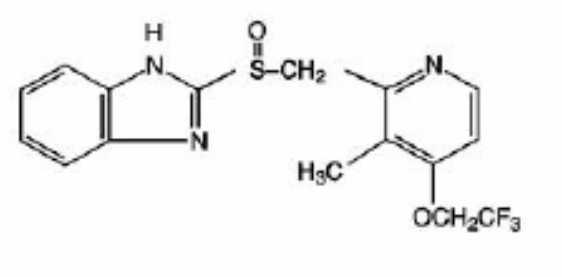
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL & COAGULATION DRUG PRODUCTS

Medical Officer's Review of Efficacy Supplements: 20-406/S-057, 21-281/S-014, and 21-428/S-004

PREVACID (lansoprazole)



NDA#/Supplement#:	**20-406/S-057, 21-281/S-014, and 21-428/S-004**
Proposed Indications:	**The short-term treatment of non-erosive GERD and erosive esophagitis (EE) in pediatric patients between 12 and 17 years old**
Drug Class:	Substituted benzimidazole proton pump inhibitor
Formulation and Route of administration:	Oral capsule
Proposed regimens:	Non-erosive GERD: 15 mg once daily for up to 8 weeks EE: 30 mg once daily for up to 8 weeks
Applicant:	TAP Pharmaceutical Products Inc.
Documents Reviewed:	Electronic submitted sNDA and Data Sets
Division Director:	Robert Justice, M.D., M.S.
Deputy Director:	Joyce Korvick, M.D., M.P.H.
Medical Team Leader:	Ruyi He, M.D.
Medical Officer:	Eric Brodsky, M.D.
Biopharmaceutics Reviewer:	Suliman Al-Fayoumi, Ph.D.
Statistician:	Wen-Jen Chen, Ph.D.
Project Manager:	Melissa Furness

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) are recommended for approval for the treatment of GERD [non-erosive gastroesophageal reflux disease (GERD) and erosive esophagitis (EE)] in pediatric patients between 12 and 17 years old.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

From a clinical perspective, this medical officer does not recommend phase 4 studies or risk management steps in pediatric GERD patients between 12 and 17 years old.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

TAP Pharmaceutical Products Inc. (TAP) submitted two clinical study reports (Studies M97-640 and M00-158) to support the efficacy and safety of lansoprazole in the treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old. These studies, conducted exclusively in the United States, included a total of 150 adolescent GERD patients (between 12 and 17 years old) who all received upper endoscopies at baseline.

Study M97-640 was a randomized, double-blinded, multi-center (10 sites), pharmacokinetic (PK), and pharmacodyamic (PD) trial of lansoprazole in the treatment of pediatric GERD patients, ages 12 to 17 years old. Patients were randomized to two lansoprazole treatment groups: 15 mg/day (n = 32) or 30 mg/day (n = 31) for 5 consecutive days. The PKs and PDs of lansoprazole were assessed by plasma concentrations and 24-hour pH monitoring, respectively.

Study M00-158 was an uncontrolled, open-label, multi-center (20 sites) trial of lansoprazole in the treatment of GERD in pediatric patients, ages 12 to 17 years. Baseline upper endoscopies categorized pediatric GERD patients into two groups: non-erosive GERD (n = 64) and EE (n = 23). Non-erosive GERD patients received 15 mg of oral lansoprazole once daily for 8 weeks and EE patients received 30 mg of lansoprazole once daily for 8 weeks. EE patients with completely healed

EE after 8 weeks of treatment were considered to have completed the therapy. In contrast, EE patients with unhealed EE after 8 weeks of treatment were treated with 30 mg of lansoprazole for an additional 4 weeks (12 weeks of total treatment).

The safety evaluation included assessment of the data from the two clinical studies, post-marketing data, and literature reports in pediatric patients between 12 and 17 years old, who received lansoprazole.

B. Efficacy

Study M00-158: Sixty-four non-erosive GERD patients were treated with 15 mg of lansoprazole for 8 weeks and 23 EE patients were treated with 30 mg of lansoprazole for 8 to 12 weeks. The efficacy results are summarized below.

The co-primary endpoints were the change from baseline in the frequency and severity of GERD symptoms during the 8 week treatment period based on patient diary data. The patient diary results demonstrated an improvement in GERD symptoms during 8 weeks of lansoprazole treatment. The median percentage of days with GERD symptoms decreased from 88.9% to 33.3%. This was a statistically significant change ($p<0.001$). Furthermore, the average severity of GERD symptoms (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) decreased from 1.6 (mild to moderate) to 0.5 (none to mild) and this was statistically significant ($p<0.001$). No placebo group was included in this trial.

The most important secondary endpoint was the proportion of patients who had endoscopically-documented complete esophageal healing at the week 8 and 12 visits. In this study, the appearance of the esophagus was scored by the TAP Esophagitis Grading Scale (developed by a committee of the sponsor's consultant gastroenterologists). Patients with normal appearing mucosa (grade 0) or mucosal edema, hyperemia and/or friability (grade 1) were classified to have non-erosive GERD. Patients with the appearance of at least one erosion/ulceration in the esophagus mucosa (grades 2, 3, or 4) were categorized to have EE.

Complete healing of EE was defined as the return of the esophageal mucosa to grade 0 or 1 (non-erosive GERD). Twenty-one of twenty-two (95.5%) EE patients were completely healed after 8 weeks of lansoprazole treatment. One patient remained unhealed after 12 weeks of lansoprazole treatment. However, all EE patients had grade 2 or 3 lesions; no EE patient had a grade 4 lesion in this study. These efficacy results support the proposed EE indication in pediatric patients between 12 and 17 years old.

Additional secondary endpoints were the change from baseline in the amount and frequency of antacid use during the first 8 weeks of lansoprazole treatment based on patient diary data. Rescue antacid use decreased from a median of 54.5% of the days during the pretreatment period to a median of 5.5% of the days during the lansoprazole treatment period ($p<0.001$). Furthermore, the amount of rescue antacid used, decreased from a median of 1.4 teaspoons/day during the baseline pretreatment period to a median of 0.2 teaspoons/day during the lansoprazole treatment period ($p<0.001$).

An additional secondary endpoint was the change from baseline in the severity of GERD symptoms at the week 8 visit based on investigator interviews. Investigators classified the patient's overall GERD symptoms on a 0 to 3 scale (none = 0, mild = 1, moderate = 2, and severe = 3). After 8 weeks of lansoprazole treatment, GERD patients who had severe (3) baseline symptoms, moderate (2) baseline symptoms, mild (1) baseline symptoms, improved their average GERD score to 0.67., 0.71, 0.71, respectively.

Study M97-640: The major endpoints evaluated were pharmacokinetic (C_{max} and AUC_{0-24}) and pharmacodynamic (after 5 days of lansoprazole treatment, the change from baseline in the mean 24 hour intra-gastric pH and the percentages of time that the pH exceeded 3 and 4) variables .

The results of this study demonstrated that the pharmacokinetics of lansoprazole are similar between the adolescents GERD patients in this study and previously observed healthy adult subjects. The mean dose-normalized C_{max} variables for the adolescent GERD patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 27.7, 33.5, and 27.5 ng/mL/mg, respectively. The mean dose-normalized AUC_{0-24} values for the adolescent patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 67.8, 83.0, and 71.1 ng·hour/mL/mg, respectively.

For both lansoprazole treatments, compared to baseline measurements, the increase in the mean 24-hour intra-gastric pH and the percentages of time the mean intra-gastric pH were above 3 and 4 at the Day 5 Visit were statistically significant. The mean 24-hour intra-gastric pH for the adolescent GERD patients was 2.71 at baseline and 3.84 after 5 days of lansoprazole (15 mg/day), and was 2.81 at baseline and 3.89 after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 3 for the adolescent GERD patients was 26.7% at baseline and 58.9% after 5 days of lansoprazole (15 mg/day) and was 29.1% at baseline and 59.6% after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 4 for the adolescent GERD patients was 20.0% at baseline and 46.9% after 5 days of lansoprazole (15 mg/day) and was 20.4% at baseline and 48.9% after 5 days of lansoprazole (30 mg/day).

Summary: The efficacy of lansoprazole in the proposed indication was demonstrated by similar lansoprazole pharmacokinetics in adolescent GERD patients compared to healthy adult subjects; by the increase in intra-gastric pH after 5 days of lansoprazole treatment in adolescent GERD patients; by the efficacy in the complete healing of EE after 8 weeks of lansoprazole treatment (95.5%) in adolescent GERD patients; and efficacy results of lansoprazole treatment in adult GERD patients.

C. Safety

All patients in Studies M97-640 and M00-158 who received at least one dose of lansoprazole were included in the safety analyses. The Integrated Summary of Safety (ISS) included data on 150 pediatric GERD patients between 12 and 17 years old. Of the total population, 64 (43%) and 81 (54%) patients received 1 to 9 days and 42 to 70 days of lansoprazole, respectively.

Five patients had serious adverse drug events [gastroenteritis, a suicide attempt, a torn hamstring muscle, and a collection of symptoms (including chest pain, abdominal pain, and increased cough)]

that required hospitalization. All of these serious adverse events were not likely related to lansoprazole and all of these patients were able to continue in the trials.

Two patients withdrew from the lansoprazole trials due to adverse drug events (AEs). The investigators believed that both of the AEs were possibly related to the study drug. One patient discontinued lansoprazole treatment after 40 days of therapy because of mild dizziness and moderate vomiting. Another patient with a past medical history of asthma, allergies, and eosinophilic esophagitis, developed hives, peripheral edema, and a generalized papular rash after 3 days of lansoprazole treatment.

The most frequent experienced AEs that were possibly, probably, or definitely caused by lansoprazole treatment included headache, abdominal pain, nausea, and dizziness occurring in 4%, 3%, 2%, and 3% of patients, respectively. The AE profile in these pediatric patients resembled that of adult patients and pediatric patients (between ages 1 and 11) taking lansoprazole.
No hematology or chemistry serum test, urine test, or vital sign abnormality were likely due to lansoprazole therapy. Five patients in Study M00-158 developed serum gastrin levels over 200 pg/mL (normal gastrin range is 25 to 111 pg/mL) after 8 weeks of lansoprazole. Similar high serum levels of gastrin are seen in adults treated with lansoprazole. Hypergastrinemia is a well-documented effect of all the PPIs in adults. Furthermore, hypergastrinemia was documented in GERD studies in pediatric patients between ages 1 to 11 years old.

No drug interaction studies of lansoprazole were conducted in adolescents. Based on the known potential drug interactions of lansoprazole with theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin in adults; similar precautions should be taken when these medications are given concomitantly with lansoprazole in adolescent patients.

D. Dosing

This medical officer recommends a lansoprazole dose of 15 mg once daily for 4 to 8 weeks for the treatment of non-erosive GERD and a lansoprazole dose of 30 mg once daily for 6 to 8 weeks for the treatment of EE in pediatric patients between the ages of 12 to 17 years old. The evidence for this dosing recommendation is from numerous GERD studies in adult patients and the two supportive pediatric studies submitted in this sNDA.

Since the efficacy of non-erosive GERD and EE treatment with lansoprazole in adolescent patients is primarily based on the safety and efficacy of lansoprazole in adult patients, the pediatric regimen should be similar to the safe and effective adult regimen. The treatment of non-erosive GERD in adults with lansoprazole for 2 weeks is less effective than 4 to 8 weeks of lansoprazole treatment. Similarly, the treatment of EE in adults with lansoprazole for 2 to 4 weeks is less effective than 6 to 8 weeks of lansoprazole treatment. Therefore, the adolescent dose of lansoprazole in the treatment of non-erosive GERD and EE should be at least 4 weeks and 6 weeks, respectively.

E. Special Populations

1. **Gender:** The total pediatric GERD population included 66 males and 84 females. A similar percentage of females and males experienced AEs (55% and 48%, respectively) in the two studies. There was no evidence that gender affected the development of AEs during treatment with lansoprazole.

2. **Age:** The treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old is the focus of this review. The mean age of all patients was 14.1 years.

   Lansoprazole is approved for the treatment of non-erosive GERD and EE in adults and in pediatric patients between 1 and 11 years old.

3. **Race:** No safety or efficacy evaluation of racial subgroups was conducted in this pediatric population because the overwhelming majority (80.0%) of the adolescent patients was Caucasian.

4. **Hepatic and Renal Impairment:** Patients with severe renal or hepatic impairment were excluded from participating in the two studies; therefore, no comment can be made regarding pediatric patients with these conditions. Given similar PKs of lansoprazole in pediatric patients between 12 and 17 years old and healthy adults, the adult recommendations should be applicable to this age group. The current lansoprazole label recommends no dosage adjustment for adult patients with renal insufficiency and dose adjustment should be considered for adults with severe hepatic disease.

5. **Pregnancy:** No patient was or became pregnant during the two studies. According to the current label, lansoprazole is considered Pregnancy Category B for adult patients.

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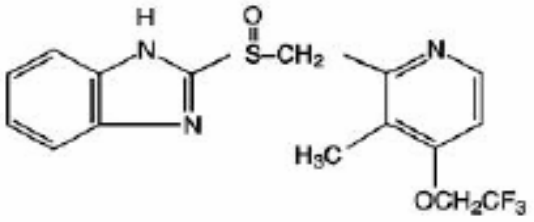
Clinical Review

I. Introduction and Background

A. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

1 Drug: **PREVACID (lansoprazole)**



2 Proposed indications: **The short-term treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old.**

3 Proposed regimens: GERD: 15 mg once daily for up to 8 weeks
EE: 30 mg once daily for up to 8 weeks

4 Proposed age group: Pediatric patients between 12 to 17 years old

5 Molecular formula: $C_{16}H_{14}F_3N_3O_2S$

6 Chemical name: 2-[[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole

7 Drug class: Substituted benzimidazole proton pump inhibitor

8 Formulation and route of administration: Oral capsule

Lansoprazole is a proton pump inhibitor which has been approved in the United States since May 10, 1995 for the treatment of a variety of acid-related esophageal, gastric, and duodenal disorders. Lansoprazole inhibits gastric acid secretion by blocking the proton pump [(H+,K+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. Inhibition of the proton pump, the final step of stomach acid secretion, decreases intra-gastric acid concentration (increases intra-gastric pH).

Lansoprazole is available by prescription in three oral formulations ─ prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) ─ and an intravenous formulation, prevacid I.V. (lansoprazole) for injection. All three oral formulations contain 15 mg or 30 mg of lansoprazole and the intravenous formulation contains 30 mg of lansoprazole.

Lansoprazole was approved for the treatment of non-erosive GERD and EE in adults and pediatric patients between the ages of 1 and 11 years old; but not for pediatric patients between 12 and 17 years old. On August 8, 1999, the Division of Gastrointestinal and Coagulation Drug Products (The Division) issued the Pediatric Written Request (WR) to the sponsor. The Lansoprazole Pediatric WR was amended several times and the final amended version was issued on June 3, 2003. The Division requested the sponsor to conduct two lansoprazole studies in pediatric GERD patients between ages 12 to 17 years old: a PK, PD, symptom assessment, 5-day study in at least 30 patients with symptomatic and/or endoscopically proven GERD (Study Three) and a 8-week, open-label, parallel group, clinical outcome study in at least 80 pediatric sGERD patients (Study Four).

In this sNDA submission, the sponsor provided one resubmitted study report (M97-640) and one new study report (M00-158) in response to Studies Three and Four of the Lansoprazole Pediatric WR to support the following new lansoprazole indications: the treatment of non-erosive GERD and EE in pediatric patients between ages 12 to 17 years old.

B. State of Armamentarium for Indication(s)

Prevacid® (lansoprazole) was approved for the following indications: the treatment of GERD (non-erosive GERD and EE) in adults and pediatric patients between the ages of 1 and 11 years old; but not for pediatric patients between 12 and 17 years old.

Prilosec® (omeprazole) is the only proton pump inhibitor (PPI) approved for the treatment of non-erosive esophagitis and EE in pediatric patients between 12 and 17 years old, in the United States. Please see Table 1 for the recommended starting doses of PPIs in the treatment of GERD in adolescents. Safe and effective use of other PPIs including aciphex® (rabeprazole), protonix® (pantoprazole), and nexium® (esomeprazole) have not been established in the treatment of acid-related gastrointestinal disorders for pediatric patients between 12 and 17 years old.

Several histamine-2 receptor antagonists (H_2RAs) including zantac® (ranitidine), pepcid® (famotidine), and tagamet® (cimetidine) are approved for the treatment of GERD in adolescents in the U.S. Please see Table 1 for the recommended doses of H_2RAs in the treatment of GERD in adolescents. Safe and effective use of axid® (rizatidine) has not been established for the treatment of pediatric patients with GERD.

Table 1: Recommended starting doses of PPIs and H_2RAs in the treatment of GERD in adolescents

DRUG	DRUG CLASS	NON-EROSIVE GERD	EE
Omeprazole (Prilosec®)	PPI	20 mg/day	20 mg/day
Lansoprazole (Prevacid®)	**PPI**	**Proposed dose is 15 mg/day**	**Proposed dose is 30 mg/day**
Rabeprazole (Aciphex®)	PPI	Not Established	Not Established
Pantoprazole (Protonix®)	PPI	Not Established	Not Established
Esomeprazole (Nexium®)	PPI	Not Established	Not Established
Ranitidine (Zantac®)	H_2RA	150 mg BID	150 mg QID
Famotidine (Pepcid®)	H_2RA	0.5 mg/kg BID	0.5 mg/kg BID
Cimetidine (Tagamet®)	H_2RA	800 mg BID or 400 mg QID	800 mg BID or 400 mg QID
Rizatidine (Axid®)	H_2RA	Not Established	Not Established

PPI = proton pump inhibitor; H_2RAs = histamine-2 receptor antagonists; Adapted from most recent approved labels

C. Important Milestones in Product Development

On October 8, 1998, TAP submitted a Proposed Pediatric Study Request (PPSR) for lansoprazole. In response, on August 8, 1999, The Division issued a Lansoprazole Pediatric Written Request (WR) pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act to obtain needed information about the use of lansoprazole in pediatric patients.

The Division made additional minor amendments to the Lansoprazole Pediatric WR on June 18, 2002, December 18, 2002, and June 3, 2003. The most recent amended Lansoprazole Pediatric WR required that all pediatric studies be submitted to the FDA by December 31, 2005 to obtain an additional six months of lansoprazole marketing exclusivity. This amended WR asked the sponsor to complete four major studies in the treatment of GERD in pediatric patients. The following is a summary of the 4 major studies:

Study One: This study will consist of four parts: two PK, PD, and safety studies of lansoprazole and two randomized withdrawal efficacy and safety studies of lansoprazole will be conducted in infants with GERD.

Study Two: This study will be a multi-center, open-label, 8 to 12-week, PK, PD, and clinical outcome study with age-appropriate formulation(s) of lansoprazole in at least 60 pediatric patients aged 1 to 11 years with symptomatic and/or endoscopically proven GERD.

Study Three: This study will be a multi-center, randomized, double-blind, 5-day, PK, PD, and symptom assessment study of lansoprazole in at least 30 patients with symptomatic and/or endoscopically proven GERD in pediatric patients aged 12 to 17 years.

Study Four: This study will be a multi-center, open-label, parallel group, 8 to 12-week, clinical outcome study of lansoprazole in at least 80 pediatric symptomatic GERD (sGERD) patients aged 12 to 17 years in whom gastrointestinal endoscopy has been performed.

On December 19, 2003, the sponsor submitted this sNDA for priority review for the treatment of GERD in pediatric patients between 12 and 17 years old, for the three oral lansoprazole formulations: capsules (NDA 20-406/S-57), suspension (NDA 21-281/S-14), and disintegrating tablets (NDA 21-428/S-4). All of the studies submitted in this sNDA follow the design of the Lansoprazole Pediatric WR. Study M97-640 follows Study Three and Study M00-158 follows Study Four of the Lansoprazole Pediatric WR.

D. Other Relevant Information

On May 10, 1995, The Division approved the first lansoprazole formulation for the treatment of several acid related conditions in adults. Please see Table 2 for the approval dates of all the lansoprazole formulations in adults.

Table 2: Approval dates of lansoprazole in adults

DATE	NDA #	FORMULATION	INDICATION	POPULATION
May, 5, 1995	20-406	oral capsules	several acid-related disorders	adults
May 31, 2001	21-281	oral suspension	several acid-related disorders	adults
August 30, 2002	21-428	oral disintegrating tablets (solutab)	several acid-related disorders	adults

Lansoprazole is approved for the treatment of the following conditions in adults in the U.S.:

1) Active duodenal and active gastric ulcers
2) Active NSAID-associated gastric ulcers in patients that continue NSAID use
3) Maintenance of healed duodenal ulcers
4) Prevention of NSAID-associated gastric ulcers in patients with a past history of a gastric ulcer (who require NSAID treatment)
5) Eradication of *H. pylori* in patients with an active duodenal ulcer or a history of a duodenal ulcer within the last year
6) Pathologic hypersecretory conditions (like Zollinger-Ellison Syndrome)
7) Symptomatic GERD, active EE, and maintenance of healed EE

On July 31, 2002, The Division approved lansoprazole for the treatment of GERD in pediatric patients between the ages of 1 to 11 years old (NDA 20-406/S-47, NDA 21-281). Please see Table 3 for the approved lansoprazole regimens in pediatric GERD patients. The safety and effectiveness of lansoprazole in pediatric patients between 12 and 17 years old and less than 1 year old have not been established.

Table 3: FDA-approved indications of lansoprazole in pediatric patients

	INDICATION	DOSE
1	Treatment of GERD	15 mg q day for pediatrics (1 to 11 years old) less than or equal to 30 kg and 30 mg q day for pediatrics (1 to 11 years old) greater than 30 kg for 12 weeks*
2	Treatment of EE	15 mg q day for pediatrics (1 to 11 years old) less than or equal to 30 kg and 30 mg q day for pediatrics (1 to 11 years old) greater than 30 kg for 12 weeks*

* The prevacid dose was increased up to 30 mg BID in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic.
Reference: last approved labeling in August 2003

Lansoprazole is approved for use to treat adults with GERD in over 100 countries in North America, South America, Africa, Asia, and Europe.

E. Important Issues with Pharmacologically Related Agents

Five proton pump inhibitors [omeprazole (prilosec®), lansoprazole (prevacid®), rabeprazole (aciphex®), pantoprazole (protonix®), and esomeprazole (nexium®)] are currently approved for several acid-related conditions in the U.S.

The sponsor of prilosec® fulfilled their Pediatric WR and obtained pediatric exclusivity. Prilosec is approved for pediatric patients older than 2 years of age for the treatment of symptomatic GERD and EE. The FDA-approved dose of prilosec® for the treatment of sGERD or EE is 10 mg/day for pediatric patients ≤ 20 kg and 20 mg/day for pediatric patients > 20 kg.

Pediatric WRs have been issued to all sponsors who have approved reference listed proton pump inhibitors. At the time of this sNDA submission, the sponsors of aciphex, protonix, and nexium have not submitted any pediatric study reports in response to their pediatric WRs.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry: The chemistry study reports of this sNDA were reviewed by Dr. Ramesh Raghavachari, the chemistry reviewer in The Division. Dr. Raghavachari found that the chemistry, manufacture, and controls of lansoprazole in this sNDA were unchanged from the original NDA submission (NDA 20-406) except that over-encapsulation of the drug product was performed in the double-

blind M97-640 study. Dr. Raghavachari required that the sponsor provide "comparative dissolution data for the over-encapsulated drug product used in (Study M97-640) and the commercial drug product." Dr. Raghavachari recommended approval of this sNDA, pending evaluation of the dissolution data for the over-encapsulated drug product. Please see Dr. Raghavachari's review of this sNDA dated April 1, 2004 for details.

Animal Pharmacology and Toxicology: No new non-clinical studies or non-clinical information were submitted in this sNDA.

Microbiology: This sNDA has no pertinent microbiology issues.

Statistics: Dr. Wen Jen Chen conducted the statistical review of this sNDA. Dr. Chen concluded that from a statistical perspective, the efficacy of lansoprazole in the treatment of GERD in pediatric patients between 12 and 17 years old is supported by the study data.

III. Human Pharmacokinetics and Pharmacodynamics

Dr. Suliman Al-Fayoumi, the biopharmaceutics reviewer in The Division, performed the PK and PD review. In this sNDA submission, Study M97-640 contained the only PK and PD data of lansoprazole in pediatric GERD patients between ages 12 and 17 years old. No PK or PD data were obtained in Study M00-158.

Study M97-640 was a randomized, double-blinded, multi-center study of lansoprazole in the treatment of pediatric GERD patients, ages 12 to 17 years old. Patients were randomized to two treatments: 15 mg/day (n=32) or 30 mg/day (n=31) of lansoprazole for 5 consecutive days. Baseline upper endoscopies were performed on all patients. The major efficacy endpoints were PK variables (C_{max}, T_{max}, AUC_{0-24}, and the half-life), PD variables (the change from baseline in the mean 24 hour intra-gastric pH and the percentages of time that the pH exceeded 3 and 4), and symptom relief.

Please see Dr. Al-Fayoumi's review of this sNDA for details regarding study M97-640.

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor provided one new study report (Study M00-158) and one resubmitted study report (Study M97-640) in this sNDA submission. Study M97-640 included 63 GERD patients and the primary objective was to assess the PKs and intra-gastric pH of lansoprazole in the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 to 17 years. Study M00-158 included 87 GERD (non-erosive GERD and EE) patients and the primary objectives were to assess the safety and efficacy of once daily administration of 15 mg or 30 mg of lansoprazole in pediatric patients, ages 12 to 17 with symptomatic GERD.

Because the efficacy of lansoprazole in the treatment of GERD in pediatric patients between 12 and 17, is primarily based on efficacy data in adult GERD patients, lansoprazole GERD trials in adult patients were used as a source in this review. Studies M95-300 and M87-092 were previously-submitted adult lansoprazole trials in non-erosive GERD and EE patients, respectively. Study M95-300 was a U.S. multi-center, double-blind, placebo-controlled, lansoprazole 8-week study of 214 adult patients with frequent GERD symptoms, but no esophageal erosions by endoscopy. Study M87-092 was a U.S., multi-center, double-blind, placebo-controlled, lansoprazole, 8-week study of 269 adult patients with an endoscopic diagnosis of esophagitis.

Post-marketing data and literature reports served as supportive evidence for the efficacy and safety of lansoprazole in adolescent GERD patients.

B. Tables Listing the Clinical Trials

Table 4 lists the two clinical studies submitted in this sNDA.

Table 4: Tabular listing of all clinical trials in this NDA

Type of Study	Study Identifier	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration and Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients
Phase II Efficacy	M00-158	Safety and efficacy of QD administration of lansoprazole 15 mg or 30 mg in adolescents, ages 12-17 years with GERD	Open-label, multi-center	Lansoprazole 15 mg capsule QD orally (for subjects with non-erosive GERD) Lansoprazole 30 mg capsule QD orally (for subjects with erosive esophagitis) Duration: 8 weeks; if erosive esophagitis was unhealed at Week 8 endoscopy, subjects were treated for an additional 4 weeks with 30 mg QD	64 23	Adolescents, aged 12 to 17 years, with a history of GERD symptoms for at least 3 months and currently symptomatic
Phase I PK, PD	M97-640	Safety, PK, and PD of QD administration of lansoprazole 15 mg or 30 mg in pediatric subjects, ages 12 to 17 years with symptomatic GERD	Randomized, double-blind, multi-center	Lansoprazole 15 mg capsule QD orally Lansoprazole 30 mg capsule QD orally Duration: 5 days	32 31	Adolescents, aged 12 to 17 years, with symptomatic, endoscopically and/or histologically proven GERD

Reference: Study M00-158 ─ "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment."

C. Postmarketing Experience

According to the National Disease and Therapeutic Index (NDTI), physicians in the United States recommended the use of lansoprazole in the treatment of pediatric patients (between 12 and 16 years old) approximately 56,000 times in 2001. The NDTI is a survey conducted by IMS HEALTH, designed to provide statistical information about the patterns and treatment of disease encountered in office-based practices in the United States. The Division has not received or

identified any significant safety issues from post-marketing reports related to the use of lansoprazole in this population.

D. Literature Review

The sponsor submitted published literature regarding the treatment of non-erosive GERD and EE in adolescents with lansoprazole. With PK, PD, safety, and efficacy data, the literature supported the conclusions of this medical officer that lansoprazole is safe and effective for the treatment of pediatric GERD patients between 12 and 17 years old.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy evaluation of the proposed indication is based on lansoprazole trials in adult GERD patients; the bioequivalence of lansoprazole in pediatric GERD patients between the ages of 12 to 17 years old (Study M97-640) to historical adult subjects; and the efficacy of EE healing after 8-12 weeks of lansoprazole administration in pediatric patients between the ages of 12 to 17 years old (Study M00-158).

The safety evaluation of the proposed indication is based on lansoprazole trials in adult GERD patients; 150 pediatric GERD patients between the ages of 12 to 17 years old who used lansoprazole from 5 days to 12 weeks (Studies M97-640 and M00-158); post-marketing reports from the use of lansoprazole in pediatric adolescent patients; and literature assessment of the use of lansoprazole in pediatric adolescent patients.

B. Overview of Materials Consulted in Review

Supplemental NDA 20-406/S-057, NDA 21-281/S-014, and NDA 21-428/S-004 are completely electronic submissions which included the following sections: Labeling (Volume 2), CMC (Volume 5), and Clinical (Volume 6). In this review, I have examined material in the Labeling (Volume 2) and Clinical (Volume 6) Sections.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audit was done of the study sites since the phase II study was multicenter involving 20 sites and no one site contributed more than 10 patients or 11% of the total number of GERD patients in the phase II trial.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, the study was conducted in accordance with the protocol, International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines governing clinical study conduct, all applicable local regulations, and the ethical principles stated in the Declaration of Helsinki (1996 revision). The investigators assured that the study was conducted in accordance

with prevailing local laws and customs and complied with the provisions as stated in the ICH guidelines.

E. Evaluation of Financial Disclosure

The sponsor has submitted FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In Study M00-158, the frequency and severity of the adolescent's GERD symptoms significantly decreased during 12-weeks of lansoprazole therapy compared to the baseline Pretreatment Period. The frequency and amount of rescue antacid used during the 12-week treatment period was significantly lower compared to the baseline Pretreatment Period. Furthermore, the trial demonstrated 95.5% complete healing of EE after 8 weeks of lansoprazole therapy. Study M00-158 demonstrated support of the efficacy of lansoprazole in the treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old.

B. General Approach to Review of the Efficacy of the Drug

Two study reports (Studies M97-640 and M00-158) were submitted in this sNDA. Study M97-640, a PK and PD study, was reviewed by Dr. Suliman Al-Fayoumi, the biopharmaceutics reviewer in The Division (see his review for details). This medical officer reviewed Study M00-158, the safety and efficacy study, in this sNDA.

C. Detailed Review of Trials by Indication

Study M00-158.

1 Title: "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after eight to twelve weeks of treatment."

2 Objectives: Assess the safety and efficacy of lansoprazole in the treatment of GERD (non-erosive GERD and EE) in pediatric patients, ages 12 to 17 years.

3 Study Design: This was an open-label, multi-center (20 sites), U.S. trial of lansoprazole in the treatment of GERD (non-erosive GERD and EE) in pediatric patients, ages 12 to 17 years, for 8 to 12 weeks. All of the pediatric patients had baseline upper endoscopies to categorize their GERD into one of two groups:

1) Treatment Group I: Patients with non-erosive GERD at the Pretreatment Visit were treated with 15 mg of oral lansoprazole once daily for eight weeks.

2) Treatment Group II: Patients with EE at the Pretreatment Visit were treated with 30 mg of oral lansoprazole once daily for eight weeks. Patients with completely healed EE at the Week 8 Visit completed study participation at this Week 8 Visit. In contrast, patients with unhealed EE at the Week 8 Visit were to be treated with 30 mg of oral lansoprazole once daily for an additional four weeks (12 weeks of total treatment) and completed study participation at the Week 12 Visit.

Therefore, all EE patients had post-treatment upper endoscopies to assess esophageal healing.

Medical Reviewer's Comments: The design's inclusion of baseline upper endoscopies in all of the GERD patients and the post-treatment upper endoscopies in EE patients is acceptable.
The design of Study M00-158 follows the design of Study Four of the LPWR issued by the Division of Gastrointestinal and Coagulation Drug Products (The Division). The LPWR was equivocal in its request for a controlled study; therefore, the sponsor has satisfied Study Four of the LPWR.

4 Study Population:
4.1 Number of patients: The sponsor's intention was to enroll a minimum of 20 patients with non-erosive GERD and a minimum of 20 patients with EE. The remaining patients were to be enrolled in the appropriate treatment group based on endoscopic findings. The sponsor aimed for a total number of 80 GERD patients.

4.2 and 4.3 Inclusion and Exclusion Criteria: Please see Table 5 for the eligibility criteria in this study.

Table 5: Eligibility criteria

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ 12 to 17 years of age at the time he/she received the first dose of study drug. ➢ Patients with GERD symptoms (for example: regurgitation, sour taste, heartburn, retro-sternal pain, vomiting, etc.) for at least 3 months prior to the Pretreatment Period. Patients had to be symptomatic with GERD at screening. ➢ Patients' pretreatment diaries reflected at least one episode of moderate, severe, or very severe GERD symptom(s) within the 6 days prior to the Treatment Period. ➢ Patients with Barrett's esophagus, with no known dysplastic changes in the esophageal mucosal, were eligible to enter the study. ➢ Laboratory, biochemical, and hematology parameters within normal laboratory limits as listed in the (b) (4) except: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were less than 2 times the upper limit of normal; creatinine was less than or equal to 2.0 mg/dL; patients with Gilbert's disease were eligible for the study; or if the blood tests were abnormal, the tests were judged clinically acceptable by the investigator. ➢ Females had a negative pregnancy test; were not lactating; and were using and agreed to continue to use effective means of birth control (documentation of abstinence was acceptable) if sexually active. ➢ Discontinue use of antacids (other than the Mylanta provided during the study), histamine (type 2) receptor antagonists, sucralfate, anticholinergics, and	➢ Duodenal and/or gastric ulcer(s) ≥3 mm in diameter at the Pretreatment Visit. ➢ Current esophageal stricture requiring dilatation. Strictures could not have been dilated within the 12 weeks prior to the pretreatment upper endoscopy. ➢ Acute upper gastrointestinal (UGI) bleed. Patients stabilized after an acute UGI bleed were eligible for the study provided they were hemodynamically stable (for example: hemoglobin ≥10.0 g/dL with no associated hypotension or tachycardia) at the time of the pretreatment upper endoscopy. ➢ Coexisting disease affecting the esophagus (for example: scleroderma; eosinophilic esophagitis; viral, bacterial, or fungal infection). Furthermore, recent esophageal radiation or esophageal trauma. ➢ Patients with evidence of Zollinger-Ellison syndrome, esophageal varices, symptomatic pancreatobiliary tract disease, cholecystitis, rheumatoid arthritis, or lupus. ➢ Patients had no evidence of malignancy (except basal cell carcinoma) requiring active treatment. ➢ Evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurologic, or endocrine disease, or other abnormality (other than the disease being studied). Patients with neurologic impairment such as, but not limited to, cerebral palsy or Down's syndrome were eligible; however, they had to be able to understand and cooperate with study requirements. ➢ History of gastric, duodenal, or esophageal surgery. (Exceptions: simple oversew of an ulcer, esophageal atresia repair, fundoplication, or gastrostomy tube placement.) ➢ Evidence of alcohol abuse, illegal drug use, or drug abuse in the 12 months prior to the Pretreatment Period. ➢ Received blood products within the 12 weeks prior to the first dose of study drug. ➢ Received an investigational drug within one month prior to the first dose of study drug.

prokinetics prior to the Pretreatment Period. ➢ If they required continuous treatment with theophylline derivatives, phenytoin, phenobarbital, digoxin, and/or carbamazepine, then they were eligible. However, they had serum drug levels monitored during the study to assure that proper levels of these drugs were being maintained. ➢ Patients receiving chronic tricyclic antidepressant therapy were eligible; however, they could not begin a new course of therapy during participation in the study (including the Pretreatment Period). ➢ The parent or legal guardian, with agreement of the patient, had to understand, sign, and date the informed consent form prior to the patient having any study related procedures. The patient had to be able to understand and cooperate with study requirements.	➢ Known allergy to proton pump inhibitors. ➢ Required chronic anticoagulant therapy. ➢ Chronic use (> 12 doses per month) of the following medications within 30 days prior to the pretreatment upper endoscopy: a) Non-steroidal anti-inflammatory drugs including COX-2 inhibitors. b) Oral or intravenous corticosteroids ≥ the equivalent of 10 mg of prednisone per day. ➢ Received bisphosphonates, tetracycline, doxycycline, ferrous sulfate, or the oral formulation of cromolyn sodium within the 30 days prior to the pretreatment upper endoscopy. ➢ Received proton pump inhibitors within 14 days prior to the Pretreatment Period. ➢ Received antacids (other than the mylanta provided during the study), histamine (type 2) receptor antagonists, sucralfate, anticholinergics, and prokinetics during the Pretreatment Period ➢ GERD symptoms were manifested by only extra-esophageal symptoms (for example: cough, hoarseness, wheezing, etc.)

Reference: Study M00-158: "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment."

Medical Reviewer's Comments: The inclusion and exclusion criteria were appropriate for this study. The eligibility criteria suitably selected for adolescent GERD patients and provided for a rescue medication for treatment failure.

The eligibility criteria appropriately precluded the use of concomitant medications that treat EE (including antihistamines and PPIs) and properly prohibited patients with other esophageal disease. The inclusion criteria allowed for patients with significant renal disease; however, this is acceptable because the current lansoprazole label states that no dose adjustment is needed for adult patients with significant renal failure.

4.4 Premature Discontinuation of Patients

All patients had the right to withdraw from the study at any time without prejudice to future treatment. The investigator could discontinue any patient, without consent, at any time due to an adverse event; treatment with another drug which would interfere with the evaluation of study drug; pregnancy; poor compliance; therapeutic failure; personal reasons; or if the study had been terminated by the sponsor.

5 <u>Drugs used in study</u>: Non-erosive GERD patients received 15 mg of oral lansoprazole capsules daily for eight weeks and EE patients received 30 mg of oral lansoprazole capsules daily for 8 to 12 weeks. No placebo medication was used in this trial.

All GERD patients in the trial were supplied with mylanta® to take if necessary. The patients, who did not achieve relief of their heartburn symptoms, were permitted to take the approved dose of mylanta®, the rescue medication, anytime during the Pretreatment and Treatment Periods (except within 30 minutes of study drug administration.) The approved dose of mylanta® is 10 to 20 mL every 4 hours, if necessary, for the relief of heartburn, acid indigestion, or sour stomach. Ten milliliters of mylanta® contains the following active ingredients: 400 mg of aluminum hydroxide, 400 mg of magnesium hydroxide, and 40 mg of simethicone.

Medical Reviewer's Comments: The approved dose of lansoprazole for the treatment of sGERD and EE in pediatric patients from one year to eleven years is 15 mg/day for patients ≤ 30 kg and 30 mg/day for pediatrics > 30 kg. The approved lansoprazole dose for the treatment of sGERD in adult patients is 15mg/day and the approved lansoprazole dose for the treatment of EE in adult patients is 30 mg/day. Therefore, the proposed lansoprazole doses for pediatric patients, ages 12 to 17, are acceptable. Furthermore, the lansoprazole doses used in this trial were the exact doses recommended by the PPWR.

6 Schedule of Procedures and Evaluations: The study consisted of two periods: a Pretreatment Period (7 to 14 days) and a Treatment Period (8 to 12 weeks). Please see Table 6 for the Schedule of Procedures and Evaluations. All non-erosive GERD patients had an 8-week Treatment Period. EE patients who had completely healed EE at 8 weeks had an 8-week Treatment Period and EE patients who were not healed at 8 weeks had a 12-week Treatment Period.

Table 6: Schedule of procedures and evaluations for Study M00-158

Study Procedures	Pretreatment Period (7 to 14 days)		Treatment Period (8 to 12 weeks)			
	Pretreatment Visit(s) (Day -14 to Day -2)	Day -1 Visit	Day 1[a]	Week 4 Visit	Week 8 Visit[b]	Final Visit[c] (Week 8 Visit or Week 12 Visit)
Informed Consent and Assent	X					
Complete Medical and Social History	X					
Interim Medical History		X				
Brief Physical Examination		X		X	X	
Complete Physical Examination	X					X
Vital Signs	X	X		X	X	X
Endoscopy with Biopsies	X[d]	X[d]			X[e]	X[e]
Routine Fasting Laboratory Evaluations	X			X	X	X
Fasting Serum Gastrin Determinations	X			X	X	X
Pregnancy Test (females)	X			X	X	X
Theophylline, Phenytoin, Phenobarbital, Digoxin, and/or Carbamazepine Levels (if applicable)	X			X	X	X
Overall GERD Symptom Assessment Based on Investigator Interview	X	X		X	X	X
Prior and Concomitant Medication Record	X	X		X	X	X
Adverse Event Assessment				X	X	X
Dispense Study Drug/Drug Accountability		X		X	X	
Diary Instruction/Dispense Diary	X	X		X	X	
Return Study Drug/Drug Accountability				X	X	X
Return/Review Diary		X		X	X	X
Dispense Mylanta	X	X		X	X	
First Day of Study Drug Administration			X			
Follow-up Instructions (eg, non-study follow-up visit/therapy)						X

a This was the first day of treatment; it was not a study visit.
b Week 8 Visit applied to patients with unhealed EE at the Week 8 Visit. These patients were treated for an additional 4 weeks, and completed study participation at the Week 12 Visit.
c Final Visit was the Week 8 Visit for all non-erosive GERD patients and EE patients with complete healing at the Week 8 Visit. Whereas, the Final Visit was the Week 12 Visit for EE patients who had unhealed EE at the Week 8 Visit. Finally, the Final Visit was the last visit in the Treatment Period for patients who prematurely terminated from the study.
d The endoscopy was to be performed at any time during the Pretreatment Period (Day -14 through Day -1).
e Follow-up endoscopies were performed only on patients who had EE at the Pretreatment Visit. They were performed at the Week 8 Visit, Week 12 Visit (if unhealed at the Week 8 Visit), and the Final Visit for patients who prematurely terminated study participation.
Reference: Study M00-158 – "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment."

Medical Reviewer's Comments: The schedule of procedures and evaluations appears to be organized, clear, and sufficient for this study.

6.1 Pretreatment Period: During the Pretreatment Period, between Day -14 and Day -1, informed consent/assent was obtained and the patients underwent the following procedures to determine eligibility for the Treatment Period: complete medical histories; overall GERD symptoms; prior and concomitant medications; social histories; physical examinations including height, weight, and vital signs; routine fasting laboratory evaluations including serum gastrin levels and pregnancy tests,

phenytoin, digoxin, phenobarbital, carbamazepine, and/or theophylline drug levels if applicable; and **upper endoscopies** with biopsies.

Patients were not permitted to use bisphosphonates, tetracycline, doxycycline, ferrous sulfate, oral cromolyn sodium, investigational drugs (other than the study medication), chronic anticoagulant therapy, antacids (other than the mylanta® provided during the study), prescription and over-the-counter type 2 histamine receptor antagonists, sucralfate, anticholinergics, prokinetics, and proton pump inhibitors (other than the study medication). Patients were not permitted to use more than 12 doses per month of the following medications: NSAIDS including COX-2 inhibitors and corticosteriods greater than or equal to the equivalent to 10 mg of prednisone per day.

During the Pretreatment Period, mylanta® was dispensed to patients. If the GERD patients did not achieve relief of their heartburn symptoms, they were permitted to take the approved dose of mylanta®, the rescue medication, anytime.

During the Pretreatment Period, diaries were dispensed to patients. Patients, their parents, or their caregivers (PPC) maintained the daily diary, in which they recorded the severity of their GERD symptoms and the amount and frequency of their mylanta usage.

Medical Reviewer's Comments: The study procedure lacked specific dietary instructions for the patients to observe. The treatment of GERD includes dietary and lifestyle changes. Patients should be on a consistent diet between the two comparative periods (throughout the Pretreatment and Treatment Periods) because the dietary changes can influence the outcome of GERD treatment. Furthermore, some patients can completely treat their GERD, if they make dietary and lifestyle changes.

6.1.1 Pretreatment Endoscopies: All patients had baseline upper endoscopies during the Pretreatment Period. One upper endoscopy with three biopsies and photographic documentation was used to assess the presence and severity of the following: EE, Barrett's esophagus with dysplastic changes, esophageal stricture requiring dilatation, esophageal varices, acute UGI bleed, and gastric and/or duodenal ulcers $\geq$ 3 mm in diameter.

During the baseline endoscopies, the endoscopist graded the appearance of the esophageal mucosa using the TAP Esophagitis Grading Scale (developed by a committee of the sponsor's consultant gastroenterologists). According to the TAP Esophagitis Grading Scale (Table 7), patients with grade 0 or 1 were classified to have non-erosive GERD and patients with grade 2, 3, or 4 were classified to have EE. Therefore, the endoscopic appearance of the esophageal mucosa determined the assigned treatment: Patients with non-erosive GERD and EE were placed in Treatment Group I and Treatment Group II, respectively.

Table 7: TAP Esophagitis Grading Scale

GRADE	ESOPHAGEAL MUCOSA APPEARANCE BY UPPER ENDOSCOPY	CATEGORY
0	Normal appearing mucosa by endoscopy	Non-erosive GERD
1	Mucosal edema, hyperemia and/or friability or red streaks (linear erythematous areas)	Non-erosive GERD
2	One or more erosion(s)/ulcerations(s) involving less than 10% of the distal 5 cm of the esophagus	EE
3	Erosions/ulcerations involving 10 to 50% of the distal 5 cm of the esophagus or a single ulcer measuring 3 to 5 mm in diameter	EE
4	Multiple erosions/ulcerations involving greater than 50% of the distal 5 cm of the esophagus or a single large ulcer greater than 5 mm in diameter	EE

An ulcer is a discrete lesion with appreciable depth and ≥ 3 mm in diameter.
An erosion is a superficial break in the esophageal mucosa which is < 3 mm in diameter.
Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 39, Table 9.5b

During the baseline endoscopies, the endoscopists also performed five full mucosal thickness gastric biopsies on each patient. The biopsies were evaluated for active and chronic inflammation, atrophy, intestinal metaplasia, endocrine cell evaluation, and *H. pylori* status by a blinded pathologist. Patients who tested positive for *H. pylori* were allowed to complete the study.

6.1.2 Pretreatment Patient Evaluations: At the Pretreatment Visit (7 to 14 days prior to Day 1), all of the patients' GERD symptoms (including the predominant symptom) were identified and documented by the investigators. The investigators instructed the patients, their parents, and/or their caregivers (PPCs) to daily classify the severity of their worst GERD symptoms (please see Table 8) and the amount and frequency of their mylanta use in their diaries.

Table 8: Patient's GERD symptoms severity grading scale

SEVERITY	GRADE	DEFINITIONS
0	**None**	No GERD symptoms.
1	**Mild**	Bothered a little and/or symptoms present part of the day or night but caused little or no discomfort. Did not interfere with sleep.
2	**Moderate**	Bothered some and/or symptoms present half of day or night, annoying. Did not interfere with daily routine and/or occasionally interfered with sleep.
3	**Severe**	Bothered a lot and/or symptoms present most of the day or night and/or interfere with daily routine or sleep.
4	**Very Severe**	Bothered intensely and/or experienced constant symptoms and/or marked interference with daily routine or sleep.

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 42, Table 9.5e.

6.1.3 Pretreatment Investigator Evaluations: On the last day of the Pretreatment Period (day -1), all patients had visits with the investigators. The investigators performed interim medical histories, recorded prior and concomitant medications, documented patient GERD symptoms, performed brief physical examinations, assessed the patient's diaries, and dispensed study and rescue drugs. The investigators documented the severity of the patient's overall GERD symptoms during the week (day -7 to day -1) prior to the last day of the Pretreatment Period. Please see Table 9.

Table 9: Investigator's GERD symptom severity grading scale

	GRADE	DEFINITION
0	None	No symptoms.
1	Mild	GERD symptoms do not last long and are easily tolerated
2	Moderate	GERD symptoms cause discomfort and interrupts usual activities
3	Severe	GERD symptoms cause great interference with usual activities and may be incapacitating

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Adapted from Volume 7, page 42, Table 9.5f.

6.1.4 Pretreatment Laboratory Evaluations: All patients were instructed to fast at least 8 hours before the Pretreatment (baseline) laboratory samples were drawn. Laboratory evaluations included determinations of the following:

1) Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count.

2) Blood Chemistry Determinations: total protein, glucose, blood urea nitrogen, creatinine, gamma glutamyl transferase, hepatic panel, total cholesterol, calcium, inorganic phosphorus, sodium, potassium, chloride, and uric acid.
3) Serum Gastrin Determinations: Samples were drawn before the endoscopy procedure or 24 hours after the endoscopy procedure. Gastrin specimens were frozen immediately and shipped to (b) (4) on 5 pounds of dry ice on the day of collection.
4) Urinalysis: specific gravity, pH, glucose, ketones, protein, and microscopic examination.
5) Pregnancy Tests: A serum pregnancy test was completed for all female patients and results were to be negative for the patient to enter and, subsequently, to continue in the study.
6) Theophylline, Phenytoin, Phenobarbital, Digoxin, and/or Carbamazepine Levels: Patients taking these drugs were to have serum drug levels monitored to assure that proper levels of these drugs were being maintained. The time of the last dose of medication was recorded each time a drug level was drawn.

When an individual patient had a laboratory value that was outside the sponsor's thresholds for potentially concerning laboratory results, a listing of all related values for that patient was generated and reviewed by the sponsor to determine whether further action was needed.

6.2 Treatment Period:

6.2.1 Treatment Period for non-erosive GERD patients: Non-erosive GERD patients who completed all pretreatment procedures and met all eligibility requirements were allowed to start the Treatment Period. The Treatment Period began when the first dose of study drug (15 mg of oral lansoprazole) was taken (Day 1) and ended after eight weeks of treatment or when the patient prematurely discontinued from the study. Non-erosive GERD patients did not have follow-up upper endoscopies.

Patients were not permitted to use bisphosphonates, tetracycline, doxycycline, ferrous sulfate, oral cromolyn sodium, investigational drugs (other than the study medication), chronic anticoagulant therapy, antacids (other than the mylanta® provided during the study), histamine2-receptor antagonists, sucralfate, anticholinergics, prokinetics, and PPIs (other than the study medication). Patients were not permitted to use more than 12 doses per month of the following medications: NSAIDS including COX-2 inhibitors and corticosteriods greater than or equal to the equivalent to 10 mg of prednisone per day.

Before the Treatment Period, mylanta® was dispensed to non-erosive GERD patients. If the patients did not achieve relief of their heartburn symptoms, they were permitted to take the approved dose of mylanta® anytime (except within 30 minutes of study drug administration.)

Patients, their parents, and/or their caregivers (PPC) maintained the daily diary, in which they recorded the severity of their GERD symptoms and the amount and frequency of their mylanta use.

Patient visits occurred at Week 4 and Week 8. If a patient withdrew from the study early, then the final visit occurred on the last day of study drug treatment. At all these visits, the following procedures were performed: concomitant medication assessments, brief physical exams, vital signs measurements, adverse event assessments, and laboratory evaluations including fasting serum

gastrin levels. Furthermore, the investigators documented the severity of the patient's overall GERD symptoms during the one-week prior to each visit (see Table 9).

6.2.2 Treatment Period for EE patients: EE patients followed similar procedures and evaluations as the non-erosive GERD patients. Below highlights some differences.

In contrast to the non-erosive patients, EE patients were treated for 8 weeks with 30 mg of oral lansoprazole per day. At the Week 8 Visit, all EE patients had follow-up upper endoscopies to assess EE healing. The endoscopist graded the appearance of the esophageal mucosa by using the TAP Esophagitis Grading Scale (see Table 7). If these patients achieved a grade of 0 or 1 (non-erosive GERD), then they were classified to have complete EE healing and they finished the study (in 8 weeks).

On the 8-week follow-up endoscopy, if patients had grades of 2, 3, or 4; then they were categorized to have incomplete healing ─ these patients continued to have EE. These EE patients were treated with 30 mg of oral lansoprazole per day for an additional 4 weeks (a total of 12 weeks of treatment). At the Week 12 Visit, these EE patients had a third (and final) upper endoscopy to assess EE healing. The appearance of the esophageal mucosa of these patients was graded by the identical TAP Esophagitis Grading Scale. At the Week 12 Visit patients also received: concomitant medication assessments, complete physical exams, vital signs measurements, adverse event assessments, and lab evaluations including fasting serum gastrin levels. Furthermore, the investigators documented the severity of the patient's overall GERD symptoms during the week prior to the Week 12 visit.

Medical Reviewer's Comments: The study procedures and evaluations were acceptable.

The change in weight of the GERD patients after 8-12 weeks of the Treatment Period was not measured. If overweight GERD patients lost weight (through reduction in calories consumed and an increase in exercise performed) during the 8-12 weeks of the Treatment Period, then their GERD symptoms may have improved by this lifestyle change in addition to the study medication.

7 <u>Endpoints</u>:
7.1 Primary Efficacy Endpoint: For all (non-erosive GERD and EE) patients, the primary efficacy endpoint was the change in the frequency and severity of GERD symptoms based on **patient diary** data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the eight-week Treatment Period (day 1 to the week 8 visit).

Medical Reviewer's Comments: The efficacy of lansoprazole in the treatment of GERD is difficult to demonstrate without a control group (a placebo control, an active control, or dose-ranging control group). Pediatrics GERD patients can improve with dietary and lifestyle changes alone without medication. Therefore, the true efficacy of lansoprazole in the treatment of GERD will be difficult to demonstrate in this study alone.

However, this is a supportive study for the efficacy of lansoprazole in the treatment of GERD in adolescent patients. The sponsor will rely primarily on the efficacy of lansoprazole in the treatment

of GERD in adults. Furthermore, the sponsor will have supportive information from PK and PD studies and efficacy data in this study.

7.2 Secondary Efficacy Endpoints for all patients in this study: Four secondary efficacy endpoints for all patients were:

1) The change in frequency and severity of GERD symptoms based on **patient diary** data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the first four weeks of the Treatment Period (starting on day 2 to day 29).
2) The change in frequency and severity of GERD symptoms based on **patient diary** data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the entire Treatment Period (starting on day 2 to the Final Visit). The Final Visit for non-erosive GERD patients and EE patients, who had completely healed EE at the Week 8 Visit, was the Week 8 Visit. In contrast, the Final Visit for EE patients, who did not have completed healing at the Week 8 Visit, was the Week 12 Visit. Finally, the Final Visit for all (non-erosive GERD and EE) patients, who prematurely terminated from the study during the Treatment Period, was the last day that each patient received the study drug.
3) The change in antacid use based on **patient diary** data from the Pretreatment Period (day -14 to day -1) compared to the first four weeks of the Treatment Period (starting on day 2 to day 29), the first eight weeks of the Treatment Period (starting on day 2 to day 57), and the entire Treatment Period (starting on day 2 to the Final Visit).
4) Based on **investigator interview**, the change in the severity of the GERD symptoms from the week prior to the Treatment Period (day -7 to day -1) compared to the week prior to the Week 4 Visit (day 23 to day 29), the week prior to the Week 8 Visit (day 51 to day 57), and the week prior to the Week 12 Visit (day 79 to day 85).

7.3 Additional Secondary Efficacy Endpoint for only EE patients in this study: One additional secondary efficacy variable for only EE patients was: the percentage of patients with Pretreatment endoscopically-proven EE who had **completed healing** at the Week 8, the Week 12, and the Final Visits.

Medical Reviewer's Comments: Healing of esophageal erosions should be a co-primary endpoint for the EE patients in this study.

8 <u>Statistical Methods</u>: The primary endpoint and the three secondary endpoints for all patients will be analyzed using the sign test. The secondary endpoint for EE patients will be calculated.

9 <u>Study Deviations</u>:
Five non-erosive GERD patients were prematurely discontinued from the study (three for therapeutic failure, one due to an adverse event, and one for poor compliance) and no EE patient was prematurely discontinued from the study.

Overall, the most frequently reported study deviations were: visit date deviations; laboratory evaluations which were ill-timed, not performed, or performed without the patient fasting; missing diary data; missed doses of study drug; and biopsies not obtained. Nine patients enrolled in the study did not meet all of the admission criteria. Patient No. 422 did not have baseline laboratory

blood tests; Patient No. 105 took doxycycline throughout the pretreatment and treatment periods; Patient No. 251 started taking the study drug 27 days prior to his 12th birthday; Patient No. 121 was enrolled without having a urinalysis prior to enrollment; Patient No. 402 was enrolled with only three days of diary data in the Pretreatment Period; and Patient 463 took 4 chewable Tums on Day -13. Furthermore, some patients took concurrent medications not allowed by the study: Patient No. 105 took doxycycline throughout the pretreatment and treatment periods; Patient No. 463 took 4 chewable Tums on Day -13; Patient No. 107 took 30 mg of lansoprazole in addition to the study drug (15 mg of lansoprazole) for the last two days of the Treatment Period, Patients No. 613 and No. 321 took metoclopramide for at least 4 weeks during the Treatment Period.

Medical Officer Comments: The minor protocol deviations should not affect the overall efficacy results of the study.

10 Baseline Demographics and Other Characteristics:

10.1 Baseline Demographics: Eighty-seven adolescent patients were enrolled in the study and treated with lansoprazole. Sixty-four non-erosive GERD patients (grade 0 or 1 per the TAP Esophagitis Grading Scale) were assigned to receive 15 mg of lansoprazole and 23 EE patients (grade 2, 3, or 4 per the Grading Scale) were assigned to receive 30 mg of lansoprazole. The study was conducted at 20 centers in the United States. Table 10 delineates the baseline patient demographics including: gender, race, H. pylori status, weight, height, and age.

Table 10: Baseline patient 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

SD = standard deviation

a Race categories other than Caucasian and Black were combined into one category.

b Histologic *H. pylori* results.

c Subject No. 251 started study drug 27 days prior to his 12th birthday.

Reference: Volume 7, page 62, Table 11.2a

Medical Reviewer's Comments: Overall, the baseline demographics of the study population were acceptable. The average age of the GERD patients was 14. All of the GERD patients satisfied the strict age criteria established in the eligibility criteria, except Patient No. 251 was 11 years and 11 months old. This patient, who is one month younger than the desired population, should have similar safety and efficacy outcomes in the treatment of GERD with lansoprazole.

The study population had a similar racial makeup to the United States' population except that the study population had less Hispanics and slightly more Caucasians.

The study population had a small percentage of GERD patients who were *H. pylori* positive. This is consistent with the adolescent pediatric population in the United States. *H. pylori* is more common in adults over 50 years old than in the pediatric population in the U.S.

The sponsor did not calculate the Body Mass Index (BMI) of the GERD patients. Overweight and obese subjects are more likely to develop GERD than normal weight subjects.

Although this study had more females than males, the distribution of patients according to age is adequate for a study of this size. There is no evidence that adolescent males with GERD and adolescent females with GERD have different outcomes.

Table 11 demonstrates additional baseline demographic characteristics of the GERD patients including tobacco, alcohol, and caffeine consumption.

Table 11: Baseline patient behaviors

VARIABLE	ALL SUBJECTS N= 87 n(%)	LANSOPRAZOLE 15 MG QD N= 64 n(%)	LANSOPRAZOLE 30 MG QD N= 23 n(%)	OVERALL P-VALUE#
TOBACCO				
TOBACCO NONUSER$	83 (95.4)	61 (95.3)	22 (95.7)	
TOBACCO USER	4 (4.6)	3 (4.7)	1 (4.3)	0.947
ALCOHOL				
NONDRINKER&	83 (95.4)	61 (95.3)	22 (95.7)	
DRINKER	3 (3.4)	2 (3.1)	1 (4.3)	
UNKNOWN	1 (1.1)	1 (1.6)	0	0.793
CAFFEINE				
CAFFEINE NONUSER	11 (12.6)	7 (10.9)	4 (17.4)	
CAFFEINE USER	73 (83.9)	56 (87.5)	17 (73.9)	
UNKNOWN	3 (3.4)	1 (1.6)	2 (8.7)	0.350

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 113, Table 14.1_2.1

Medical Reviewer's Comments: The pediatric patient GERD adolescent population in this study used less tobacco than the national average for adolescents.

This study did not provide a procedure for counseling patients on non-pharmacologic methods for treating GERD including decreasing alcohol, caffeine, and tobacco consumption. Standard medical practice in the treatment of pediatric GERD includes non-pharmacologic therapy.

10.2 <u>Past medical history of GERD in the study population</u>:
Of the 87 patients in this study, 30 had a history of GERD less than one year; 13 had a history of GERD one to two years; 28 had a history of GERD greater than two years, but less than five years; and 16 had a history of GERD greater than five years. The most frequently reported predominant GERD symptoms were heartburn, generalized abdominal pain, epigastric abdominal pain, chest pain, regurgitation, sour taste, nausea, and vomiting. Some patients reported several predominant symptoms.

Medical Reviewer's Comments: According to the inclusion criteria in this study, GERD patients must have a history of GERD for at least 3 months prior to the Pretreatment Period and must be symptomatic. Approximately 66% of the patients had a history of GERD over one year and

approximately 18% of the patients had a history of GERD more than five years. The study population satisfied the sponsor's anticipated GERD population.

10.3 Baseline GERD characteristics: Fifty-three (61%) of the 87 patients in this study had received previous medical therapy for their GERD within 12 months prior to the start of the study; 18 patients (21%) had been treated previously with a PPI.

Table 12 displays the baseline frequency and severity of GERD in the study population according to the patients' diaries. The severity of GERD symptoms is classified according to patient diaries as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe (see Table 8). Given that the data is not symmetric, the data is reported as the median values.

Table 12 also displays the baseline amount and frequency of the rescue antacid (mylanta) use according to the patients' diaries.

Table 12: Baseline frequency and severity of GERD and mylanta use based on patient diaries

	N	% of Days with GERD	Daily Severity[a] of GERD	% of Days Antacid Used	Amount of Antacid Used in Teaspoons/ Day
		Median	Median	Median	Median
All Patients	87	88.9	1.61	54.5	1.36
Non-Erosive GERD	64	90.7	1.56	55.1	1.35
EE	23	84.6	1.89	50.0	1.56

a GERD Severity scored as 0=none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe
Reference: Volume 7, page 116-7, Table 14.1_3.1

Medical Reviewer's Comments: The pediatric study population had considerable GERD because the median percentage of GERD symptoms was 89% of the days at baseline. Furthermore, they required antacids 55% of the days at baseline. The study population satisfied the sponsor's anticipated GERD population.

10.4 Baseline Upper Endscopy Results: From the baseline appearance of the esophageal mucosa, endoscopists classified patients into two treatment groups: Treatment Group I (non-erosive GERD patients) and Treatment Group II (EE patients). See Table 13 for a summary of the baseline appearance of the patients' esophageal mucosa.

Table 13: Baseline esophageal mucosa appearance by endoscopy

	Baseline Esophagitis Grade	All Subjects (N = 87) 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

Reference: Study M00-158 – "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 64, Table 14.1_2.1

Medical Reviewer's Comments: The majority of all the GERD patients [79% (69/87)] had baseline abnormalities in the appearance of their esophageal mucosa: 72% (46/64) of the non-erosive GERD patients had a grade 1 appearance (mucosal edema, hyperemia, red streaks, and/or friability) and 100% (23/23) of the EE patients had a grade 2 or 3 appearance.

At baseline, 76% (66/87) of the GERD patients in this study had a grade 1 or grade 2 appearance.

All grades of EE were present in the study population except grade 4 EE.

10.5 Baseline Investigator Interview Results: During the Pretreatment Period interviews, investigators estimated the severity of the patients' GERD (please see Table 14).

Table 14: Baseline GERD severity according to the investigators

	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

Reference: Study M00-158 – "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 66, Table 14.1_3.2

Medical Reviewer's Comments: Several patients with EE had moderate symptoms and several patients with non-erosive GERD had severe symptoms. These results are consistent with the lack of correlation of the severity of GERD symptoms with the severity of esophageal damage. Because symptoms do not correlate with esophageal healing, post-treatment upper endoscopies are required for the EE patients.

11 Efficacy Results:

11.1 Primary Efficacy Endpoint: The pre-specified primary efficacy endpoint was the change in the frequency and severity of GERD symptoms based on patient diary data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the eight-week Treatment Period (day 1 to the Week 8 Visit). Table 15 displays the median percentage of days that patients had GERD symptoms in the Pretreatment Period and the first 8 weeks of the Treatment Period. The values are reported in the median because the data is not symmetric.

Table 15: Median frequency of GERD symptoms

		Entire Pretreatment Period	First 8 Weeks of Treatment Period	Change
	N[a]	Median	Median	Median
Non-Erosive GERD	64	90.7	43.1	-31.8*
EE	23	84.6	16.0	-54.4*
All Patients	87	88.9	33.3	-38.8*

a Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis; * $p < 0.001$; Reference: Adapted from Volume 7, page 179, Table 14.2_1.2

For all GERD patients, the change in the median percentage of days with GERD symptoms in the Pretreatment Period compared to the Treatment Period was statistically significant ($p < 0.001$). Most patients decreased the frequency of their GERD symptoms by about half.

Table 16 displays the mean severity of GERD symptoms in the Pretreatment Period and the first eight weeks of the Treatment Period based on the patient diaries. Table 8 summarizes the grading system used in this study for the severity of GERD symptoms based on the patient diaries: GERD severity is scored as 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.

Table 16: The severity[a] of GERD symptoms

		Entire Pretreatment Period	First 8 Weeks of Treatment Period	Change
	N[b]	Median	Median	Median
Non-Erosive GERD	64	1.6	0.6	-0.7*
EE	23	1.9	0.2	-1.1*
All Patients	87	1.6	0.5	-0.8*

a The severity scale includes: 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe;
b Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis
* $p < 0.001$; The p-value is based on the sign test for significant change from the Pretreatment Period.
Reference: Adapted from Volume 7, page 179, Table 14.2_1.2

For the GERD patients in this study, the change in the median severity of GERD symptoms from the Pretreatment Period compared to the Treatment Period was statistically significant ($p < 0.001$). Patients at baseline had mild to moderate GERD symptoms and patients had none to mild GERD during lansoprazole treatment.

Medical Reviewer's Comments: These efficacy results are difficult to interpret because no placebo group was included in this study. GERD symptoms can improve after non-pharmacologic intervention including lifestyle and dietary changes. Furthermore, adolescent GERD patients may have random waxing and waning of their symptoms and as many as 50% of GERD symptoms may resolve long-term without medication. Therefore, the efficacy of the study medication at the reduction of frequency of GERD symptoms is difficult to assess in this trial.

However, this is a supportive study for the efficacy of lansoprazole in the treatment of GERD in adolescent patients. The sponsor will rely primarily on the efficacy of lansoprazole in the treatment of GERD in adults. Furthermore, the sponsor will have supportive information from PK and PD studies and efficacy data in this study.

11.2 Secondary Efficacy Results:

11.2.1 Secondary Efficacy Variable for EE patients: The percentage of patients with Pretreatment endoscopically-proven EE who had complete healing at the Week 8, the Week 12, and the Final Visits.

All EE patients had baseline esophageal mucosa grades of 2 or 3 in this study. Complete healing was defined as a return of the esophageal mucosa to an esophagitis grade of 0 or 1 (non-erosive GERD). The complete healing rates of the EE in this study are displayed in Table 17.

Twenty-one of twenty-two patients (95%) were completely healed at the Week 8 Visit. Patient No. 471 did not have complete healing at the Week 8 Visit; therefore, Patient No. 471 received an additional 4 weeks of lansoprazole (30 mg per day) for a total of 12 weeks of treatment. Patient No. 471's esophagitis (grade 2) remained unchanged from baseline at both the Week 8 and the Week 12 Visits.

Table 17: Esophageal healing rates for EE patients

Visit	% Healed	n/N
Week 8 Visit	95.5%	21/22
Final Visit	95.5%	21/22

% Healed is defined as the conversion of the esophageal mucosa from grade 2, 3, or 4 (EE) to grade 0 or grade 1 (non-erosive GERD)
n = the number of patients who had complete healing of their EE
N = the total number of EE patients
Reference: Volume 7, page 72, Table 14.2_3

Medical Reviewer's Comments: This secondary endpoint of complete healing in the EE group should have been a pre-specified co-primary endpoint. Many important EE trials have used the complete healing of EE by endoscopy appearance as a primary endpoint.

The endoscopists in this study were not blinded to the patient's clinical status. The endoscopists knew that all the EE patients who received post-treatment endoscopies were treated with 30 mg of lansoprazole for 8 weeks. This may have introduced observation bias to the study.

In addition, Study M00-158 had no control group (no placebo-control, no active control, and no dose-ranging control group.) However, the efficacy of complete healing of EE was 95.5% (21/22) in this study.

Furthermore, these results are similar (or slightly better) than the results of adult EE treatment studies with lansoprazole. In Study M88-269, complete EE healing at 8-weeks occurred in 89% of adult EE patients after treatment with 30 mg of lansoprazole. Similarly, in Study M87-092, complete healing at 8-weeks occurred in 82% of adult EE patients after treatment with 30 mg of lansoprazole.

11.2.2 Secondary Efficacy Variable for non-erosive GERD and EE patients: Another secondary efficacy variable was the change in rescue antacid use based on patient diary data from the Pretreatment Period (day -14 to day -1) compared the first eight weeks of the Treatment Period (starting on day 2 to day 57.) Table 18 summarizes the proportion of days of rescue antacid (mylanta) use during the Pretreatment and Treatment Periods based on the patient diaries. All values are reported in the median because the values are not symmetric. During the Treatment period, the median days patients required antacid was about 6%; in contrast, during the Pretreatment period, the median days patients required antacid was about 55%.

Table 18: Frequency of mylanta use in the Pretreatment and Treatment Periods

		Entire Pre-treatment Period	First 8 Weeks of Treatment Period	Change between the First 8 Weeks and the Pretreatment Period
	N[a]	Median	Median	Median
Non-Erosive GERD	64	55.1	7.3	-37.3*
EE	23	50.0	1.8	-28.6*
All Patients	87	54.5	5.5	-37.0*

a Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis; * $p < 0.001$
Reference: Adapted from Volume 7, page 178 (Table 14.2_1.1) and page 180 (Table 14.2_1.2) and page 182 (Table 14.2_1.3)

Table 19 summarizes the average amount of mylanta used in teaspoons per day in the Pretreatment and Treatment Periods according to the patient diaries.

Table 19: Amount[a] of mylanta use in the Pretreatment and Treatment Periods

		Entire Pre-treatment Period	First 8 Weeks of Treatment Period	Change between the First 8 Weeks and the Pretreatment Period
	N[b]	Median	Median	Median
Non-Erosive GERD	64	1.3	0.3	-0.9*
EE	23	1,6	0.1	-1.1*
All Patients	87	1.4	0.2	-1.0*

a Amount of Mylanta is reported in teaspoons per day
b Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis; * $p < 0.001$
Reference: Adapted from Volume 7, page 178 (Table 14.2_1.1) and page 180 (Table 14.2_1.2) and page 182 (Table 14.2_1.3)

Medical Reviewer's Comments: The improvement in the amount and frequency of rescue medication from baseline to the Treatment Period supports the efficacy of the use of lansoprazole for the treatment of GERD.

11.2.3 Secondary Efficacy Variable for non-erosive GERD and EE patients: Based on investigator interview, the change in the severity of the GERD symptoms from the week prior to the Treatment Period (day -7 to day -1) compared to the week prior to the Week 4 Visit (day 23 to day 29), the week prior to the Week 8 Visit (day 51 to day 57), and the week prior to the Week 12 Visit (day 79 to day 85). Table 9 outlines the grading system that the investigators used in their assessment of the severity of patients' GERD as follows: none = 0, mild = 1, moderate = 2, and severe = 3. Table 20 displays the results of this secondary variable according to the investigators' interviews during the baseline, Week 4, Week 8, and Final Visits.

Table 20: GERD severity according to the investigators' interviews

		SEVERITY OF OVERALL GERD SYMPTOMS			
VISIT	N	None	Mild	Moderate	Severe
Baseline Visit	87	1	16	61	9
Week 4 Visit	85	21	49	14	1
Week 8 Visit	80	35	34	11	0
Final Visit	86	36	36	13	1

Reference: Adapted from Volume 7, page 72, Table 11.4c

Medical Reviewer's Comments: According to the investigator interviews, as the GERD severity decreases after a longer duration of lansoprazole treatment in this study. This secondary endpoint supports the efficacy of the use of lansoprazole for the treatment of adolescent GERD.

Table 21 categorizes the GERD patients into subgroups based on their baseline GERD severity and shows the average GERD severity of all the subgroups after 8 weeks of lansoprazole.

Table 21: The change in GERD severity at the 8-week visit

BASELINE SYMPTOMS (0-3)	N	None (0)	Mild (1)	Moderate (2)	Severe (3)	Mean GERD Score (0-3) at the 8-week visit
None (0)	1	1	0	0	0	0.00
Mild (1)	14	5	8	1	0	0.71
Moderate (2)	56	25	22	9	0	0.71
Severe (3)	9	4	4	1	0	0.67

Reference: Adapted from Volume 7, page 191, Table 14.2_5.2

Medical Reviewer's Comments: All the GERD severity subgroups decreased their average GERD symptom severity after lansoprazole treatment. This secondary endpoint supports the efficacy of the use of lansoprazole for the treatment of adolescent GERD.

D. Efficacy Conclusions

In Study M00-158, the median frequency of the adolescent's GERD symptoms significantly decreased from 88.9% of the days in the baseline Pretreatment Period to 33.3% of the days in the 8-week lansoprazole Treatment Period based on patient diaries. Furthermore, compared to the baseline period, the median severity of the adolescent's GERD symptoms significantly decreased during the 8-week lansoprazole Treatment Period based on patient diaries. Therefore, the co-primary endpoints were achieved. Compared to the baseline period, the frequency and amount of rescue antacid use during 8 weeks of lansoprazole treatment decreased, based on patient diary data. Additionally, the severity of patients' GERD symptoms decreased after 8 weeks of lansoprazole treatment based on investigator interviews. Even though this trial had major design flaws — it was uncontrolled and open-labeled — and was subject to bias, the trial serves as a supportive study in the treatment of GERD and EE in adolescents. Furthermore, the trial demonstrated efficacy in the complete healing of EE after 8 weeks of lansoprazole administration; over 95% (21/22) of the EE patients achieved complete healing at 8 weeks.

Study M97-640 demonstrated that the pharmacokinetic variables (C_{max}, T_{max}, AUC_{0-24}, and the half-life) of adolescent GERD patients after 5 days of lansoprazole was similar to the pharmacokinetics in previously observed healthy adult subjects. Additionally, this study demonstrated that the intra-gastric pH of the adolescent GERD patients improved after 5 days of lansoprazole. Specifically, the mean 24 hour intra-gastric pH and the percentages of time that the intra-gastric pH exceeded 3 and 4 after 5 days of lansoprazole treatment was statistically significant compared to the baseline intra-gastric pH variables.

There was no difference in efficacy between non-erosive GERD and EE patients in overall GERD symptoms, pH parameters, and PK variables after lansoprazole treatment. The efficacy of

lansoprazole in complete healing of EE in adolescent patients with severe EE is not known. Study M00-158 included patients with grade 2 and grade 3 EE; but not patients with grade 4 EE.

Several patients with EE had moderate symptoms and several patients with non-erosive GERD had severe symptoms. These results are consistent with the lack of correlation of the severity of GERD symptoms with the severity of esophageal damage. Because symptoms do not correlate with esophageal healing, post-treatment upper endoscopies are required for the EE patients.

In summary, the efficacy of lansoprazole in the proposed indication was demonstrated by similar lansoprazole pharmacokinetics in pediatric patients between 12 and 17 years old in Study M97-640 compared to healthy adult subjects; by the improvement of intra-gastric pH after 5 days of lansoprazole treatment in Study M97-640; by the efficacy in the complete healing of EE after 8 weeks of lansoprazole treatment in Study M00-158; and efficacy results of lansoprazole treatment in adult GERD patients

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The sponsor has demonstrated the safety of oral lansoprazole in the treatment of GERD and EE in pediatric patients between the ages of 12 and 17 years old (adolescents). A safety review of the two trials uncovered no safety concerns. Analysis of this data demonstrates that the safety profile of this drug in this pediatric population is similar to the safety profile in the adult population and in the pediatric population, between the ages of 1 year to 11 years old. In summary, the combination of data in this ISS, the data in the clinical GERD trials of adults and pediatrics between the ages of 1 year to 11 years old (children), and the post-marketing and literature GERD data from adults and pediatrics, all combine to establish the safety of oral lansoprazole in the treatment of GERD and EE in pediatric patients between the ages of 12 and 17 years old.

B. Description of Patient Exposure

The Integrated Summary of Safety (ISS) consisted of two studies containing 150 GERD patients who received at least one dose of lansoprazole. Table 22 shows the exposure of pediatric GERD patients ages 12 to 17 years old (adolescents), to lansoprazole in the two clinical trials in this supplemental NDA submission. Of the total ISS population, 96 patients received 15 mg of lansoprazole per day and 54 patients received 30 mg of lansoprazole per day. Of the 150 subjects who received lansoprazole in Studies M00-158 and M97-640, 80% were Caucasian and 56% were females. The mean age for all patients was 14.1 years (range: 11-17 years). Additionally, 4.7% were tobacco users, 2.7% were alcohol users, and 82.7% were caffeine users.

Table 22: Patient exposure to lansoprazole in the two studies

Study	# of Sites	Duration of Treatment	Dose of Oral Lansoprazole	# of Patients Entered in Each Group	# of Patient Withdrawals	# of Patient Withdrawals Due to an AE
M00-158	20	8 weeks	15 mg/ day for non-erosive GERD patients	64	5	1
			30 mg/day for EE patients	23	0	0
M97-640	10	5 days	15 mg per day	32	1	1
			30 mg per day	31	0	0
All Studies	30			150	6	2

Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 76, Table 1

The distribution of study drug exposure during the lansoprazole adolescent GERD clinical program directly reflected the different study durations in the 12-week (M00-158) and 5-day (M97-640) studies. A summary of the duration of lansoprazole use in the adolescent GERD studies is presented in Table 23.

Table 23: Duration of lansoprazole use in adolescent patients

Total Duration of Treatment	n (%)		
	All Subjects (N=150)	M00-158 (8-12 weeks) (N=87)	M97-640 (5 days) (N=63)
0 - 9 Days	64 (42.7%)	1 (1.1%)	63 (100.0%)
>9 - 42 Days	4 (2.7%)	4 (4.6%)	0
>42 -70 Days	81 (54.0%)	81 (93.1%)	0
>70 Days	1 (0.7%)	1 (1.1%)	0
Range	4.0 - 88.0	4.0 - 88.0	4.0 - 9.0[a]

SD = Standard Deviation
a Some subjects received greater than 5 days of lansoprazole due to scheduling conflicts.
Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 17, Table 2.4a

Medical Reviewer's Comments: The overall exposure to lansoprazole in the study population is small (N=150), considering that GERD is a chronic disorder. However, the sponsor intends to use this safety data as supportive evidence of the safety of lansoprazole in pediatric patients, ages 12 to

17 years old and additional copious data includes clinical trial and post-marketing safety data from adult and pediatric GERD patients.

C. Methods and Specific Findings of Safety Review

1 Safety Endpoints: Safety endpoints included changes in blood and urine tests, vital signs, gastritis findings (from endoscopies) from the Pretreatment Period compared to the Treatment Period.

2 Safety Analysis: The percentage of patients having adverse events (AEs) will be tabulated using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) and using body systems. Descriptive statistics for changes from the Pretreatment Period in laboratory tests and vital signs results will be presented. The changes will be analyzed by one-sample t-tests.

3 Adverse Events in the Adolescent GERD Studies:

3.1 Deaths: No patients died during the GERD studies in pediatric patients between 12 and 17 years old.

3.2 Serious Adverse Events (SAEs): Five patients in the adolescent GERD studies had serious adverse events (SAEs). During Study M00-158, four patients in the lansoprazole 15 mg per day dose group experienced SAEs and all required hospitalization. Three patients experienced events (suicide attempt, dehydration due to gastroenteritis, and a torn hamstring muscle) that were considered not related to the study drug and one experienced an AE (acute cholecystitis) that was considered unlikely to be related to the study drug.

During Study M97-640, one patient in the lansoprazole 30 mg per day dose group experienced a SAE (moderate gastrointestinal disorder with symptoms of chest pain, abdominal pain, and increased cough) and required hospitalization. The sponsor considered this SAE due to an exacerbation of the patient's GERD; but not related to lansoprazole, the study drug. Table 24 summarizes the five SAEs experienced by patients in Studies M00-158 and M97-640.

Table 24: Serious reported adverse events

	Study #	Patient #	Age	Sex	Total Days in Study	Treatment Day of Onset	Treatment Day Stopped	SAE	Severity
1	M00-158	301	13	F	40	53	54	Suicide Attempt	Mild
2	M00-158	107	14	M	55	52	57	Dehydration due to Gastroenteritis	Severe
3	M00-158	131	12	F	57	9	35	Torn Left Hamstring	Severe
4	M00-158	132	16	F	58	26	40	Acute Cholecystitis	Severe
5	M97-640	64	16	F	6	7	13	Exacerbation of GERD	Moderate

Reference: Adapted from Volume 7, page 222, Table 14.3.2_1 and Integrated Summary of Safety Volume 9, Page 137, Table 7.2

The following are the four SAEs narratives in Study M00-158:

1) Patient No. 301: A 13-year-old Caucasian female, with a history of depression, was hospitalized for a suicide attempt by intentional acetaminophen overdose on Day 53 (13 days post-treatment). The patient took approximately fifty 500 mg acetaminophen tablets. She was taken to the emergency room and treated with activated charcoal and mucomyst®. Four hours after ingestion, her acetaminophen level was 148, which was considered to be a borderline hepatotoxic level and she was hospitalized. The event was considered resolved on Day 54 and the patient began follow-up therapy with her psychologist.

Concomitant medications at the time of the event included paxil CR®. The investigator considered this SAE (suicide attempt) not related to the study drug. The patient was not taking the study drug (15 mg of lansoprazole) at the time of the SAE because the patient was previously discontinued from the study on treatment day 41 due to mild dizziness and moderate. The AEs on day 41 were considered possibly related to the study drug.

2) Patient No. 107: A 14-year-old Caucasian male with a history of a head injury due to a motor vehicle accident, attention deficit hyperactivity disorder, lower intestine bacterial overgrowth, and recent infections with mononucleosis and Streptococcal throat, developed 3 days of vomiting, diarrhea, and increased temperature. He was diagnosed with dehydration due to severe gastroenteritis and he required hospitalization on Day 55. He was treated with intravenous fluids, potassium, and Rocephin®. The events resolved on Day 57 and the patient was discharged from the hospital.

Concomitant medications at the time of admission included omnicef®, tussionex®, tylenol® with codeine, adderall®, zyrtec®, fibercon®, and hyoscyamine. The investigator considered this SAE

not related to the study drug. The patient developed this SAE after he completed the full 8-week treatment period with the study drug (15 mg of lansoprazole.)

3) Patient No. 131: A 12-year-old Caucasian female, with no significant past medical history, experienced a severe torn left hamstring while performing a cheerleading jump on Day 9. The investigator described the event as causing significant disability. The subject developed immediate pain and could not walk. She was treated with rest, leg elevation, and tylenol® and the event resolved on Day 35. No concomitant medications were reported.

The investigator considered the SAE not related to the study drug. The patient did not stop the study drug (15 mg of lansoprazole) during the SAE.

4) Patient No. 132: A 16-year-old Caucasian female patient with a history of recent weight loss and a healed gastric ulcer developed severe nausea on day 26. The patient had an ultrasound (normal) and a HIDA scan which indicated non-filling of the gallbladder consistent with acalculous cholecystitis. She was hospitalized and had a laparoscopic cholecystectomy. The event was considered resolved on Day 40.

The investigator considered this SAE not likely related to the study drug (lansoprazole 15 mg). Concomitant medications at the time of the hospital admission included lexapro®, zofran®, trazodone®, and birth control pills. During the nausea the study drug was temporarily discontinued and then restarted post-operatively.

The following is the one SAE narrative in Study M97-640:

5) Patient 64: A 16-year-old female, with a past medical history of headaches, received 30 mg of lansoprazole for six days and completed Study M97-640. On Post-Study Day 1, the investigator started her on 30 mg BID of lansoprazole for an exacerbation of GERD (moderate cough, abdominal pain, and chest pain.) On Post-Study Day 3, the investigator further increased the lansoprazole to 60 mg BID. However, the patient continued to have these symptoms; therefore, she was hospitalized on Post-Study Day 5. She was treated with intravenous zantac® and her chest pain improved. She experienced a mild-moderate headache for 6 days; therefore, on Post-Study Day 6, lansoprazole was discontinued. The investigator felt the headaches were not related to the study drug; but due to a tension headache. On Post-Study Day 7, she was started on prilosec® 20 mg BID; her GERD symptoms returned to baseline, her headache resolved, and she was discharged from the hospital. Following her discharge from the hospital, the patient reported recurring headaches, as well as persistent GERD symptoms despite increasing the prilosec® to 40 mg BID, and then to 40 mg TID. At the Post-Study Day 24 follow-up visit, her concomitant medications included prilosec® 40 mg TID, ranitidine 300 mg QHS, propulsid® 20 mg BID, and paxil® 30 mg QD.

The investigator felt that her SAE (chest pain, abdominal pain, and her cough) were not related to the study drug; but due to an exacerbation of her GERD.

Medical Reviewer's Comments: Based on the information presented, this reviewer is in agreement with the sponsor that the SAEs were not related or not likely related to the lansoprazole.

3.3 Withdrawals Due to Adverse Events:

Two patients withdrew from the lansoprazole studies due to AEs:

1) Patient No. 301 (see above) in Study M00-158 discontinued treatment after 40 days of therapy because of mild dizziness and moderate vomiting. The investigator believed that these AEs were possibly related to the study drug (15 mg of lansoprazole.)

2) Patient No. 69 in Study M97-640: A 14-year-old male with a past medical history of asthma, allergies, and eosinophilic esophagitis, developed hives, peripheral edema, and a generalized papular rash on Study Day 3. The patient was treated with Benadryl® on Study Day 3. The patient discontinued the study drug (lansoprazole 15 mg per day) on Study Day 4. The mild AEs resolved on Post-Study Day 3. The investigator felt that these AEs had a possible relationship to the study drug.

Medical Reviewer's Comments: Based on the information presented, this reviewer is in agreement with the sponsor that these two AEs were possibly related to the study drug (lansoprazole.)

3.4 Frequent Adverse Events: Among all patients, 78/150 (52%) experienced one or more treatment AEs. The most frequently reported treatment-related AEs in pediatric patients between 12 and 17 years old, were headache (13%), abdominal pain (9%), pharyngitis (9%), vomiting (6%), diarrhea(6%), and dizziness (5%). Table 25 displays the most frequent AEs (by body system) experienced by pediatric GERD patients between 12 and 17 years old, who received at least one dose of lansoprazole in Studies M00-158 or M97-640.

Table 25: Most frequently experienced AEs for all patients

Body System/ COSTART Term	All Subjects (N=150)	M00-158 (N=87)	M97-640 (N=63)
Any Event	78 (52%)	57 (66%)	21 (33%)
Body as a Whole			
Abdominal Pain	13 (9%)	12 (14%)	1 (2%)
Headache	19 (13%)	14 (16%)	5 (8%)
Infection	7 (5%)	6 (7%)	1 (2%)
Pain	7 (5%)	5 (6%)	2 (3%)
Accidental Injury	6 (4%)	5 (6%)	1 (2%)
Asthenia	4 (3%)	4 (5%)	0
Flu Syndrome	5 (3%)	5 (6%)	0
Fever	3 (2%)	3 (3%)	0
Viral Infection	2 (1%)	2 (2%)	0
Digestive System			
Vomiting	9 (6%)	9 (10%)	0
Diarrhea	9 (6%)	8 (9%)	1 (2%)
Nausea	7 (5%)	6 (7%)	1 (2%)
Dyspepsia	2 (1%)	2 (2%)	0
Gastroenteritis	2 (1%)	2 (2%)	0
Metabolic and Nutritional System			
SGOT Increased	2 (1%)	2 (2%)	0
Nervous System			
Dizziness	8 (5%)	7 (8%)	1 (2%)
Respiratory System			
Pharyngitis	13 (9%)	8 (9%)	5 (8%)
Cough Increased	5 (3%)	5 (6%)	0
Sinusitis	5 (3%)	4 (5%)	1 (2%)
Rhinitis	3 (2%)	3 (3%)	0
Skin and Appendages			
Urticaria	3 (2%)	2 (2%)	1 (2%)
Vesiculobullous Rash	2 (1%)	2 (2%)	0

To be included in this table, AEs had to have occurred in two or more patients. Adapted from Integrated Summary of Safety, Volume 9, Page 20, Table 3.1a

Table 26 displays the most frequent experienced AEs that are possibly, probably, or definitely caused by lansoprazole treatment according to the investigators.

Table 26: Most frequently experienced AEs that are possibly, probably, or definitely caused by lansoprazole treatment

Body System/ COSTART Term	All Subjects (N=150)	M00-158 (N=87)	M97-640 (N=63)
Any Event	18 (12%)	13 (15%)	5 (8%)
Body as a Whole			
Headache	6 (4%)	6 (7%)	0
Abdominal Pain	4 (3%)	4 (5%)	0
Digestive System			
Nausea	3 (2%)	3 (3%)	0
Nervous System			
Dizziness	4 (3%)	3 (3%)	1 (2%)

To be included in this table, AEs had to have occurred in two or more patients.
Adapted from Integrated Summary of Safety, Volume 9, Page 21, Table 3.1b

Medical Reviewer's Comments: Unfortunately, no comparison of the AE frequency can be made in these two studies, since both studies did not have a comparator group.

The adverse event profile in these pediatric patients resembled that of adult patients and pediatric patients (between ages 1 and 11) taking lansoprazole. The incidence of possibly, probably, or definitely treatment-related abdominal pain was 3%, 2.1%, and 1.2% in these pediatric patients, in lansoprazole-treated adults in the current label, and in placebo-treated adults in the current label, respectively. The incidence of possibly, probably, or definitely treatment-related nausea was 2%, 1.3%, and 1.2% in these pediatric patients, in lansoprazole-treated adults in the current label, and in placebo-treated adults in the current label, respectively.

There were no AEs reported in these two trials that were not previously reported in adults or pediatric patients between ages 1 and 11.

There was little difference in the pattern of AEs experienced by patients receiving lansoprazole 15 mg per day compared to patients receiving lansoprazole 30 mg per day in the analysis of AEs by dose in the adolescent GERD studies.

4 Clinical Laboratory Evaluations: Laboratory tests were preformed at baseline (during the Pretreatment Period), at the Week 4 Visit, at the Week 8 Visit, and the Final Visit (if applicable). The Final Visit for non-erosive GERD patients and EE patients, who had completely healed EE at the Week 8 Visit, was the Week 8 Visit. In contrast, the Final Visit for EE patients, who did not have completed healing at the Week 8 Visit, was the Week 12 Visit. Finally, the Final Visit for all (non-erosive GERD and EE) patients, who prematurely terminated from the study during the Treatment Period, was the last day that each patient received the study drug.

Laboratory evaluations included the following:

1) Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count.
2) Blood chemistry determinations: total protein, glucose, blood urea nitrogen, creatinine, gamma glutamyl transferase, hepatic panel, total cholesterol, calcium, inorganic phosphorus, sodium, potassium, chloride, and uric acid.
3) Serum gastrin determinations: samples were drawn before the endoscopy procedure or 24 hours after the endoscopy procedure. Gastrin specimens were frozen immediately and shipped to (b) (4) on 5 pounds of dry ice on the day of collection.
4) Urinalysis: specific gravity, pH, glucose, ketones, protein, and microscopic examination.
5) Pregnancy Tests: a serum pregnancy test was completed for all female patients and results were to be negative for the patient to enter and, subsequently, to continue in the study.
6) Theophylline, phenytoin, phenobarbital, digoxin, and/or carbamazepine levels: patients taking these drugs were to have serum drug levels monitored to assure that proper levels of these drugs were being maintained. The time of the last dose of medication was recorded each time a drug level was drawn.

When an individual patient had a laboratory value that was outside the sponsor's thresholds for potentially concerning laboratory results, a listing of all related values for that patient was generated and reviewed by the sponsor to determine whether further action was needed.

No consistent clinical changes were identified in changes from baseline to the final visit for any hematology, chemistry, or urinalysis value. Among all laboratory variables, no trends were identified and no changes were medically relevant.

Statistically significant mean changes in several laboratory variables from baseline to final visit were identified in the two adolescent pediatric GERD studies. Most of these changes were small and not considered clinically significant.

Table 27 shows the fasting serum gastrin levels in both adolescent GERD studies. The normal serum gastrin range according to the laboratory used in the studies was 25 to 111 pg/mL.

Table 27: Fasting gastrin levels in Study M00-158

			QUARTILES			
VISIT	**N**	**MEAN (SD)** in pg/mL	**25%** in pg/mL	**MEDIAN** in pg/mL	**75%** in pg/mL	**P-VALUE**
Baseline	85	58.8 (92)	38.0	45.0	55.0	N/A
Week 4	78	89.9 (74)	52.0	71.0	99.0	0.005
Week 8	74	76.3 (51)	43.0	65.5	88.0	0.057
Final	86	80.1 (69)	44.0	64.0	88.0	0.015

Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 51, Table 6.0a

Five subjects had fasting serum gastrin levels of ≥ 200 pg/mL during Study M00-158. Table 28 documents the five serum gastrin level outliers in pg/mL.

Table 28: Elevated serum gastrin values during Study M00-158

Subject No./ Gender/Age (years)	Lansoprazole Dose	Gastrin Level (pg/mL)		
		Baseline	Week 4 Visit	Week 8 Visit
245/F/12	15 mg QD	66	247	42 (Day 56, 1 Day Post-treatment)
621/F/13	30 mg QD	51	220	83 (Day 58, 1 Day Post-treatment)
213/F/13	15 mg QD	66	200	162 (Day 60, 1 Day Post-treatment)
511/F/15	30 mg QD	512 (Day -13) 880 (Day -1)	350	366 (Day 52, 1 Day Post-treatment)[a]
113/F/17	15 mg QD	106	538	No follow-up gastrin value available due to premature termination

Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 52, Table 6.0b

Medical Reviewer's Comments: Hypergastrinemia is a well-documented effect of all the PPIs in adult subjects and patients. Furthermore, hypergastrinemia was documented in GERD studies in pediatric patients between ages 1 to 11 years old. PPIs significantly lower gastric acid output, which is thought to trigger a compensatory increase in gastrin production and finally an increase in gastrin serum levels.

Similar degrees of gastrin elevation were seen in the pediatric children, pediatric adolescent, and adult populations. The current labeling for lansoprazole states that "in over 2100 (b) (4) patients, median fasting gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with lansoprazole." In these two adolescent GERD studies, post-treatment follow-up gastrin levels were not performed; therefore, no comment can be made on reversibility. However, these high levels will most likely return to normal after lansoprazole is withdrawn.

Elevated gastrin has been trophic for enterochromaffin-like (ECL) cells; which has been shown to lead to ECL carcinoid tumors in rats. However, long-term use of PPIs has not been shown to cause gastric carcinoids in human adults. Less data exists for the effects of elevated gastrin in the pediatric population.

5 Vital Signs and Physical Findings: Most of the vital signs and physical findings during treatment were unchanged from baseline in both adolescent GERD studies. Occasionally, statistically significant mean changes in physical exam findings including vital signs occurred.

Medical Reviewer's Comments: None of the statistically significant mean changes in the physical exams (including vital signs) were clinically significant.

6 Drug Interactions:

No drug interaction studies were conducted for lansoprazole in adolescents.

Based on the known potential drug interactions of lansoprazole in adults, theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin levels, were to be monitored during the Treatment Periods of Studies M00-158 and M97-640. However, no patients took these drugs during these studies.

Medical Reviewer's Comments: According to the oral lansoprazole label, "lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies (in adults) have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. When lansoprazole was administered concomitantly with theophylline (b)(4) , a minor (10%) increase in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels."

According to the lansoprazole label, "lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin)."

Additionally, lansoprazole should be taken at least 30 minutes prior to sucralfate because lansoprazole's bioavailability was reduced by 17% when administered concomitantly with sucralfate in adult subjects.

Since pediatric GERD patients between ages 12 and 17 have similar PKs and PDs of lansoprazole as adult patients, similar precautions should be taken when medications are given concomitantly with lansoprazole in adolescent patients.

D. Adequacy of Safety Testing

Overall, the sponsor has adequately assessed the safety of lansoprazole for the proposed indications. The duration of lansoprazole exposure was sufficient, given that the indications are for short term therapies. Additional supportive safety data exists in adult GERD patients.

E. Summary of Critical Safety Findings and Limitations of Data

Overall, lansoprazole appears safe to use in pediatric patients, ages 12 to 17 years of age. In the two adolescent trials, no adverse events were reported that were not previously reported in adults or pediatric patients between ages 1 and 11 years old. Furthermore, adolescents that received 15 mg or 30 mg of lansoprazole per day experienced little difference in their pattern of adverse events. Long-term data is needed on the effect of hypergastrinemia on ECL cells in the adolescent population.

VIII. Dosing, Regimen, and Administration Issues

This medical officer recommends a lansoprazole dose of 15 mg once daily for (b) (4) 8 weeks for the treatment of non-erosive GERD and a lansoprazole dose of 30 mg once daily for (b) (4) 8 weeks for the treatment of EE in pediatric patients between the ages of 12 to 17 years old. The evidence for this dosing recommendation is from numerous GERD studies in adult patients and the two supportive pediatric studies submitted in this sNDA.

Since the efficacy of non-erosive GERD and EE treatment with lansoprazole in adolescent patients is primarily based on the safety and efficacy of lansoprazole in adult patients, the pediatric regimen should be similar to the safe and effective adult regimen. Two weeks of lansoprazole treatment of non-erosive GERD in adults is less effective than four to eight weeks of lansoprazole therapy. Similarly, four weeks of lansoprazole treatment of EE in adults is less effective than six to eight weeks of lansoprazole therapy. Therefore, the adolescent dose of lansoprazole in the treatment of non-erosive GERD and EE should be at least 4 weeks and 6 weeks, respectively.

Lansoprazole is available in three oral formulations: delayed-release capsules, delayed-release oral suspension, and delayed-release orally disintegrating tablets (solutab). Lansoprazole products should be taken before eating. No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

Lansoprazole delayed-release capsules should be swallowed whole; they should not be crushed or chewed. Alternatively, for patients who have difficulty swallowing capsules, lansoprazole delayed-release capsules can be opened and administered as follows: open capsule; sprinkle intact granules on one tablespoon of either applesauce, ensure®, pudding, cottage cheese, yogurt, or strained pears; and swallow immediately. The capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows: open capsule; sprinkle intact granules into a small volume of apple juice, orange juice, or tomato juice (60 mL); mix briefly; and then swallow immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. The use of the capsules in other foods and liquids has not been studied clinically and is therefore not recommended.

(b) (4)

The delayed-release orally disintegrating tablets (solutab) are not designed to be swallowed intact, chewed, or crushed. The tablet typically disintegrates in less than 1 minute. Place the tablet on the tongue and then allow it to disintegrate with or without water until the particles can be swallowed.

The delayed-release oral suspension should be administered as follows: open packet; to prepare a dose, empty the packet contents into a container containing 2 tablespoons of water (do not use other liquids or foods); stir well; and then drink immediately. If any material remains after drinking, add more water, stir, and drink immediately. This product should not be given through enteral administration tubes.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

A similar percentage of females and males experienced AEs (55% and 48%, respectively). A higher percentage of females experienced dizziness, infection, pain, cough increased, sinusitis, and asthenia (8%, 6%, 6%, 6%, 5%, and 4%, respectively) compared to males (2%, 3%, 3%, 0%, 2%, and 2%, respectively). Conversely, a higher percentage of males experienced abdominal pain and flu syndrome (12% and 6%, respectively) compared to females (6% and 1%, respectively). Table 29 demonstrates the most frequent AEs by gender in both adolescent GERD studies

Table 29: Most frequently experienced AEs by gender

Body System/ COSTART Term	n (%) Females (N=84)	Males (N=66)
Any Event	46 (55%)	32 (48%)
Body as a Whole		
Headache	9 (11%)	10 (15%)
Abdominal Pain	5 (6%)	8 (12%)
Infection	5 (6%)	2 (3%)
Pain	5 (6%)	2 (3%)
Accidental Injury	4 (5%)	2 (3%)
Asthenia	3 (4%)	1 (2%)
Fever	2 (2%)	1 (2%)
Flu Syndrome	1 (1%)	4 (6%)
Digestive System		
Diarrhea	6 (7%)	3 (5%)
Nausea	4 (5%)	3 (5%)
Vomiting	4 (5%)	5 (8%)
Nervous System		
Dizziness	7 (8%)	1 (2%)
Respiratory System		
Pharyngitis	6 (7%)	7 (11%)
Cough Increased	5 (6%)	0 (0%)
Sinusitis	4 (5%)	1 (2%)
Dyspnea	2 (2%)	0 (0%)
Rhinitis	2 (2%)	1 (2%)
Skin and Appendages		
Rash	2 (2%)	0 (0%)
Urticaria	2 (2%)	1 (2%)
Vesiculobullous Rash	0	2 (3%)

Reference: Integrated Summary of Safety, Volume 9, Page 26, Table 3.2c

Medical Reviewer's Comments: There was little difference in the pattern of AEs experienced by females compared to males in the analysis of AEs by gender in the adolescent GERD studies.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Evaluations of AEs by race and age were not prepared by the sponsor, since the overwhelming majority of patients (80.0%) were Caucasian and all were between 11 and 17 years of age.

C. Evaluation of Pediatric Program

In the United States, lansoprazole is approved for the treatment of GERD and EE in pediatric patients between the ages of 1 to 11 years old. The treatment of GERD and EE in pediatric patients between the ages of 12 to 17 years old, with lansoprazole is the subject of this sNDA.

The sponsor has not started pediatric studies in pediatric GERD patients less than one year of age. Prior to initiation of these studies, the sponsor will need to develop an age-appropriate lansoprazole formulation and will need to perform a 4-week repeated dose toxicity study in neonatal rats and a 90-day repeated dose toxicity study in neonatal dogs.

D. Comments on Data Available or Needed in Other Populations

The sponsor has not started pediatric studies in pediatric GERD patients less than one year of age. Prior to initiation of these studies, the sponsor will need to develop an age-appropriate lansoprazole formulation and will need to perform a 4-week repeated dose toxicity study in neonatal rats and a 90-day repeated dose toxicity study in neonatal dogs.

X. Conclusions and Recommendations

A. Conclusions

Lansoprazole has a favorable benefit/risk profile in the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 and 17 years old (adolescents). The safety and efficacy of prevacid® (lansoprazole) delayed-release capsules in the treatment of non-erosive GERD and EE are based on adequate and well-controlled trials in adult GERD patients and additional safety, efficacy, pharmacokinetic, and pharmacodynamic studies performed in pediatric GERD patients between 12 and 17 years old.

The safety and efficacy of prevacid® (lansoprazole) delayed-release oral suspension and prevacid® (lansoprazole) delayed-release orally disintegrating tablets for these indications in adolescents are based on adult PK and PD studies that demonstrated bioequivalence of these oral formulations to the delayed release capsules.

In the clinical trials presented in this efficacy supplement, lansoprazole administration decreased the frequency and severity of GERD symptoms in adolescents with GERD (the co-primary endpoints) and achieved complete healing of EE in over 95% of the pediatric adolescent EE patients. Furthermore, lansoprazole demonstrated an acceptable safety profile in these studies.

Studies M00-158 and M97-640 satisfy Studies Three and Four, respectively, of the Lansoprazole Pediatric Written Request issued by the Division of Gastrointestinal and Coagulation Drug Products.

B. Recommendations

From a clinical perspective, this medical officer recommends that this sNDA is approvable pending labeling changes. If the sponsor accepts the labeling changes, then this medical officer recommends approval of prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) for the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 and 17 years old. Please see my labeling recommendations in the Appendix.

Since the pharmacokinetics of lansoprazole are similar in pediatric adolescent GERD patients and healthy adult subjects; similar precautions should be taken when theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin are given concomitantly with lansoprazole in adolescent patients.

XI. Appendix

A. Review of Label

For my labeling recommendations, words formatted with ***bold and italics*** signify an addition and words formatted with a ~~strikethrough~~ indicate a deletion.

The following are my recommendations for labeling changes in the "**Pediatric Use**" subsection of the "**PRECAUTIONS**" section of the lansoprazole oral label:

1) In the first paragraph, the sponsor proposes the following label change:

(b) (4)

Medical officer's comments: These changes are acceptable. However, to improve the clarity of the label, I recommend the following changes to the paragraph:

> The safety and effectiveness of PREVACID have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis. Use of PREVACID in this population is supported by evidence from adequate and well controlled studies of PREVACID in adults with additional clinical, pharmacokinetic, ***and*** pharmacodynamic~~s~~ (b) (4) studies performed in pediatric patients. The adverse events profile in pediatric patients is similar to that of adults. There were no adverse events reported in U.S. clinical studies that were not previously observed in adults. ***The*** ~~S~~safety and effectiveness ***of PREVACID in patients < 1 year of age*** have not been established (b) (4) (b) (4)

2) The sponsor proposes the following subtitles: "**1 to 11 years of age**" and "**12 to 17 years of age**".

Medical officer's comments: This change to the label is acceptable.

3) The sponsor proposes to change the word "ml" to "mL".

Medical officer's comments: This change to the label is acceptable.

4) The sponsor proposes to change "lansoprazole" to "PREVACID".

Medical officer's comments: This change to the label is acceptable. This change maintains consistency throughout this subsection.

5) The sponsor proposes to [redacted] (b) (4)

Medical officer's comments: This change to the label is acceptable. This changes the location of these sentences; these sentences are added to the label in another part of this subsection.

6) The sponsor proposes the following addition to the label:

[redacted] (b) (4)

(b) (4)

In an ***uncontrolled,*** open-label, U.S. multi-center study, 87 adolescent patients (12 to 17 years of age) with symptomatic GERD ***were treated with PREVACD for 8 to 12 weeks. Baseline upper endoscopies classified pediatric GERD patients into*** [redacted] ***two groups: 64 (74%) non-erosive GERD and 23 (26%) erosive esophagitis (EE). The non-erosive GERD patients received PREVACID 15 mg q.d. for 8 weeks and the EE patients received PREVACID 30 mg q.d. for 8 to 12 weeks*** [redacted] At baseline, 89% of ***these*** patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). [redacted]

During 8 weeks of PREVACID treatment, adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results. Twenty-one of 22 ***(95.5%)*** adolescent erosive esophagitis patients were healed after 8 weeks of PREVACID treatment. One patient remained unhealed after 12 weeks of treatment.

GERD symptoms and EE healing in pediatric patients (12 to 17)

GERD	Final Visit
Symptomatic GERD (All Patients) Improvement in Overall GERD Symptoms[a]	73.2% (60/82)[b]
Non-erosive GERD Improvement in Overall GERD Symptoms[a]	71.2% (42/59)[b]
Erosive Esophagitis Improvement in Overall GERD Symptoms[a]	78.3% (18/23)

a Symptoms assessed by patient diary (parents/caregivers as necessary).
b No data available for 5 patients.
c Data from one healed patient ***was*** excluded from this analysis due to timing of final endoscopy

The above paragraph adds clarity to the label. It is important to divulge the uncontrolled study design and to add a title to the table.

7) The sponsor proposes to add this sentence to the label:

[redacted]

[redacted] (b) (4)

Medical officer's comments: This change to the label is acceptable. However, I have the following minor labeling recommendations:

"In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/mL at baseline to 64 pg/mL [interquartile range (25th – 75th percentile) of 44 – 88 pg/mL] at the final visit. ***(Normal serum gastrin levels are 25 to 111 pg/mL.)***

The safety of PREVACID Delayed-Release Capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients ~~with GERD~~, 6% (5/87) took PREVACID for <6 weeks, 93% (81/87) for 6-10 weeks, and 1% (1/87) for >10 weeks.

The most frequently reported (at least 3%) treatment-related adverse events in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in < 1% of adult patients, was reported in this study by 3 adolescent patients with non-erosive GERD, who had dizziness concurrently with other events (such as migraine, dyspnea, and vomiting)."

B. Abbreviations

Please see Table 30 for a list of abbreviations used in this review.

Table 30: List of abbreviations

AEs	adverse drug events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24}	area under the plasma concentration-time curve
BID	two times a day
BMI	body mass index
C_{max}	maximum observed plasma concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CYP	cytochrome
ECL	enterochromaffin-like
EE	erosive esophagitis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
H. pylori	*Helicobacter pylori*
H_2RAs	histamine-2 receptor antagonists
ICH	International Conference on Harmonisation
ISS	Integrated Summary of Safety
LPWR	Lansoprazole Pediatric Written Request
mg	milligram
mL	milliliter
NDTI	National Disease and Therapeutic Index
ng	nanogram
NSAID	non-steroidal anti-inflammatory drugs
PD	pharmacodynamic
pg/mL	picograms per milliliter
PK	pharmacokinetic
PPC	patients, their parents, or their caregivers
PPI	proton pump inhibitor
PPSR	Proposed Pediatric Study Request
q d	once daily
SAE	serious adverse event
sGERD	symptomatic GERD
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
TAP	TAP Pharmaceutical Products Inc. (the sponsor)
The Division	Division of Gastrointestinal and Coagulation Drug Products
T_{max},	time to reach the observed maximum plasma concentration
UGI	upper gastrointestinal
WR	written request

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/s/

Eric Brodsky
6/15/04 10:15:08 AM
MEDICAL OFFICER

Ruyi He
6/15/04 11:14:39 AM
MEDICAL OFFICER