)	82.6% (19)
Black	16.1% (14)	15.6% (10)	17.4% (4)
Other[a]	3.4% (3)	4.7% (3)	0
***H. pylori* Status**[b]			
N	86	63	23
Positive	3.5% (3)	1.6% (1)	8.7% (2)
Negative	96.5% (83)	98.4% (62)	91.3% (21)
Age (years)			
N	87	64	23
Mean (SD)	14.1 (1.6)	14.1 (1.7)	14.3 (1.3)
Range	11-17[c]	11-17[c]	13-17
Weight - Females (pounds)			
N	53	41	12
Mean (SD)	135.4 (31.3)	135.6 (32.3)	134.6 (28.9)
Range	74-222	74-222	100-198
Weight - Males (pounds)			
N	34	23	11
Mean (SD)	139.7 (49.4)	132.0 (46.8)	155.7 (52.9)
Range	65-290	65-225	86-290
Height - Females (inches)			
N	53	41	12
Mean (SD)	63.2 (2.5)	63.2 (2.7)	63.3 (2.0)
Range	57-69	57-69	60-66
Height - Males (inches)			
N	33	22	11
Mean (SD)	65.3 (4.8)	64.3 (5.1)	67.3 (3.6)
Range	54-73	54-73	62-72

Table 3.1.1.2 indicated that the except for gender and H.pylori status, the baseline demographics were comparable between the two treatment groups, lansoprazole 15 mg QD and lansoprazole 30 mg QD.

As for the baseline characteristics, of the 87 subjects, 30 had a history of GERD less than one year, 13 had a one- to two-year history of GERD, 28 had a history of GERD greater than two years and less than five years, and 16 had a history of GERD greater than five years.

The most frequently reported predominant GERD symptoms were heartburn, abdominal / stomach pain, epigastric pain, chest pain, regurgitation, sour taste, nausea, and vomiting. Some subjects reported more than one predominant symptom. In addition, fifty-three (61%) of the 87 subjects had received previous gastrointestinal therapy within 12 months prior to the study start and 18 of these had been treated previously with a PPI.

Sponsor's Efficacy Analysis Results and Conclusions

For symptom relief assessed using the subject diary, the Week 4 Period includes the time from Day 1 through the first 4-week treatment period; the Week 8 Period includes the time from Day 1 through the first 8-week treatment period; and the Final Visit Period includes the time from Day 1 through the entire treatment period (8 or 12 weeks). A summary of the analysis results on diary data is presented in Table 3.1.1.3 (extracted from the sponsor's Table 11.4a at page 68 of Volume 7).

Table 3.1.1.3 (Sponsor's) Diary results from the pretreatment period to Week 4, Week 8 and Final Visit [a]

	Pretreatment Period Median	Week 4 Period Median	Week 8 Period Median	Final Visit Period Median
All Subjects (N=87)				
GERD Symptioms				
% of Days with GERD Symptoms	88.9	42.9*	33.3*	33.3*
Average Daily Severity [b] of GERD Symtoms	1.6	0.6*	0.5*	0.5*
Antacid Use				
% of Days Used	54.5	7.1*	5.5*	5.5*
Average number of Teaspoons/Day	1.4	0.1*	0.2*	0.2*
Non-erosive GERD subjects (N=64) Lansoprazole 15 mg QD				
GERD Symptioms				
% of Days with GERD Symptoms	90.7	50.9*	43.1*	43.1*
Average Daily Severity [b] of GERD Symtoms	1.6	0.7*	0.6*	0.6*
Antacid Use				
% of Days Used	55.1	9.1*	7.3*	7.1*
Average number of Teaspoons/Day	1.3	0.3*	0.3*	0.3*
Erosive Esophagitis Subjects (N=23) Lansoprazole 30 mg QD				
GERD Symptioms				
% of Days with GERD Symptoms	84.6	18.5*	16.0*	15.7*
Average Daily Severity [b] of GERD Symtoms	1.9	0.3*	0.2*	0.2*
Antacid Use				
% of Days Used	50.0	0.0*	1.8*	1.7*
Average number of Teaspoons/Day	1.6	0.0*	0.1*	0.1*

a: Each subject's daily diary results were averaged over the evaluated time period and the median value for treatment group is reported in this table; b: Severity score as 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe;

***: Statistically significant different from pretreatment at significance level of 0.001 using Sign rank tests.**

Table 3.1.1.3 indicates that for all subjects (87), non-erosive GERD subjects (64), and erosive esophagitis subjects (23), statistically significant ($p < 0.001$) reductions from the pretreatment period to the Week 4, Week 8, and Final Visit Periods were reported in the percentage of days the subjects had GERD symptoms, the average daily severity of GERD symptoms, the percentage of days antacid was used, and the average number of teaspoons of antacid taken per day

As for the relief of the overall GERD symptoms judged by the subjects at the Final Visit, Table 3.1.1.4 (extracted from the sponsor's Table 11.4b at page 71 of Volume 7) presents the results.

Table 3.1.1.4 (Sponsor's) Diary Results for Relief of Overall GERD Symptoms judged by the subjects at the Final Visit

Overall GERD Symptoms	All Subjects (N = 82)[a]	Non-erosive GERD Lansoprazole 15 mg QD (N=59)	Erosive Esophagitis Lansoprazole 30 mg QD (N=23)
	n (%)	n (%)	N (%)
Better	60 (73.2%) *	42 (71.2%) *	18 (78.3%) *
No change	19 (23.2%)	14 (23.7%)	5 (21.7%)
Worse	3 (3.7%)	3 (5.1%)	0

a: No data available for 5 subjects;
*** : Significant higher percentage on "better" declared at significance level of 0.001 using Sign tests.**

Table 3.1.1.4 shows that a statistically significantly ($p < 0.001$) higher percentage of subjects in all treatment categories (all subjects, lansoprazole 15 mg, and lansoprazole 30 mg) judged their overall GERD symptoms as "better" than the percentage judged as having "no change" or being "worse."

In addition, for the healing of erosive esophagitis, twenty-three subjects who had erosive esophagitis at the baseline endoscopy had follow-up endoscopies at the Final Visit (Week 8 or Week 12). One subject (No. 424) had his endoscopy for the Week 8 Visit and was not eligible for this analysis. However, his endoscopy did show healing (Grade 0) of esophagitis. Analysis of healing rates for the 22 eligible erosive esophagitis subjects is presented in Table 3.1.1.5.

Table 3.1.1.5 (Sponsor's) Analysis of Healing Rates for Erosive Esophagitis Subjects

Visit	Erosive Esophagitis Subjects	
	% Healed[a]	n/N
Week 8 Visit	95.5%	21/22
Week 12 Visit	0	0/1
Final Visit	95.5%	21/22

a: Defined as a return of the esophageal mucosa to Grade 0 or Grade 1.

Table 3.1.1.5 showed that of the twenty-two subjects, twenty-one were healed at the Week 8 Visit. One subject (No. 471) was unhealed at the Week 8 Visit and received an additional 4 weeks of treatment with lansoprazole 30 mg QD. His esophagitis (Grade 2) remained unchanged from Baseline at both the Week 8 and the Week 12 Visits.

Finally, for the overall GERD symptoms assessed by investigator interview, the sponsor indicated that the majority subjects experienced overall GERD symptoms resolved or improved from Baseline to the Final Visit. The difference between Baseline and Final Visit was statistically significant for the two treatment groups and for all subjects combined ($p < 0.001$). Actually, among all subjects, 63 (74%) of 85 who had Baseline symptoms were resolved or improved by the Final Visit based on investigator assessment of overall GERD symptoms. Of the 63 resolved or improved subjects, 41 (65%; 41/63) were non-erosive GERD subjects treated with lansoprazole 15 mg QD and 22 (100%; 22/22) were erosive esophagitis subjects treated with lansoprazole 30 mg QD. The sponsor further emphasized that results for all subjects were similar at the Week 4 and Week 8 assessments.

Reviewer's Analysis and Comments

In order to validate the sponsor's efficacy claim, this reviewer first, comments on the status of Baseline GERD disease for the enrolled subjects and then, performs the following two analyses 1) Exact test on overall GERD symptoms and 2) Subgroup analysis. Data used in this reviewer's analysis were submitted by the sponsor on Feb., 24, 2004. Subgroup analyses are reported in section 4 of review.

Reviewer's comments on Baseline GERD disease conditions

The Baseline esophagitis grades and Baseline GERD symptoms assessed by the investigator's interview are presented in Table 3.1.1.6 (extracted from sponsor's Table 11.2b in Volume 7) and Table 3.1.1.7 (extracted from sponsor's Table 11.2f in Volume 7), respectively, for all enrolled subjects.

Table 3.1.1.6 Esophagitis Grade at Baseline Endoscopy

		All Subjects (N = 87)
	Baseline Esophagitis Grade	**n (%)**
Non-erosive GERD		
	Grade 0	18 (20.7%)
	Grade 1	46 (52.9%)
Erosive Esophagitis		
	Grade 2	20 (23.0%)
	Grade 3	3 (3.4%)
	Grade 4	0

Table 3.1.1.7 (sponsor's) Baseline Overall GERD Symptoms Based on Investigator Assessment

	Severity of Overall GERD Symptoms				
	N	**None**	**Mild**	**Moderate**	**Severe**
All Subjects	87	1	16	61	9
Non-erosive GERD Subjects (Lansoprazole 15 mg QD)	64	0	15	45	4
Erosive Esophagitis Subjects (Lansoprazole 30 mg QD)	23	1	1	16	5

For esophagitis disease, Table 3.1.1.6 indicates that only 26% (23/87) of enrolled subjects had erosive esophagitis at baseline and only 3.4% (3/87) of subjects had esophagitis grade greater than 2. Therefore, due to lack of sufficient more severe esophagitis subjects enrolled, the efficacy of lansoprazole is not clear for the use in the treatment of more severe esophagitis disease in children of ages 12 to 17 years old.

Similarly, for overall GERD symptoms, Table 3.1.1.7 indicates that low percentages of enrolled subjects for the two treatment groups had severe baseline overall GERD symptom assessed by the investigator's interview (6% for lansoprazole 15 mg and 22% for lansoprazole 30 mg), showing most of the enrolled patients not with the severe GERD symptoms. As a result, due to lack of sufficient subjects enrolled with severe GERD symptoms, the study did not provide sufficient evidence to demonstrate the efficacy of lansoprazole to treat children with more severe GERRD symptoms.

Reviewer's analysis

i.) Exact test on overall GERD symptoms

For the analysis, this reviewer applied exact test to the improvements (better responses) on the overall GERD symptoms from baseline to the Final Visit using patient diary data from ITT population. The exact test is used for testing the null hypothesis (H_0) that the probability of improvements is not greater than .5. Table 3.1.1.8 presents the results by treatment group.

Table 3.1.1.8 (Reviewer's) Diary results of exact test for improvements on GERD symptoms at the Final Visit

TREATMENT GROUP	BETTER RESPONSE % (n/N)	P-VALUE FOR TESTING H_0 [a]
Lansoprazole 15 mg QD (N=59)	71% (42/59)	0.0013*
Lansoprazole 30 mg QD (N=23)	78% (18/23)	0.009*

a: null hypothesis (H_0) that probability of improvements is not greater than .5.
*: Significant at the .05 significance level.

Table 3.1.1.8 indicates that for both treatment groups, the patient had a probability significantly higher than 50% for the improvement on the relief of overall GERD symptoms at Final Visit when compared with the pre-treatment period.

3.1.2 Study M97-640

Study Design and Endpoints

This was a randomized, double-blind study designed to evaluate the pharmacokinetics and pharmaeodynamics of once daily administration of lansoprazole 15mg or 30mg in adolescents, ages 12 to 17 with symptomatic GERD.

This study was conducted in the United States with ten sites enrolled 63 children with symptomatic, endoscopically and/or historically proven GERD. Of these, 32 were randomized

to receive lansoprazole 15mg QD dose and 31 subjects were randomized to receive lansoprazole 30mg QD dose for 5 days. Subjects were to be assessed the drug efficacy and safety throughout the treatment period.

Efficacy variables included symptom relief based on investigator interview and the percentage of days/nights with heartburn or other predominant symptom, severity of the heartburn or other predominant symptom, and Gelusil use recorded on subject diaries.

As for the sample size, the sponsor indicated that a total of 60 subjects were to be enrolled into the study, with 30 subjects assigned to each of the two treatment groups. If the incidence rate for an adverse event was 15% for a treatment, the probability that the event would be observed in three or more subjects in a group was 0.8.

Patient Disposition

Table 3.1.2.1 presents the number of subjects planed and analyzed by treatment group.

Table 3.1.2.1 (Sponsor's) Number of subjects planed and analyzed by treatment group

	Lansoprazole 15 mg QD	Lansoprazole 30 mg QD
Number of subjects planned	30	30
Number of subjects enrolled	32	31
Number of subjects received study drug	32	31

Table 3.1.2.1 indicates that a total of 63 adolescent subjects were enrolled in the study. Of these, 32 were randomized to receive lansoprazole 15 mg QD and 31 were randomized to receive lansoprazole 30 mg QD. One subject (b) (6) in the lansoprazole 15 mg QD group was prematurely discontinued from the study after four days of therapy due to adverse events of peripheral edema, maculopapular rash, and urticaria. Therefore, a total of 62 subjects (31 lansoprazole 15 mg QD and 31 lansoprazole 30 mg QD) completed dosing in the study and analyzed.

Baseline Demographics

There were no statistically significant differences between the treatment groups with respect to gender, race, weight, or height. In addition, the mean age of the 63 adolescent subjects enrolled in this study was 14.1 years (range: 11 to 17 years) and the mean weight of the male and female subjects was 137.3 and 126.1 pounds, respectively.

Fifty-one percent (51%) of the subjects were male and 49% of the subjects were female. However, the distribution of males and females by treatment group showed that the majority of the subjects in the lansoprazole 15 mg QD group were male (63%) while the majority of the subjects in the lansoprazole 30 mg QD group were female (61%). Most of the subjects were Caucasian (79%), followed by black (10%), and "other" races (11%).

Statistical Methodologies

Symptom relief from Baseline to Day 5 Visit, based on investigator interview, was tabulated. The average severity score and the percentage of days and nights with heartburn or other predominant symptom as recorded in the subject diaries during the pre-treatment and treatment periods were summarized.

Sponsor's Efficacy analysis Results and Conclusions

i. Results for symptom assessments based on investigator's interview

At 5% significance level, no statistically significant differences were observed between the lansoprazole 15 mg QD and lansoprazole 30mg QD groups for relief of heartburn based on investigator interview. However, for each of the two treatment groups, subjects had statistically significant reductions from Baseline to the Day 5 Visit in the severity of heartburn. Additionally, from baseline to the Day 5 Visit, subjects in the lansoprazole 15mg QD group had statistically significant reductions in the severity of regurgitation, nausea, abdominal pain, and flatulence while subjects in the lansoprazole 30mg QD group had a statistically significant reduction in the severity of abdominal distention.

ii. Results for diary data analysis

Subjects in both the lansoprazole 15 mg QD and lansoprazole 30 mg QD groups demonstrated reductions [but no results from statistical inferences were reported] from the pretreatment period to the Day 5 Visit in the percentage of days with heartburn or other predominant symptom, the percentage of nights with heartburn or other predominant symptom, the percentage of days or nights with heartburn or other predominant symptom, the severity of the heartburn or other predominant symptom, the percentagc of days GeIusil was used, and the average number of Gelusil tablets used per day during the treatment period. In addition, no statistically significant differences were observed between the two treatment groups for any of these diary variables during the pretreatment period or the treatment period. Table 3.1.2.2 presented a summary of the diary results during the pretreatment and treatment periods by treatment group.

Table 3.1.2.2 (Sponsor's) Diary results during the pretreatment and treatment periods

Variable	Lansoprazole Group (Median)			
	15 mg QD		30 mg QD	
	Pretreatment (N=31)[a]	Treatment (N=32)	Pretreatment (N=31)	Treatment (N=31)
Daytime Heartburn or Other Predominant Symptom				
% of Days with Heartburn or Other Predominant Symptom	85.7	77.5	62.5	25.0
Average Severity/Day[b]	1.25	0.90	1.00	0.50
Nighttime Heartburn or Other Predominant Symptom				
% of Nights with Heartburn or Other Predominant Symptom	16.7	0.0	50.0	25.0
Average Severity/Night[b]	0.25	0.0	0.67	0.25
Heartburn or Other Predominant Symptom (Day or Night)				
% of Days or Nights with Heartburn or Other Predominant Symptom	85.7	77.5	85.7	50.0
Average Maximum Severity[c]	1.29	0.90	1.25	0.75
Gelusil® Use				
% of Days Used	50.0	20.0	50.0	0.0
Average Number of Tablets Taken/Day	1.13	0.40	0.78	0.0

a One subject did not have diary results during the Pretreatment Period.
b Severity scored as: none = 0; mild = 1; moderate = 2; and severe = 3.
c Maximum severity of day or night heartburn or other predominant symptom scored as: none = 0; mild = 1; moderate = 2; and severe = 3.
Cross-reference: Tables 14.2__2.1 and 14.2__2.2

Statistical Reviewer's analysis

For this study, there is no statistical analysis performed by this reviewer.

3.2 EVALUATION OF SAFETY

3.2.1 Study M00-158

Of the 87 subjects enrolled, fifty-seven (65.5%) experienced one or more treatment-emergent adverse event(s). Headache in 14 (16.1%) subjects and abdominal pain in 12 (13.8%) subjects were the most frequently reported adverse events. As for the treatment related adverse events, the sponsor indicated that twelve (18.8%) of 64 subjects in the non-erosive GERD treatment group (lansoprazole 15 mg QD) and 1 (4.3%) of 23 subjects in the erosive esophagitis treatment group (lansoprazole 30 mg QD) experienced adverse events that were considered possibly or probably treatment-related. No adverse event was considered to be definitely treatment-related.

Most adverse events were mild or moderate in severity. Four subjects reported SAEs, 3 of these experienced 4 events (suicide attempt, gastroenteritis, dehydration, accidental injury) that were described as not related to study drug and 1 of these experienced an event (cholecystitis) that was described as unlikely to be related to study drug. One subject was terminated prematurely from the study due to dizziness and vomiting described as possibly related to study drug.

3.2.2 Study M97-640

The incidence of treatment-emergent adverse events was comparable between the lansoprazole 15 mg QD and the lansoprazole 30 mg QD treatment groups (28% and 39%, respectively). Pharyngitis (6%; 2/32) was the most commonly reported treatment-emergent adverse event among subjects in the lansoprazole 15 mg QD group, whereas headache (13%, 4/3 1) was the

most commonly reported treatment-emergent adverse event among subjects in the lansoprazole 30 mg QD group. The sponsor indicated that most of the adverse events were not considered related to study drug administration and all adverse events were considered to be mild or moderate in severity.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE, AND AGE

Study M00-158

In order to assess the consistency of the treatment effect of prevacid across subgroups, this reviewer performed the subgroup analysis using signed rank test on the percentage of days with GERD symptoms change from baseline to Week 8 Visit (PDGSCH8) and average daily severity of GERD symptoms change from baseline to Week 8 Visit (ADSGSCH8) based upon ITT patient population. Since this NDA submission is for pediatrics use on children from ages 12 to 17, the subgroups analyzed are only for Gender (Male and Female), Race (Caucasian and Non-Caucasian).

Gender (Females and Males)

Table 3.1.1.9 presents the results of treatment efficacy comparisons for prevacid by gender.

Table 3.1.1.9 (Reviewer's) GERD symptom changes from baseline to Week 8 Visit using ITT population

	CHANGE IN % DAYS WITH GERD		CHANGE IN AVERAGE DAILY SEVERITY	
	median	(p-value)[1]	median	(p-value)
Females				
Lansoprazole 15 mg QD (N=41)	-24.1	(< 0.0001*)	-0.54	(< 0.0001*)
Lansoprazole 30 mg QD (N=12)	-49.8	(0.001*)	-1.12	(0.0005*)
Males				
Lansoprazole 15 mg QD (N=23)	-41.5	(< 0.0001*)	-0.82	(< 0.0001*)
Lansoprazole 30 mg QD (N=11)	-54.4	(0.001*)	-1.0	(0.001*)

[1]: P-Value for testing GERD symptom changes from baseline to Week 8 Visit using Sign rank test;
*: Significant at significance level of .05.

For both females and males, Table 3.1.1.9 indicates that at significance level of 0.05, GERD symptom changes from Baseline to Week 8 Visit assessed by percentage of days with GERD symptoms and average daily severity with GERD symptoms are statistically significantly reduced for both treatment groups.

Race (Caucasian and Non-Caucasian)

Table 3.1.1.10 presents the results of treatment efficacy comparisons for prevacid by race.

Table 3.1.1.10 (Reviewer's) GERD symptom changes from baseline to Week 8 Visit using ITT population

	CHANGE IN % DAYS WITH GERD		CHANGE IN AVERAGE DAILY SEVERITY	
	median	(p-value)[1]	median	(p-value)
Caucasian				
Lansoprazole 15 mg QD (N=51)	-31.5	(< 0.0001*)	-0.78	(< 0.0001*)
Lansoprazole 30 mg QD (N=19)	-55.8	(< 0.0001*)	-1.11	(< 0.0001*)
Non-Caucasian				
Lansoprazole 15 mg QD (N=13)	-39.8	(0.002*)	-0.83	(0.005*)
Lansoprazole 30 mg QD (N=4)	-15.5	(0.25)	-0.72	(0.13)

[1]: P-Value for testing GERD symptom changes from baseline to Week 8 Visit using Sign rank test;
*: Significant at significance level of .05.

Similarly, for Caucasian and Non-Caucasian patients, Table 3.1.1.10 indicates that at significance level of 0.05, GERD symptom changes from baseline to Week 8 Visit assessed by percentage of days with GERD symptoms and average daily severity with GERD symptoms are statistically significantly reduced for both treatment groups with the exception of the Non-Caucasian patients in the lansoprazole 30 mg group. However, there were only four patients in this subgroup and the medians of both outcome variables are numerically less than zero, indicating the results in favor of the study drug lansoprazole 30 mg.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS - Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

5.1.1 Pivotal Study M00-158

The applicant found that for all subjects (87), non-erosive GERD subjects (64), and erosive esophagitis subjects (23), statistically significant ($p < 0.001$) reductions from the pretreatment period to the Final Visit Period were observed in the percentage of days the subjects had GERD symptoms, and the average daily severity of GERD symptoms. This reviewer's analyses did not contradict these results. However, there were the following issues:

- It is noted that less than 30% (26%; 23/87) of enrolled subjects had erosive esophagitis at baseline and only 3.4% (3/87) of subjects had esophagitis grade greater than 2. Therefore, due to lack of sufficient more severe esophagitis subjects enrolled, the efficacy of lansoprazole is not clear for the use in the treatment of more severe esophagitis disease in children of ages 12 to 17 years old.
- Similarly, most of the enrolled patients (90%; 78/87) were not with the severe GERD symptoms. Due to lack of sufficient subjects enrolled with severe GERD symptoms, the study did not provide sufficient evidence to demonstrate the efficacy of lansoprazole to treat children with more severe GERRD symptoms.

5.1.2 Supportive Study M97-640

Due to the following facts, the sponsor's efficacy analysis on the GERD symptoms assessed by investigators and patient diary data did not demonstrate significant evidence to support the efficacy of lansoprazole in the use of treatment of GERD in children of ages 12 to 17:

- Instead of assessing the drug efficacy, the objectives of this 5-day study were to evaluate the safety, pharmacokinetics, and pharmacodynamics of once daily (QD) administration of lansoprazole 15 mg or 30 mg in pediatric subjects, ages 12 to 17 with symptomatic GERD.
- Of 20 types of GERD symptoms assessed by the investigators, at 5% significance level, only 5 and 2 of them respectively for lansoprazole 15 mg and 30 mg showed significantly improved from baseline to Final Visit. In addition, the percentages of enrolled subjects with severe symptoms at baseline were small (less than 17%).
- Although the enrolled subjects underwent endoscopy exam during Screening Visit, due to short study time period (5-day study), the results of endoscopy analyses at end of the study may not provide meaningful information.

5.2 CONCLUSIONS AND RECOMMENDATIONS

- Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the efficacy of lansoprazole, assessed from the statistical perspective, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.
- If from the clinical perspective, the concern for not recruiting sufficient patients with severe esophagitis and GERD symptoms is not critical for the use of the drug in the pediatric population, then the efficacy of lansoprazole, assessed from the statistical perspective based upon the sponsor's study data, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.

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