CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-056

MEDICAL REVIEW(S)

CLINICAL REVIEW
DIVISION OF GASTROENTEROLOGY PRODUCTS

Application Type	NDA
Submission Number	22-056/000
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Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	October 15, 2007
Established Name	Omeprazole
(Proposed) Trade Name	Prilosec
Therapeutic Class	Proton Pump Inhibitor
Applicant	AstraZeneca
Priority Designation	S
Formulation	Delayed-Release Oral Suspension
Dosing Regimen	2.5 &10 mg once daily for up to 8 weeks
Indication	Short-term treatment of symptomatic gastroesophageal reflux disease and erosive esophagitis
Intended Population	0 to 2 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 22-056/000, Prilosec Delayed-Release Oral Suspension, is recommended for **Approvable** for the short-term treatment of symptomatic gastroesophageal reflux disease (GERD), and healing of erosive esophagitis in patients 0 to 2 years old.

The recommendation is based on the demonstrated safety and efficacy (Study 251) and the bioavailability (Studies 250 and D9586C00002) of the bicarbonate formulation of omeprazole.

1.2 Recommendation on Postmarketing Actions

No recommendations on postmarketing actions, based on the current application, are given.

1.2.1 Risk Management Activity

Based on the available information, no risk management activity is required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The product is Prilosec Delayed-Release Oral Suspension. It is an age-appropriate formulation of omeprazole (2.5 and 10 mg) for pediatric patients 0 to 2 years of age.

The proposed indications are short-term treatment of symptomatic GERD and erosive esophagitis.

The efficacy was studied in a Phase 3 trial (Study 251) with 106 patients with clinical diagnosed GERD aged 0 to 2 years old.

The overall safety database included 128 patients (106 in Study 251 and 25 in Study 250) who were 0.5 to 24 months old and took at least one dose of study medication. The maximum exposure was 1.5 mg omeprazole P.O. once daily for 8 weeks in 31 subjects. Postmarketing data were not submitted.

1.3.2 Efficacy

Study 251 was the major efficacy trial, and was originally submitted to NDA 19,810-S074 on December 22, 2000. Medical Officer Dr. Scheldon Kress reviewed this study.

The primary efficacy endpoint was to investigate the average number of vomiting/regurgitation episodes per patient per day in the last 72 hours of treatment as compared with the baseline.

The secondary efficacy endpoints were to investigate:

- Proportion of patients who had no moderate or severe regurgitation/vomiting symptoms during the last 72 hours;
- Proportion of patients who had no moderate or severe pain-related symptoms during the last 72 hours;
- Proportion of patients who were successfully treated, where successful treatment is defined as no moderate or severe overall evaluation, as defined by the Physician's Global Assessment.

Previous Medical Officer's Conclusion:
"It can be concluded that omeprazole administered as a bicarbonate suspension effectively reduced the number by approximately 50% and the intensity of vomiting/regurgitation episodes as well as the intensity of pain-related GERD symptoms. Patients demonstrated -4.35 (95% CI: -8.2, -0.46), -2.97 (95% CI: -7.0, 1.06) and -4.34 (95% CI: -8.5, -0.15) decrease in vomiting/regurgitation episodes per day during the last 72 hours in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, respectively. Results with a sensitivity and graphical analysis suggest greater efficacy with larger doses. All 3 dosages of omeprazole were safely administered and well tolerated in this pediatric population."

Medical Officer's Comments:
I concur with Dr. Kress's conclusion in that the product reduced the number and intensity of vomiting/regurgitation episodes. In my opinion, the interpretation of the efficacy data of Study 251 is limited by the lack of a concomitant efficacy comparator. The sponsor does not provide the proportion of patients whose vomiting episodes decreased by 50%.

1.3.3 Safety

The safety profiles were assessed with reports of adverse events (AEs), discontinuation due to adverse events (DAEs), clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis), changes to medical history, vital signs, and physical examinations. These assessments were consistent with standard of care in pediatric medical practice.

The overall safety database involved 131 patients (106 in Study 251 and 25 in Study 250) who were 0.5 to 24 months old and took at least one dose of study medication. The maximum exposure was 1.5 mg omeprazole P.O. once daily for 8 weeks in 36 subjects.

Of the 106 patients in the safety population in Study 251, 83 (78%) reported one or more adverse events (AEs) during the study. The most frequently occurring AEs were the respiratory disorder (49, 46.2%), gastrointestinal disorder (46, 43.4%), and immunity disorder (29, 27.4%).

There were no deaths in this study. There were 7 serious adverse events (SAEs). Two of the 7 experienced exacerbation of GERD symptoms and crying, leading to study discontinuation. The remaining 5 SAEs consisted of pneumonia, urinary tract infection, lymphadenitis, pertussis, and bronchiolits with croup. The investigators considered the SAEs to be unlikely related to the study drug.

Previous Medical Officer's Comments:

"Omeprazole therapy was well tolerated in all dose groups. Nearly all AEs experienced by patients were either mild or moderate in intensity. Five patients were reported with serious AEs, all of which were attributed to be unlikely related to study medication. Abnormal laboratory results that were reported as AEs were also evaluated to be unlikely related to study medication. Based upon these results, it can be concluded that omeprazole administered as a bicarbonate suspension is generally well tolerated in the 0 months to 24 month pediatric population."

Medical Officer's Comment:

I agree with Dr. Kress's conclusions on safety.

The to-be-marketed formulation has an active ingredient (magnesium) different from the suspension granules (sodium) administered in Study 251. The magnesium of the to-be-marketed formulation is ——— . To date, the upper limit of dietary magnesium allowance for infants 0 through 12 months has not been established. For children 1 to 3 years of age, the magnesium allowances are 80 mg/day (NIH, http://ods.od.nih.gov, October 12, 2007). Based on these data, depending on the benefit/risk evaluation, the magnesium level of the to-be-marketed formulation appears to be acceptable. b(4)

1.3.4 Dosing Regimen and Administration

Omeprazole doses for this pediatric population were selected based on the analysis of previous clinical data in a pediatric population. Omeprazole, administered as 0.7 mg/kg through 1.4 mg/kg, was clinically effective in the majority of those patients whose erosive esophagitis were considered to be healed. The doses selected for this study, 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg incorporate those doses already proven to be effective.

The 20 mg capsule currently approved by the FDA was used to prepare a 2 mg/mL bicarbonate suspension to facilitate appropriate dosing in this pediatric population. The 20 mg dose was shown to be effective and generally well tolerated in adults for more than 10 years of use in the United States and Europe as treatment for various acid-related gastrointestinal disorders.

Patients were randomized to receive 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg, and all patients were dosed with omeprazole suspension. This was prepared by each site by suspending the contents of 20 mg omeprazole capsules in 8.4% bicarbonate solution resulted in final concentration 2mg/mL. Patients were dosed orally once daily for approximately 56 days.

Medical Officer Comments:

The dose-selection and dosing regimen for Study 251 are adequate.

1.3.5 Drug-Drug Interactions

Omeprazole is extensively metabolized in hepatocytes by liver microsomal cytochrome P-450 mono-oxygenase system (CYP2C19 and CYP3A4). The current labeling for omeprazole provides details with respect to drug interactions. No new drug interaction data were submitted in this submission.

Medical Officer's Comments:

A potential interaction between the antifungal agent voriconazole and omeprazole was identified and submitted to NDA 21-689/SLR008 and NDA 21-153/SLR027. A review by the medical officer was included in the previous omeprazole labeling.

1.3.6 Special Populations

The age range of this submission is 0 to 2 years old. The dosing regimen is 2.5 and 10 mg daily for up to 8 weeks. No additional dosage adjustment is recommended.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Omeprazole is a benzimidazole derivative that inhibits gastric acid secretion of the gastric parietal cells. It belongs to the pharmacological class of proton pump (the H^+/K^+-ATPase) inhibitors (PPI). Omeprazole is a racemic mixture of 2 enatiomers (S-enantiomer and R-enatiomer). The established name of the product is Omeprazole and the trade name is Prilosec®. The current product is a pediatric appropriate formulation (2.5 and 10 mg). The formulation was developed for the treatment of pediatric GERD and erosive esophagitis aged 0 to 2 years old.

The indications include short-term treatment of symptomatic GERD and erosive esophagitis. The proposed treatment regimen of GERD is omeprazole [redacted] 5 mg (body weight 5 to 10 kg). The proposed treatment regimen of erosive esophagitis is 10 mg (10 to 20 kg) P.O. once daily for up to 8 weeks. b(4)

2.2 Currently Available Treatment for Indications

The treatment of gastric esophageal reflux (GER) depends on the infant's symptoms and age. Some babies may not need treatment, because GER often resolved by itself. The currently available treatment for pediatric patients with GERD and erosive esophagitis are:

- **Histamine-2 Receptor Antagonists (H_2-RAs):** Ranitidine (Zantac, 1 month to 16 years old); famotidine (Pepcid, 3 months to 16 years old); and nizatidine (Axid, 2 to 18 years old).
- **Protom Pump Inhibitors (short-term treatment):** Omeprazole (Prilosec, 2 to 16 years old), esomeprazole (Nexium, 12 to 17 years old), lansoprazole (Prevacid, 1 to 17 years old)
- **Surgical Treatment:** Available to patients who have severe symptoms such as life-threatening bronchospasm or recurrent aspiration pneumonia and have failed medical therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Omeprazole is currently marketed in the United States for the treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, treatment of symptomatic GERD in adult and adolescent patients, and combination therapies for the eradication of *Helicobacter pylori*. In addition, omeprazole is marketed for the long-term management of pathologic hypersecretory conditions.

2.4 Important Issues with Pharmacologically Related Products

Imbalanced serious cardiac events were observed in two long-term adult studies (SOPRAN and LOTUS, respectively) with omeprazole or esomeprazole. These safety issues are currently under FDA review.

The carcinogenic potential of omeprazole was assessed. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric enterochromafin-like (ECL) cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In human, ECL cell tumor has not been identified in patients with long term treatment of omeprazole.

Patients with long-term omeprazole treatment and *Helicobacter pylori* infection may develop gastric intestinal metaplasia Type I. Histopathological speaking, this is a complete type of intestinal metaplasia, i.e., the gastric mucosa changes to normal small bowel epithelium, characterized by fully developed goblet cells and enterocytes (absorptive cells) with a brush border. Paneth cells may be present. In contrast, Type II and Type III intestinal metaplasia are incomplete types of intestinal metaplasia, in which absorptive cells can not be identified. It is reported that only incomplete intestinal metaplasia is associated with pre-cancer condition of gastric adenocarcinoma.

2.5 Presubmission Regulatory Activity

In the approval letter for NDA 19,810 (S-074) dated July 12, 2002, the FDA recommended that the sponsor develop an age-appropriate formulation of Prilosec for pediatric patients 0 to 2 years of age with symptomatic GERD and/or erosive esophagitis. AstraZeneca submitted this NDA to fulfill the post-marketing commitment.

2.6 Other Relevant Background Information

Omeprazole 2.5 mg and 10 mg oral suspension is not marketed in any foreign country by the applicant. There is no information regarding pending market applications in foreign countries. Omeprazole tablets (20 and 40 mg) are currently marketed in 96 foreign countries/areas. Omeprazole capsules (20 and 40 mg) are marketed in the United States.

Omeprazole (20 mg and 40 mg tablets or capsules) has not been withdrawn for reasons related to safety or efficacy in any country where these omeprazole formulations have been marketed.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Omeprazole delayed-release capsules (20 mg and 40 mg) have been approved for patients 2 years or older. The sponsor proposed to add 2.5 mg and 10 mg dose form in the labeling for pediatric patients 0 to 2 years old. No significant CMC issues that affected clinical interpretation of the data were identified. The NDA submission was discussed with the CMC Reviewer Dr. Marie Kowblansky, and she concurred.

3.2 Animal Pharmacology/Toxicology

Omeprazole delayed-release capsules (20 mg and 40 mg) have been approved. No additional pharmacology and toxicology issues were identified in this submission. The submission was discussed with the Pharmacology/Toxicology reviewers, Drs. Sushanta Chakder and Ke Zhang, and they concurred.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data were summarized in Table 1. AstraZeneca submitted one Phase 3 clinical study **(Study 251)** to support the safety and efficacy of omeprazole for the short-term treatment of pediatric patients 0 to 2 years old with gastroesophageal reflux disease (GERD).

AstraZeneca also submitted 2 clinical pharmacology studies to support this application:

1) **Study 250** characterized the PK and PD parameters of omeprazole (single oral dose of 0.5, 1.0, and 1.5 mg) in 25 subjects 0.5 to 24 months old;
2) **Study D9586C00002** characterized bioequivalence of 3 different omeprazole formulations (20 mg sachet, 20 mg suspension, and 200 mg capsule) in 22 healthy adult subjects on Day 1 and Day 5.

In addition, the sponsor submitted a retrospective multiple dose study **(Study 292)** designed to evaluate the effect of omeprazole on esophageal or gastric pH in 43 patients aged 1 to 24 months. The average treatment duration was 45 days.

The sponsor also included **Study I-678** to characterize the dose, safety, efficacy, and tolerability of omeprazole in the treatment of erosive reflux esophagitis in patients 1 to 16 years old. However, in Study I-678, there were only 2 patients who were less than 2 years old.

Table 1: Summary of clinical studies

Study Number	Study Design	Primary Objective	Dosing Regimen	N	Study Population	Duration
Study 251	Phase 3, single-blind randomized; no control	Safety & efficacy	0.5, 1.0, & 1.5 mg/kg, daily capsules-bicarbonate	106	Pediatric subjects age 0.7 to 22 months old with GERD; Clinically diagnosed	8 weeks
Study 250	Phase 1, open-label	PK and gastric or esophageal pH	0.5, 1.0, 1.5 mg/kg; Single & multiple doses	25	Pediatric subjects age 0.5 to 24 months old with GERD	Day 1 through Day 5
Study 292	Retrospective; No control; Concomitant medications	Gastric or esophageal pH	4 to 30 mg	43	1 to 24 months with GERD	Average.45 days
Study I-678	Phase 1, open-label	Safety & efficacy	7.5 to 80 mg	2/55	Pediatric subjects age 1 to 16 years old with EE; 2 ≤2 years old; 55 >2 years old	10 to 325 days
Study D9586 C00002	Phase 1, open-label	PK parameters	20 mg sachet, suspension, & capsule	22	Healthy adults	Day 1 & Day 5

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4.2 Review Strategy

All of five clinical studies (251, 250, D9586C00002, 292, and I-678) were reviewed. As a Medical Officer, my review of this NDA laid an emphasis on the safety and efficacy data of the Phase 3 study (Study 251).

For the 2 pharmacokinetic studies (250 and D9586C00002), my overall objective was to evaluate the pharmacology data from a clinical perspective, and provide an analysis of the safety data. The evaluation of specific pharmacokinetic parameters resided primarily with the Clinical Pharmacology Review by Drs. Jane Bai and Sue Chih Lee.

4.3 Data Quality and Integrity

An audit of Studies 251, 250, D9586C00002, 292, and I-678 was not performed by the Division of Scientific Investigations or the review team.

4.4 Compliance with Good Clinical Practices

According to the sponsor, Studies 251, 250, D9586C00002, 292, and I-678 were conducted under Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA).

4.5 Financial Disclosures

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

Medical Officer's Comments:

AstraZeneca has adequately disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up any concerns which would possibly jeopardize the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Study 250: This an open-label, randomized PK/PD study with 25 pediatric patients 0 to 24 months. The primary objectives were to characterize the single dose PK parameters and intraesophageal and/or intragastric pH. Patients were randomized to receive a single oral dose of either 1.0 mg/kg or 1.5 mg/kg from a 2 mg/mL omeprazole suspension in 8.4% sodium bicarbonate.

For determination of omeprazole plasma concentrations, blood samples were collected at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, and 6 hr post-dose. For assessment of esophageal or gastric pH, a pH probe was placed in either the esophagus or stomach (when medically indicated) at least 12 hr prior to dose administration and pH was continuously measured until at least 12 hr post-dose.

Table 2: PK parameters after a single dose of omeprazole*

Ome Dose	PK Parameter	n	Geometric Mean	95% Confidence Interval
1.0 mg/kg	AUC_{0-t} (ng•h/mL)	12	658.0	(340.4,1272.1)
	$AUC_{0-\infty}$(ng•h/mL)	7	1248.5	(569.3,2738.2)
	C_{max}(ng/mL)	12	447.6	(253.6,789.9)
1.5 mg/kg	AUC_{0-t}(ng•h/mL)	12	580.7	(274.6,1227.8)
	$AUC_{0-\infty}$(ng•h/mL)	9	827.0	(352.3,1941.6)

	C_{max}(ng/mL)	12	345.6	(137.7,867.4)

*From the Sponsor's Study 250 report

Table 3: Summary of percentage of time pH<4.0*

		Predose	Postdose	Change
1.0 mg/kg	**Esophageal**			
	N	7	7	
	Mean	4.8	2.7	-2.1 ($p \leq 0.26$)
	SD	5.2	2.5	4.5
	Gastric			
	N	7	7	
	Mean	64.2	42.4	-21.8($p \leq 0.02$)
	SD	29.3	26.1	18.8
1.5 mg/kg	**Esophageal**			
	N	5	5	
	Mean	13.2	6.8	-6.4 ($p \leq 0.25$)
	SD	12.6	8.8	10.6
	Gastric			
	N	5	5	
	Mean	58.0	46.2	-11.9 ($p \leq 0.07$)
	SD	28.7	33.9	10.5

*From the Sponsor's Study 250 report

Previous Medical Reviewer's Conclusion:

Dr. Kress concluded that the geometric mean AUC_t after a single dose of omeprazole was similar for the two dose levels. The exposure reduced esophageal acid exposure and increased gastric pH in pediatric patients aged 0.5 month to 24 months.

Medical Officer's Comment:
I concur.

Study D9586C00002: This is a Phase 1, open label, 3-way cross-over bioavailability study comparing 3 different formulations of omeprazole 20 mg following single and 5 days repeated once daily oral administration in 22 healthy adult subjects.

The primary objective was to compare the relative bioavailability of 3 different formulations (20 mg gastro-resistant granules based sachet formulation) by assessment of AUC and C_{max} on Day 1.

Pharmacokinetic endpoints

- AUC and C_{max} (primary variables and secondary variables)
- AUC_t, t_{max} and $t_{½}$ (secondary variables)

Safety endpoints

- Adverse events, laboratory variables, blood pressure and electrocardiogram including heart rate (secondary variables)

Summary of pharmacokinetic results

The estimated geometric means of AUC were similar for omeprazole 20 mg sachets, suspension and capsules on days 1 and 5. The estimated geometric means of C_{max} for the omeprazole sachets and capsules were correspondingly similar, on days 1 and 5. The omeprazole suspension, however, gave a higher C_{max} than sachets and capsules. Table 4 and Table 5 show the results of day 1. In addition to the higher C_{max}, the omeprazole suspension also gave a shorter median t_{max} (~0.3 hours) than the medians for sachets and capsules (1.3 to 1.7 hours), on days 1 and 5. The geometric means of $t_{½}$ were similar for the 3 formulations (~0.8 hours), on days 1 and 5.

Table 4: Estimated geometric means and 95% CIs of AUC (µmol•h/L), C_{max} ((µmol/L), and AUC_t (µmol•h/L) on Day 1*

Variable	Treatment	N	Estimate	95% CI	
				lower	upper
AUC	Sachet	19	1.01	0.73	1.39
	Capsule	20	1.16	0.84	1.60
	Suspension	24	1.12	0.82	1.54
C_{max}	Sachet	23	0.55	0.41	0.73
	Capsule	24	0.62	0.47	0.82
	Suspension	24	1.14	0.86	1.50
AUC_t	Sachet	23	0.94	0.67	1.30
	Capsule	24	1.04	0.75	1.44
	Suspension	24	1.08	0.78	1.50

*From the Sponsor's clinical pharmacology study report

Table 5: Ratios (sachet/capsule, suspension/capsule and sachet/suspension) of geometric means and 95% CIs for AUC (µmol•h/L), C_{max} ((µmol/L), and AUC_t (µmol•h/L) on Day 1*

Variable	Ratio	N	Estimate	95% CI	
				lower	upper
AUC	Sachet/Capsule	19/20	0.87	0.73	1.04
	Suspension/Capsule	24/20	0.97	0.82	1.15
	Sachet/Suspension	19/24	0.90	0.76	1.06
C_{max}	Sachet/Capsule	23/24	0.88	0.70	1.11
	Suspension/Capsule	24/24	1.83	1.46	2.29
	Sachet/Suspension	23/24	0.48	0.38	0.61
AUC_t	Sachet/Capsule	23/24	0.90	0.76	1.06
	Suspension/Capsule	24/24	1.04	0.89	1.23
	Sachet/Suspension	23/24	0.86	0.73	1.02

*From the Sponsor's clinical pharmacology study report

Summary of safety results

All 3 formulations of omeprazole were well tolerated in this study. There were no findings that raised safety concerns.

Medical Officer's Comments:

The AUC_t and C_{max} values (90% CI) of the to-be-marketed formulation were apparently not bioequivalent to the suspension granules administered in sodium bicarbonate. However, the AUC_t value was closer to the 0.8-1.25 range, and in general, AUC correlated with the efficacy of PPIs in previous studies. The overall comparability of the to-be-marketed formulation and the suspension granules in sodium bicarbonate was acceptable. This issue was discussed with the Clinical Pharmacology Reviewers Drs. Jane Bai and Sue Chih Lee on October 3, 2007. The results of the PK study are summarized as follows:

- **The bioavailability in terms of AUC was similar for the 3 different formulations of omeprazole 20 mg, on both day 1 and day 5.**
- **The C_{max} was similar for the sachet formulation and the commercial PRILOSEC capsule, while the C_{max} was higher for the suspension, on both day 1 and day 5.**
- **The AUC_t and $t_{½}$ were similar for all 3 formulations of omeprazole 20 mg, on days 1 and 5.**
- **The t_{max} was similar for the sachet formulation and the commercial PRILOSEC capsule, while the t_{max} was shorter for the suspension, on days 1 and 5.**
- **All 3 formulations of omeprazole 20 mg were well tolerated in this study. There were no findings that raised safety concerns.**

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the delayed-release oral suspension is the short-term treatment of pediatric patients (0 to 2 years old) with GERD; [redacted] b(4)

[redacted]. However, the submission only supports short-term treatment of symptomatic GERD and reflux esophagitis.

6.1.1 Methods

Data from Study 251 were evaluated for the efficacy review. It was a Phase 3, randomized, double-blind study.

6.1.2 General Discussion of Endpoints

The basis for choice of endpoints for the proposed indication is as follows:

The current clinical guidelines for the diagnosis of pediatric GERD by North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) include patient history and physical examination. The standard care of uncomplicated pediatric GERD does not require esophageal pH monitoring or upper endoscopy. Patient diaries and Physician Global Assessments are instruments that have been used in many adult GERD clinical outcome studies. These instruments were expected to be able to provide a reasonable assessment of clinical benefit.

In Studies 250 and D9586C00002, the pharmacokinetic parameters AUC and C_{max} were characterized, because they provide the assessment of plasma drug concentrations as functions of treatment time.

6.1.3 Design of Study 251

Title: A Multicenter, Randomized, Single-Blind Study to Evaluate Omeprazole for the Treatment of Clinically Diagnosed Gastroesophageal Reflux Disease (GERD) in Pediatric Patients Ages 0 months through 24 months, Inclusive

Study Objective:

Primary: To investigate whether once-daily treatment with omeprazole safely and effectively reduced the number of regurgitation episodes related to GERD in pediatric patients 0 months through 24 months, inclusive.

Secondary: To investigate whether once-daily treatment with omeprazole safely and effectively relieved the intensity of regurgitation/vomiting episodes and pain-related symptoms of GERD collected on daily diary cards in pediatric patients 0 months through 24 months, inclusive and to evaluate the Physician's Global Assessment.

Study Design:

This was a Phase 3, multicenter, single-blind study designed to evaluate the safety and clinical outcome of omeprazole treatment in pediatric patients 0 to 2 years old with GERD. There was no control group.

Selection of Doses

Previous clinical trials in a pediatric population showed that omeprazole, administered as 0.7 mg/kg through 1.4 mg/kg, was clinically effective in the majority of those patients considered to be healed. The doses selected for this study, 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg incorporate those doses already proven to be effective. The 20 mg capsule, which is currently approved by the Food and Drug Administration (FDA), was used to prepare a 2 mg/mL bicarbonate suspension to facilitate appropriate dosing. All patients were dosed with omeprazole suspension.

Treatment Procedure

Patients were screened (Visit 1) within 2 days prior to dosing (Table 6). The study procedures were fully described to the parent/guardian. After all questions were answered and the parent/guardian provided the informed consent, a complete medical history was taken including a history of past and current medications, a complete physical examination including vital signs was performed, and a routine analysis of blood and urine was performed. In addition, information regarding any previous EGDs, pH monitoring, or other diagnostic GERD procedures was recorded. A 2-month history of various GERD symptoms and a brief summary of GERD symptoms within the previous 72 hours were recorded. Also at Visit 1, the investigator completed a Physician's Global Assessment on the overall impression of the patient's GERD symptoms. Patients who met the inclusion and exclusion criteria were dosed with 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg of omeprazole depending on the randomization schedule. Parents/guardians were then given instructions for accurate dosing and diary record completion. Patients were dosed once daily for approximately 56 days. Patients returned to the site approximately every 14 days for the next 56 days for a total of 5 visits. During Visits 2 through 5, diary card information was collected, physical exams were performed, and vital signs were taken.

During Visit 5, routine blood and urine laboratory tests were performed. In addition, the investigator completed a final Physician's Global Assessment on the overall impression of the patient's GERD symptoms. After all study procedures were satisfied, the patients were discharged from the study. Adverse events were recorded throughout the study.

The omeprazole suspension was prepared by the pharmacist according to instructions provided. This was prepared at each site by suspending the contents of 20 mg omeprazole capsules in 8.4% bicarbonate solution to make a 2 mg/mL solution.

The amount of study drug dispensed was determined by the patient's weight. The administered dose was 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg up to a maximum of 20 mg omeprazole daily.

Omeprazole suspension was administered via a syringe or, in some instances, via nasogastric or percutaneous gastrostomy tube. Omeprazole suspension was administered in the morning with breakfast.

Figure 1: Study Design

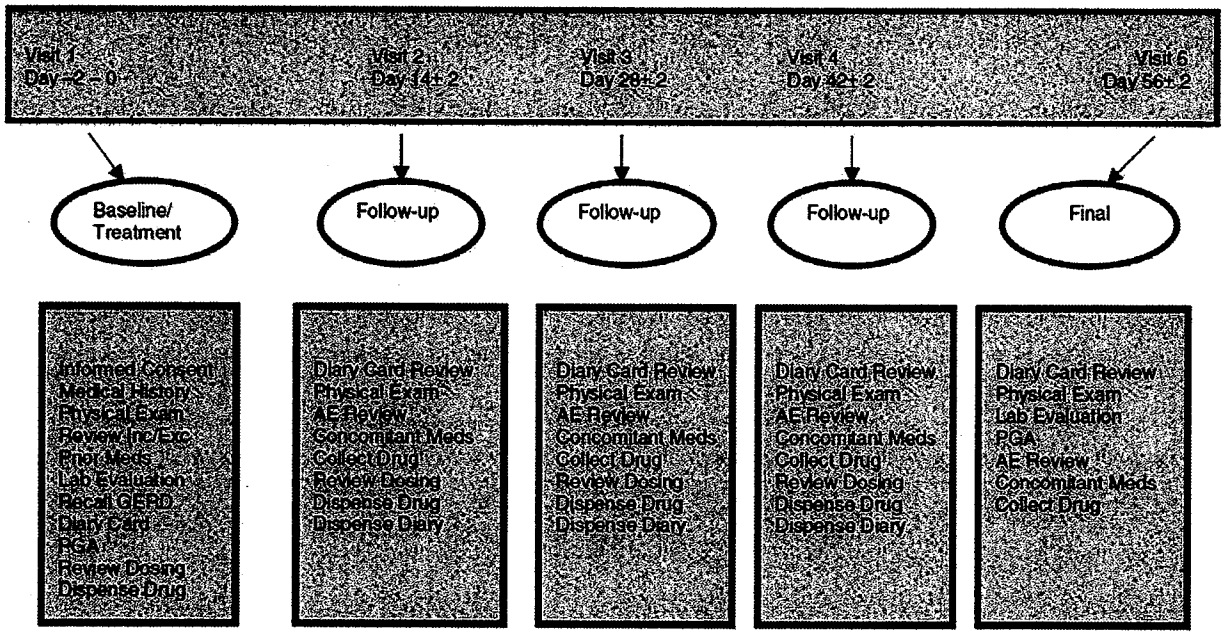


Table 6: Study Flow Chart*

Visit/Study Day	Visit 1 Day –2 -0	Visit 2 Day 14 ±2	Visit 3 Day 28 ±2	Visit 4 Day 42 ±2	Visit 5 Day 56 ±2
Informed Consent	X				
Medical History	X				
Physical Exam	X	X	X	X	X
Vital signs	X	X	X	X	X
Laboratory Evaluation	X				X
Review Inclusion/Exclusion Criteria	X				
Physician Global Assessment	X				X
Dispense Study Medication	X	X	X	X	
Review Dosing Instructions	X	X	X	X	
Return Study Medication		X	X	X	X
Distribute Symptom Diary	X	X	X	X	
Recall previous 72 hr symptoms	X				
Collect/ Review Symptom Diary		X	X	X	X
AE Reports		X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X

*From the sponsor's Study 251 reports

Randomization of Patients

Eligible patients were randomized to 1 of the 3 treatment groups (0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg) in a 1:1:1 ratio according to a randomization schedule generated by AstraZeneca. The randomization schedule allocated patients to a treatment group in a 1: 1: 1 ratio.

Prior and Concomitant Therapy

The parent/guardian of the patients was instructed that no prescription treatments for acid-related symptoms, other than the supplied study drug, were permitted during the study. Antacids were permitted except for those containing bismuth. The previous use of antisecretory or promotility agents was permitted, as long as they were discontinued at least 24 hours prior to study enrollment at the baseline evaluation. The previous use of proton pump inhibitors was permitted, as long as they were discontinued at least 72 hours prior to study enrollment at the baseline evaluation. Patients were allowed any concomitant medication which was not listed in the exclusion criteria. All concomitant medications were recorded on the CRF.

Efficacy Assessment

The assessment used the data recorded in the patient's diary card and on the Physician's Global Assessment.

Daily Diary Card

Each parent/guardian received a diary card at Visit 1 and was instructed on how to complete it for assessment of symptoms. The diary card was completed at approximately the same time each evening by the same person. The investigator checked the patient's diary card at each visit to evaluate that the symptoms were reported. Compliance with the diary card completion was evaluated at each visit and if greater than 50% of the days were incomplete for the treatment period, the patient could be discontinued from the study. Diary card data was transcribed onto CRFs and then entered into a database.

At bedtime, the parent/guardian was asked to record their child's symptoms over the past 24 hours in the diary. Every evening during the 56 day study, the parent/guardian of each patient completed the child's diary by answering the following questions:

- Number of episodes of vomiting/regurgitation during the last 24 hours?
- Maximum intensity of vomiting/regurgitation during the last 24 hours? (none, mild, moderate or severe)
- Maximum intensity of pain-related symptoms during the last 24 hours? (none, mild, moderate or severe)
- Presence or absence of expression of or signs of postprandial pain or discomfort during the last 24 hours? (yes or no)
- Presence or absence of nocturnal pain-related symptoms during the previous night? (yes or no)
- Was all study medication taken that day? (yes or no)
- Dosing time of study medication?
- Was rescue medication (MAALOX) given to the patients? (yes or no)
- What was the frequency of rescue medication (MAALOX) given to the patient?

Physician's Global Assessment

A global assessment of overall symptoms was completed by the investigator at the baseline (Visit 1) and Visit 5 or the final visit and recorded on the CRF. A secondary evaluation of the proportion of patients with successful treatment was defined by an assessment of none or mild symptoms at the end of the study. The global assessment question was: Please assess your clinical impression of overall GERD-related symptoms as one of the following:

1. None
2. Mild, symptoms present, but not interfering with daily activities
3. Moderate, symptoms present, and somewhat interfering with daily activities
4. Severe, symptoms present and greatly interfering or preventing daily activities

Primary Efficacy Endpoint: The average number of vomiting/regurgitation episodes per day per patient in the last 72 hours of treatment.

Medical Officer's Comments:

The primary efficacy endpoint should be the proportion of patients who experience reduced vomiting episodes.

Secondary Efficacy Endpoints:

- Proportion of patients who had no moderate or regurgitation/vomiting symptoms during the last 72 hours.
- Proportion of patients who had no moderate or severe pain-related symptoms during the last 72 hours.
- Proportion of patients who were successfully treated, where successful treatment is defined as no moderate or severe overall evaluation, as defined by the Physician's Global Assessment.

Study Population:

Inclusion criteria:

1. Patients had to be male or female 0 months through 24 months of age, inclusive.
2. Patients must have had at least a 2 month history of GERD-related symptoms. Some symptoms of GERD were defined as pain-related (e.g., including, but not limited to: heartburn, weight loss, arching followed by crying, posturing with/without crying not related to seizures, Sandifer's syndrome, chest pain, dysphagia, epigastric pain, pain associated with meals, and behavioral changes such as food refusal, night time crying, awakening and irritability) with episodes of regurgitation/vomiting usually occurring greater than 5 times per day
3. In the judgment of the investigator, patients who were considered for treatment with an acid inhibition agent based on symptoms of GERD.
4. Patients must have had clinically normal laboratory results and physical exam findings at screening. Abnormal laboratory results and physical findings which were not clinically significant in the judgment of the investigator did not lead to exclusion of the patient.
5. Patients' parent/guardian must have provided written informed consent.

Exclusion Criteria:

1. Patient used a proton pump inhibitor within 72 hours prior to study enrollment at the baseline evaluation (Visit 1).
2. Patient used any full-dose prescriptive or over-the-counter antireflux therapy such as H_2-receptor antagonists or prokinetics within 24 hours prior to study enrollment at the

baseline evaluation (Visit 1). Antacids were allowed, except for those containing bismuth.

3. Patient had a history of resectional or reconstructive surgery of the esophagus, stomach, duodenum or jejunum. A history of feeding tube placement in a patient for whom the feeding tube was removed 3 months before study enrollment did not preclude entry into the study.
4. Patients who could not be discontinued from any of the following drugs: bismuth containing products, barbiturates, anti-convulsants, warfarin or narcotics.
5. Concomitant use of the following medications: anticholinergics, prostaglandin analogs, antineoplastic agents, systemic corticosteroids (oral or intravenous), H_2-receptor antagonists, sucralfate, NSAIDS, salicylates, methyl-xanthines, anti-emetics, pro-motility drugs (i.e., cisapride, metoclopramide, macrolide antibiotics such as erythromycin).
6. Patient had current or historical evidence (within 3 months) of the following diseases/conditions: pancreatitis, malabsorption, active inflammatory bowel disease, severe pulmonary, renal or liver disease, chronic renal disease, or impaired renal function as manifested by serum creatinine greater than 1.5 mg/dL or markedly abnormal urine sediment on repeated examinations.
7. Patient had current or historical evidence of malignant disease.
8. Patient had unstable diabetes mellitus. Stable diabetics controlled on diet, oral agents or insulin were acceptable.
9. Patient had cerebrovascular disease such as cerebral ischemia, infarction, hemorrhage, or embolus.
10. Patient had any bleeding disorder.
11. Patient had any condition that could have required surgery during the study.
12. Patient had known recent clinically significant abnormal laboratory values as part of their medical history which were likely to still present and preclude study entry.
13. Patient had known hypersensitivity to any component of omeprazole or to MAALOX.
14. Patient had used any other investigational compound within 28 days of enrollment.
15. Patient had any condition that in the judgment of the investigator would make performance of any of the study procedures unsafe, or which would make it unlikely that the patient would complete the study and all study procedures.
16. Patient had parent or guardian who refused to sign the consent form or was not able to give fully informed consent due to mental deficiency or language problems.

Statistical population:

There were 2 populations for purposes of the efficacy analysis: intent-to-treat (ITT) population (100 subjects) and per-protocol (PP) population (96 subjects). The ITT population consisted of all patients taking at least 1 dose of omeprazole and having at least one day of diary data. The PP population consisted of a subset of the ITT population.

6.1.4 Efficacy Findings

Primary efficacy findings: changes from baseline in average number of vomiting/regurgitation episodes per day in the last 72 hours of treatment.

Patients had approximately -4.35 (95% CI: -8.2, -0.46), -2.97 (95% CI: -7.0, 1.06) and -4.34 (95% CI: -8.5, -0.15) decrease in vomiting/regurgitation episodes per day during the last 72 hours in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, respectively. All treatment groups had approximately 50% reduction in the number of vomiting/regurgitation episodes. While, no significant differences were detected between any of the pairwise comparisons in the treatment groups, the high and low dose demonstrated a significant decrease from baseline. No difference was seen between the analyses with the PP population compared to the ITT population. Table 7 summarizes the adjusted mean (LSMEAN) change from baseline at Visit 1 on the average number of vomiting/regurgitation episodes per day during the last 72 hours for each treatment group in the ITT population (100 subjects).

Table 7

Analysis of Covariance
Change from Baseline (Visit 1) on the Average Number of Vomiting/Regurgitation Episodes Per Day During the Last 72 Hours
Intention-To-Treat Population

Omeprazole Dose	n	LSM[a]	LSM[a] Standard Error	95% CI for LSM[a]	Pairwise Comparison p-value vs. 1.0 mg/kg	Pairwise Comparison p-value vs. 0.5 mg/kg
1.5 mg/kg	33	-4.35	1.99	(-8.2, -0.46)	0.59	1.00
1.0 mg/kg	33	-2.97	2.05	(-7.0, 1.06)	-	0.58
0.5 mg/kg	34	-4.34	2.14	(-8.5, -0.15)	-	-

[a] LSM = Least Square Means
Note: The analysis was based on an ANCOVA model with omeprazole dose and site

Table 8 summarizes the adjusted mean (LSMEAN) change from baseline at Visit 1 on the average number of vomiting/regurgitation episodes per day per patient during the last 72 hours for each treatment group. Three patients (Site/Patient: 003/010, 026/011, 026/012) from the ITT population were excluded from the analysis. These values were extreme outliers. Patients had approximately-5.23 (95% CI: -7.6, -2.9), -3.97 (95% CI: -6.4, -1.5) and -2.89 (95% CI: -5.4, -0.34) decrease in vomiting/ regurgitation episodes per day per patient during the last 72 hours in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, respectively. These results indicate that

the number of vomiting/regurgitation episodes per patient decreases with each increased dose group of omeprazole.

Table 8

Analysis of Covariance – Sensitivity Analysis
Change from Baseline (Visit 1) on the Average Number of Vomiting/Regurgitation Episodes Per Day During the Last 72 Hours
Intention-To-Treat Population

Omeprazole Dose	n[a]	LSM[b]	LSM[b] Standard Error	95% CI for LSM[a]	Pairwise Comparison p-value vs. 1.0 mg/kg	Pairwise Comparison p-value vs. 0.5 mg/kg
1.5 mg/kg	32	-5.23	1.21	(-7.6, -2.9)	0.43	0.14
1.0 mg/kg	32	-3.97	1.25	(-6.4, -1.5)	-	0.47
0.5 mg/kg	33	-2.89	1.30	(-5.4, -0.34)	-	-

[a] Three patients (Site/Patient: 003/010, 026/011, 026/012) were excluded from the analysis. Values were extreme outliers.
[b] LSM = Least Square Means
Note: The analysis was based on an ANCOVA model with omeprazole dose and site

Medical Officer's Comments:

Tables 5 and 6 are inappropriately presented. The proportion of patients who had decreased vomiting/regurgitation episodes should be reported. Without this information, the claim of a 50% decrease of vomiting episodes is unfounded.

Upon DGP request, the sponsor provided additional data, as follows:

1.5 mg/kg 22/33 (67%);

1.0 mg/kg 23/33 (70%);

0.5 mg/kg 23/34 (68%);

Total 68/100 (68%).

(From the sponsor's response to information request on September 27, 2007)

Secondary efficacy findings: changes from baseline in patients with no moderate or severe symptoms on the following secondary efficacy endpoints:

- Severity of overall vomiting/regurgitation of GERD
- Severity of overall pain-related symptoms of
- Physician's Global Assessment

For the severity of overall vomiting/regurgitation episodes in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, the observed rates of patients with no moderate or severe symptoms during the last 72 hours of treatment were 69.7%, 69.7% and 70.6%, respectively (Table 6). No statistical differences were detected between treatment groups.

For severity of overall pain-related symptoms of GERD, the observed rates of patients with no moderate or severe symptoms during the last 72 hours of treatment were 75.8%, 66.7% and 73.5%, respectively. No statistical differences were detected between treatment groups.

For the Physician's Global Assessment, the observed rates of patients with no moderate or severe symptoms during the last 72 hours of treatment were 93.3%, 93.3% and 96.4%, respectively. No statistical differences were detected between treatment groups.

A similar analysis shown in Table 9 performed with patients having only moderate or severe pain-related symptoms of GERD at baseline showed similar results. No statistical differences were detected between treatment groups.

Table 9

Categorical Analysis on Secondary Endpoints
Intention-To-Treat Population

Endpoint	Dose mg/kg	n	Success[a]		Failure[a]		Overall Mantel-Haenszel Chi-square (p-value)	Overall Estimated Odds Ratio	Overall 95% CI[b] of Odds Ratio
			n	%	n	%			
Severity of Overall Vomiting/Regurgitation of GERD	1.5	33	23	69.7	10	30.3	0.94	1.01	(0.78, 1.31)
	1.0	33	23	69.7	10	30.3			
	0.5	34	24	70.6	10	29.4			
Severity of Overall Pain-related Symptoms of GERD	1.5	33	25	75.8	8	24.2	0.85	0.97	(0.75, 1.27)
	1.0	33	22	66.7	11	33.3			
	0.5	34	25	73.5	9	26.5			
Physician's Global Assessment	1.5	30	28	93.3	2	6.7	0.62	1.16	(0.65, 2.04)
	1.0	30	28	93.3	2	6.7			
	0.5	28	27	96.4	1	3.6			

[a] Success = None or mild symptoms only during the last 72 hours of treatment, Failure = Moderate or severe symptoms.
[b] CI = Confidence Interval

Medical Officer's Comments:
The analysis of the secondary endpoints shows the proportion of subjects who were successfully treated. The data are appropriately presented.

Diary Card Information

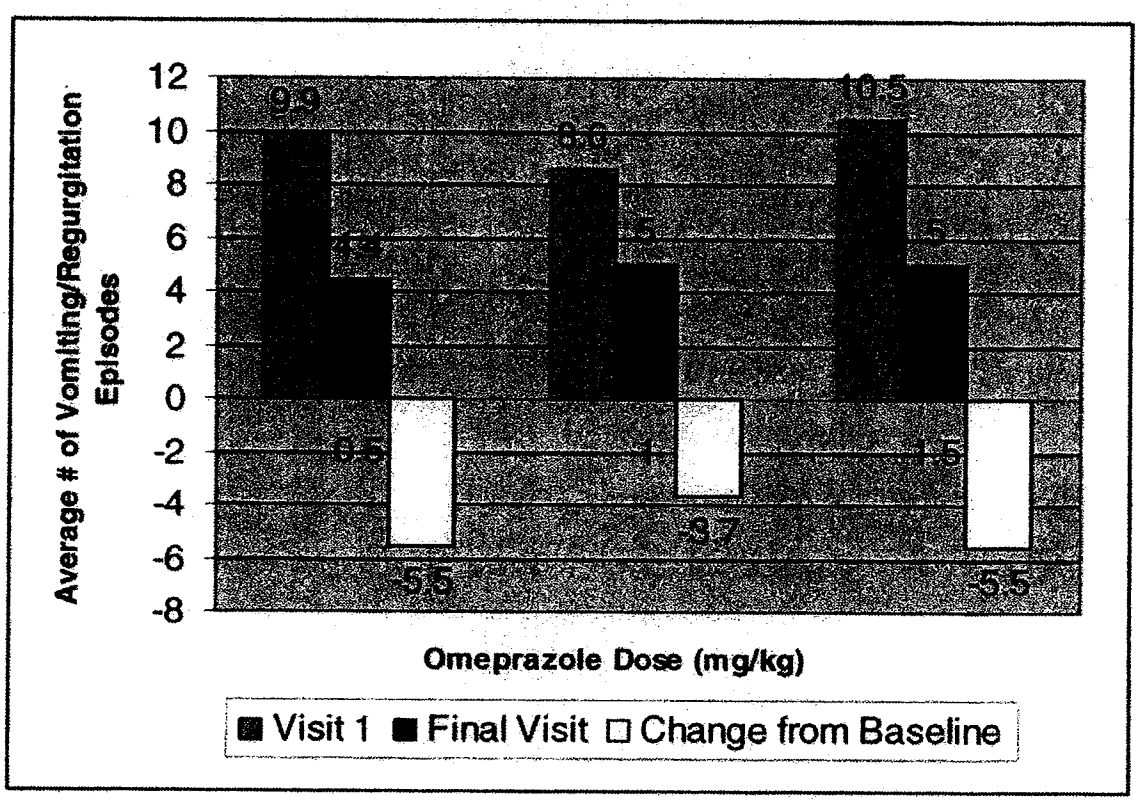
Figure 2 summarizes the average number of vomiting/regurgitation episodes at baseline (Visit 1) and Final Visit in the intention-to-treat population (100 subjects). The number of vomiting/regurgitation episodes decreased from baseline for all treatment groups. For 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg, respectively, patients had on average 9.9 (34/34), 8.6 (33/33) and 10.5 (33/33) vomiting/regurgitation episodes at baseline with a decrease in vomiting/regurgitation episodes of -5.5, -3.7, and -5.5 per day during the last 72 hours of treatment.

Figure 3, a sensitivity analysis of Figure 2, excludes three patients (Site/Patient: 003/010-1.5 mg/kg, 026/011-1.0 mg/kg, 026/012-0.5 mg/kg) with extreme values. Results show a trend in which the number of vomiting/regurgitation episodes decreases with each increased dose of omeprazole. For 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg, respectively, the patients had on average 8.6 (33/34), 8.7 (32/33) and 10.3 (32/33) vomiting/regurgitation episodes at baseline with a decrease in vomiting/regurgitation episodes of -4.7, -5.3, and -6.6 per day during the last 72 hours of treatment. For all treatment groups, the average intensity of pain-related symptoms decreased. Symptoms prior to treatment were approximately moderate and reduced to less than mild. Similar results occurred in the average intensity of vomiting/regurgitation episodes.

Only 30.0% (30 of 100) of ITT patients had pain after eating, with 69.6% (80 of 115) of randomized patients having pain after eating at baseline. Similar results were found in pain during the night.

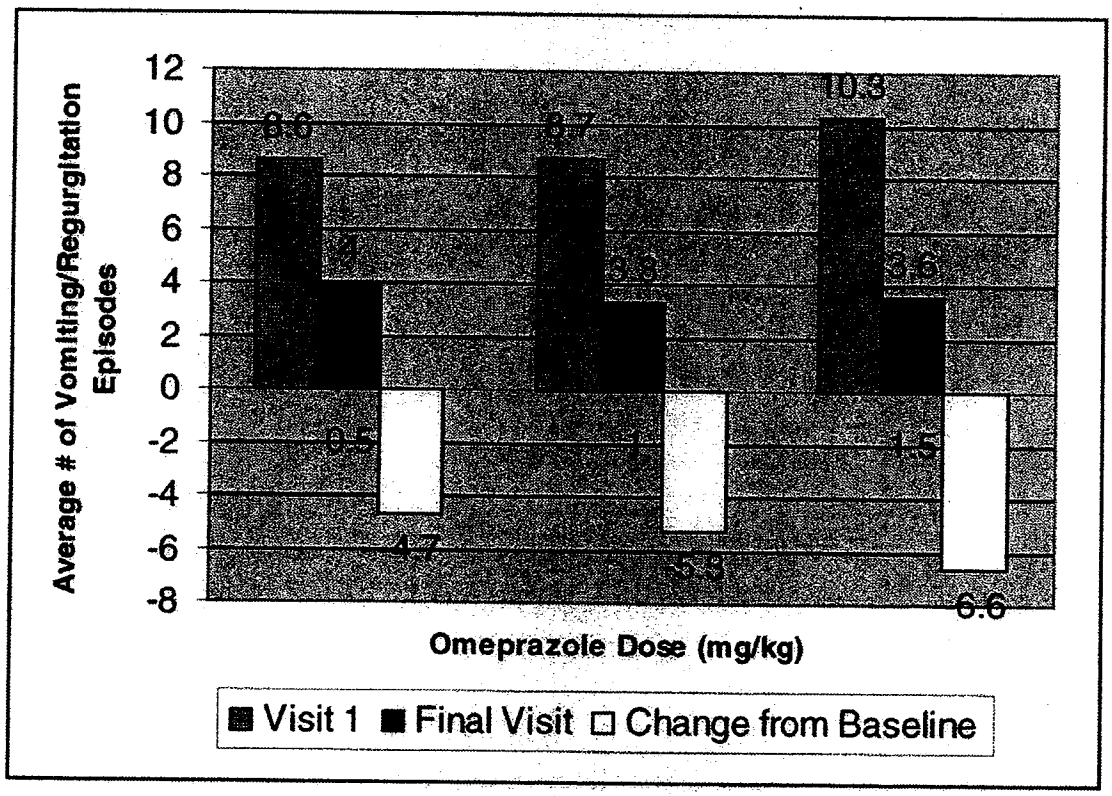
Figure 2

Average Number of Vomiting/Regurgitation Episodes
Intention-To-Treat Population



Reference: Section 14.2, Table 14.2.7.

Figure 3
Average Number of Vomiting/Regurgitation Episodes
Sensitivity Analysis
Intention-To-Treat Population



[a] Three patients (Site/Patient: 003/010, 026/011, 026/012) were excluded from the analysis. Values were extreme outliers

Physician's Global Assessment

The Physician's Global Assessment (PGA) consisted of the following question: "Please assess your clinical impression of overall GERD-related symptoms as one of the following:

- None
- Mild symptoms present, but not interfering with daily activities
- Moderate symptoms present, and somewhat interfering with daily activities

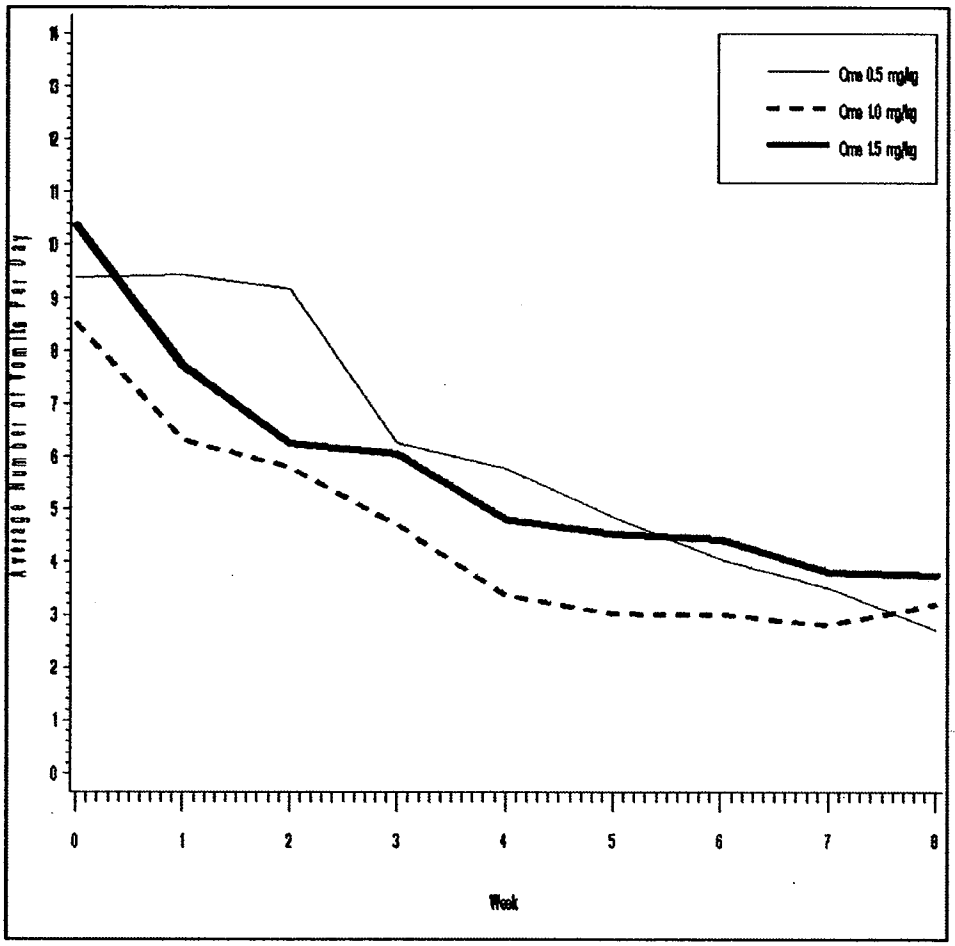
According to the results of the PGA at the final visit, omeprazole in all treatment groups improved overall GERD-related symptoms. Most patients improved (79 of 88, 90%), a few patients remained the same (8 of 88, 9%) and one got worse (1 of 88, 1 %).

Graphical Analysis

The average number of administrations of rescue medication slightly decreased overtime. Approximately 1 administration of rescue medication was given each day, on average at the beginning of the study, reducing to approximately 0.5 administrations. No differences were seen amongst treatment groups. The number of patients taking rescue medications decreased dramatically over time. Approximately 20% of patients were taking at least 1 dose of rescue medication. By the end of the study, nearly all patients stopped using their rescue medications.

The average number of vomiting/regurgitation episodes per day is presented in Figure 11 Week 0 represents baseline symptoms at Visit 1. By Week 1, the higher doses (1.0 mg/kg and 1.5 mg/kg) showed effect in decreasing the number of omiting/regurgitation episodes, while the low dose (0.5 mg/kg) did not show effect until Week 3. For all treatment groups, the number of vomiting/regurgitation episodes continues to decrease considerably until Week 3 and then begins to plateau for both .0 mg/kg and 1.5 mg/kg treatment groups at Week 4.

Figure 4
Average Number of Vomiting/Regurgitation Episodes by Week
During the Last 72 Hours of Each Week
Intention-To-Treat Population



6.1.5 Efficacy Conclusions

Previous Medical Reviewer's Conclusion:

Dr. Kress concluded that omeprazole exhibits efficacy across all treatment groups. The number of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment with omeprazole. No statistical differences were detected between any treatment groups. However, results with the sensitivity analysis show a trend towards a greater reduction in vomiting/ regurgitation episodes with each increasing dose group of omeprazole. In addition, the larger

doses (1.0 mg/kg and 1.5 mg/kg) showed effect at Week 1 while the lowest dose (0.5 mg/kg) showed effect at Week 3.

The intensity of pain-related symptoms and the intensity of vomiting/regurgitation episodes improved. On average, patients entered the study with moderate symptoms of pain-related symptoms and vomiting/regurgitation episodes. At the final visit, symptoms diminished to approximately better than mild. No statistical differences were detected between any treatment groups.

The Physician's Global Assessment indicates that omeprazole improved overall GERD-related symptoms. Most patients improved (90%), a few patients remained the same (9%) and I got worse (1%).

Statistical Reviewer's Comments:

Dr. Milton Fan concluded Study 251 that omeprazole 1.5 mg/kg and 0.5 mg/kg administered as a suspension effectively reduced the average number of vomiting/regurgitation episodes from the baseline based on the last 24 hours treatment as pre-specified in the protocol.

Medical Officer's Comments:
The sponsor provided additional data to support the 50% decrease of vomiting/ regurgitation episodes (see submission on September 27, 2007). I agree that omeprazole effectively decreased the number of vomiting/regurgitation episodes and improved the overall GERD-related symptoms.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety and tolerability of omeprazole in pediatric patients aged 0 to 2 years old were assessed in Study 251. The safety variables included adverse events (AE), clinical laboratory results and physical examinations.

Of the 115 patients enrolled into the study, 106 (92.2%) patients took at least one dose of study medication and are included in the safety analysis. Of this safety population, 83 (78.3%) patients reported one or more adverse events during the study. Twenty-six of those patients (31.3%) were dosed with omeprazole 0.5 mg/kg, 26 (31.3%) were dosed with omeprazole 1.0 mg/kg, and 31 (37.3%) were dosed with omeprazole 1.5 mg/kg.

Summary of Adverse Events

A modified WHO Adverse Reaction Terminology (WHOART) dictionary with a body system hierarchy was used for the coding of AEs from this study. Terms listed are the "preferred term". Table 10 presents a summary of incidence rates, according to body system classification for all AEs.

The most frequently occurred AEs were related to the Respiratory System, the Gastrointestinal System (GI), and the Resistance Mechanism System with total percentages of 46.2%, 43.4%, and 27.4%, respectively (Table 10). Respiratory infection (23.6%, 25 out of 106 patients) and rhinitis (14.2%, 15 out of 106 patients) were the most frequently occurring AEs within the Respiratory System. In the GI System, diarrhea (22.6%, 24 out of 106 patients) and constipation (12.3%, 13 out of 106 patients) were the most frequently occurring AEs. Otitis media (22.6%, 24 out of 106 patients) was the most frequent AE in the Resistance Mechanism System.

Five patients experienced a serious adverse event during the course of this study. These were pneumonia, urinary tract infection, lymphadenitis, pertussis, and bronchiolitis with croup. In all 5 cases, the investigators considered the SAE to be unlikely related to the study drug. In addition all SAEs were either mild or moderate in intensity. There was no apparent relationship of the serious AEs to the omeprazole dose the patient received.

No deaths occurred during this study. One patient had 5 AEs that caused discontinuation of the study.

Table 10: Number (%) of Patients with Adverse Events by Body System

Body System[a]	Ome 0.5 mg/kg (n=35)	Ome 1.0 mg/kg (n=35)	Ome 1.5 mg/kg (n=36)	Total (n=106)
Patients with ≥1 Adverse Event	26 (74.3%)	26 (74.3%)	31 (86.1%)	83 (78.3%)
Respiratory System Disorder	14 (40.0%)	14 (40.0 %)	21 (58.3%)	49 (46.2%)
GI System Disorder	12 (34.3%)	16 (45.7%)	18 (50.0%)	46 (43.4%)
Resistance Mechanism Disorder	10 (28.6%)	9 (25.7%)	10 (27.8%)	29 (27.4%)
Skin Appendage Disorder	7 (20.0%)	9 (25.7%)	8 (22.2%)	24 (22.6%)
Body as a Whole	10 (28.6%)	7 (20.0%)	5 (13.9%)	22 (20.8%)
Psychiatric Disorder	3 (8.6%)	8 (22.9%)	3 (8.3%)	14 (13.2%)
Hearing Vestibule Disorder	2 (5.7%)	1 (2.9%)	2 (5.6%)	5 (4.7%)
Central Peripheral Nervous System	1 (2.9%)	1 (2.9%)	0 (0.0%)	2 (1.9%)
Platelet Bleed Clot	1 (2.9%)	1 (2.9%)	0 (0.0%)	2 (1.9%)
Urinary System Disorder	1 (2.9%)	0 (0.0%)	1 (2.8%)	2 (1.9%)
Cardiovascular Disorder	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (0.9%)
Liver Biliary System Disorder	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (0.9%)
Metabolism Nutrition Disorder	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Muscular Skeletal System Disorder	0 (0.0 %)	0 (0.0%)	1 (2.8%)	1 (0.9%)
Myo, Endo, Pericardial Valve Disorder	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (0.9%)
Neonate Infant Disorder	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (0.9%)
Neoplasms	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (0.9%)
Vision Disorder	0 (0.0%)	2 (5.7%)	2 (5.6%)	4 (3.8%)
WBC & Resistance Disorder	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (0.9%)

a If an adverse event occurred more than once for a patient, it was only counted once for that patient. If a patient had multiple adverse events within one body system, the patient was only counted once for that body system.

Reference: Section 14.3, Table 14.3.1.1 and Appendix 16.2.7.1

There were no clinically important findings and trends in hematology, clinical chemistry, urinalysis, vital signs, or physical examination (including medical history) observed across or within the omeprazole treatment groups.

7.1.1 Deaths

No patients died during the study.

7.1.2 Other Serious Adverse Events

Five patients experienced serious adverse events (SAEs) as shown in Table 11. They were not attributed to the study drug by the investigator.

Table 11: Listing of serious adverse event (Safety population)

Site #/Patient #	Ome Dose	Age (M) Gender Race	Adverse Event preferred term (verbatim term)	Day of SAE Onset	Relationship to Study Drug
005/001	1.5 mg/kg	14.7 Male Black	Pneumonia (Pneumonia)	40	Unlikely
006/004	0.5 mg/kg	1.9 Female Caucasian	Urinary Tract Infection (Urinary Tract Infection)	12	Unlikely
008/007	1.0 mg/kg	14.1 Male Caucasian	Lymphadenitis (Lymphadenopathy)	51	Unlikely
017/001	1.5 mg/kg	2.1 Female Black	Pertussis (Pertussis)	62	Unlikely
026/008	0.5 mg/kg	15.8 Female Caucasian	Bronchiolitis with Croup (Respiratory Disorder)	22	Unlikely

Reference Section 14.3: Table 14.3.2.1 and Appendix 16.2.7.1

Medical Officer's Comments: The narratives of the 5 SAEs listed in Table 11 were reviewed. I agree with the investigator that these SAEs appear not to be related to the test article.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 6 patients discontinued from the study because of adverse events (Table 12). The 6 patients had 11 adverse events: 10 of the 11 adverse events were considered possibly treatment related (Table 12). The adverse events included exacerbation of GERD symptoms, increase of irritability, vomiting, rash, repetitive motion behavior, and abnormal crying.

Table 12: Listing of Adverse Events Resulting in Discontinuation of Study

Site	Pat No.	Omeprazole Dose	Age (M)	SEX	RACE	Adverse Event*	Start Day+	Stop Day+	Relation to Study Drug	Maximum Intensity	Action Taken w/ Drug
003	003	1.0 mg/kg	4.8	F	C	EXACERBATION OF GERD SYMPTOMS GASTROESOPHAGEAL REFLUX	2	7	Probable	Moderate	Drug Stopped
	004	1.5 mg/kg	4.8	M	C	EXACERBATION OF GERD SYMPTOMS GASTROESOPHAGEAL REFLUX	1	7	Probable	Severe	Drug Stopped
008	006	0.5 mg/kg	1.1	F	C	INCREASED IRRITABILITY NERVOUSNESS	2	Cont.	Possible	Moderate	Drug Stopped
						INCREASED VOMITING VOMITING	2	Cont.	Possible	Moderate	Drug Stopped
010	002	0.5 mg/kg	8.2	M	C	RASH RASH	4	19	Possible	Mild	Drug Stopped
	003	1.0 mg/kg	2.1	F	C	CRYING CRYING ABNORMAL	5	Cont.	Probable	Severe	Drug Stopped
015	004	1.0 mg/kg	3.6	F	C	IRRITABILITY NERVOUSNESS	.	47	Possible	Moderate	Drug Stopped
						LACK OF VERBAL COMMUNICATION PERSONALITY DISORDER	.	47	Possible	Moderate	Drug Stopped
						LOSS OF APPETITE ANOREXIA	.	47	Unlikely	Mild	Drug Stopped
						NO EYE CONTACT PERSONALITY DISORDER	.	47	Possible	Moderate	Drug Stopped
						REPEDITIVE MOTION BEHAVIOR UNUSUAL BEHAVIOUR	.	47	Possible	Moderate	Drug Stopped

*From the sponsor's Table 14.3.2.2 of Study 251.

7.1.4 Other Search Strategies

No other search strategies or markers for a particular toxicity were performed.

7.1.5 Common Adverse Events

The most frequently occurred AEs were related to the Respiratory System, the Gastrointestinal System (GI), and the Resistance Mechanism System with total percentages of 46.2%, 43.4%, and 27.4%, respectively (Table 7). Respiratory infection (23.6%, 25 out of 106 patients) and rhinitis (14.2%, 15 out of 106 patients) were the most frequently occurring AEs within the Respiratory System. In the GI System, diarrhea (22.6%, 24 out of 106 patients) and constipation (12.3%, 13

out of 106 patients) were the most frequently occurring AEs. Otitis media (22.6%, 24 out of 106 patients) was the most frequent AE in the Resistance Mechanism System.

In general the AEs reported were consistent with the known safety profile of omeprazole in adult population. No new safety signals were identified in the pediatric population of 0 to 2 years old.

7.1.6 Laboratory Findings

Laboratory tests consisted of hematology, serum chemistry, and urinalysis. There were no clinically significant trends within or between treatment groups with respect to hematology, clinical chemistry, or urinalysis.

Medical Officer's Comment:
The clinical laboratory profiles appeared unremarkable.

7.1.7 Vital Signs

There were no clinically important trends within or between treatment groups with respect to vital signs or physical examination findings identified. ECGs were not performed in this study.

7.1.8 Electrocardiograms (ECGs)

ECGs were not conducted in this study.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary safety data sources used in conducting the review was the Phase III study (Study 251). Patients were between 0.7 and 22 months of age. Patients had clinically diagnosed GERD.

7.2.1.1 Demographics

The distribution of males and females at baseline were 43.5% and 56.5%, respectively. The most patients were Caucasian (85.2%). The mean of age was 6.3 months (Table 13)

Table 13: Demographic and baseline characteristics of the full data set

	Ome 0.5 mg/kg (n=37)		Ome 1.0 mg/kg (n=38)		Ome 1.5 mg/kg (n=40)		Total (n=115)	
	n	%	n	%	n	%	n	%
Gender								
Female	15	40.5	17	44.7	18	45.0	50	43.5
Male	22	59.5	21	55.3	22	55.0	65	56.5
Race								
Caucasian	31	83.8	33	86.8	34	85.0	98	85.2
Black	5	13.5	5	13.2	5	12.5	15	13.0
Other	1	2.7	0	0.0	1	2.5	2	1.7
Age (Months)								
Mean	7.0		6.2		5.8		6.3	
SD[a]	4.9		4.5		4.1		4.5	
Minimum	1.1		1.3		0.7		0.7	
Maximum	21.8		20.2		17.6		21.8	

[a] SD = Standard Deviation
Note: See Appendix 16.2.4.1 for complete listings of patients.

7.2.1.2 Extent of exposure (dose/duration)

A total of 115 patients were randomized into the study. Of the 115 patients randomized, 106 (92.2%) patients took at least one dose of study medication. Nine patients (7.8%) were randomized to study drug, but never took any medication. Table 14 summarizes the exposure by treatment group.

Table 14: Summary of Exposure to Study Medication

	Patients Randomized into Study (n=115)		
Dose of study medication	Ome 0.5 mg/kg n=37	Ome 1.0 mg/kg n=38	Ome 1.5 mg/kg n=40
Total number of patients exposed to one dose of study medication	35	35	36
Maximum number of doses any one patient took	63	61	61
Maximum actual daily dose (mg)	10.6	13.3	16.0

Reference: Section 14.1, Table 14.1.5, Section 14.3, Table 14.3.5.1.

7.2.2 Adequacy of Overall Clinical Experience

Medical Officer's Comments:

The patient population consisted of 106 subjects. Among them, the data of 100 (ITT)/96 (PP) were used for efficacy analysis. Seventy-nine patients completed the 8-week study. Three dose levels (0.5, 1.0, and 1.5 mg/kg, once daily for 8 weeks) were studied. The proposed market dose is 2.5 mg or 10 mg once daily for up to 8 weeks. The overall clinical experiences appeared adequate to assess safety for the intended use.

7.2.3 Assessment of Quality and Completeness of Data

Medical Officer's Comments:

The safety data base included 106 pediatric subjects age 0.7 to 22 months old with clinically diagnosed GERD. The study report included investigator comments, serious adverse event analysis, and summary of frequent adverse event. The explanations by the investigators helped the review. The overall quality and completeness of the data were acceptable.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Medical Officer's Comments:

The profile of drug-related adverse events of omeprazole in pediatric patients 0 to 2 years old is similar to that of 12 to 18 years old and adults. Gastrointestinal disorders (vomiting and diarrhea) appeared to be the most common treatment-related adverse events (see Table 7, Treatment Related Adverse Events).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Omeprazole delayed-release oral suspension (0.5, 1.0, and 1.5 mg/kg once daily for 8 weeks) were studied in pediatric patients 0.7 to 22 months old with GERD.

- The results support the recommended doses and dosing regimen.
- The mean exposures of ITT population (N=106) were 56 days.
- Dose-toxicity relationship at the range of 5 to 20 mg was not identified.

8.2 Drug-Drug Interactions

Omeprazole is largely metabolized in the liver by the liver microsomal cytochrome P450 enzyme system. The drug-drug interactions are described in the existing label. A potential interaction between the antifungal agent voriconazole and omeprazole was recently identified, and should be added to the proposed labeling. No new data in the pediatric submission were identified.

8.3 Special Populations

No dose modification for race and gender is suggested for the submission. No special dosing for hepatic or renal insufficiency in pediatric patients was studied.

8.4 Pediatrics

Omeprazole delayed-release suspension has been approved for pediatric patients 2 to 16 years old with GERD. The current submission supports the indication for pediatric patients 0 to 2 years old with GERD.

9 OVERALL ASSESSMENT

9.1 Conclusions

Based on the comparable bioavailability studies (Study 250 and Study 9586C0002) and the safety and efficacy study (Study 251) in the pediatric patients, NDA 22,056 is recommended for **Approvable**.

In this submission, omeprazole was generally safe and well tolerated in pediatric GERD patients aged 0.7 to 22 months old. There was no death. There were 6 treatment-related dropouts due to adverse events (exacerbation of GERD symptoms, vomiting, and crying, Table 9). The most common adverse events reported from this population were consistent with the known adverse events of omeprazole. In addition, there were no clinically important findings or trends in hematology, clinical chemistry, vital signs, or physical examination observed across treatment groups.

9.2 Recommendation on Regulatory Action

The clinical recommendation is **approvable** for the short term treatment of pediatric patients 0 to 2 years old with GERD or with erosive esophagitis.

9.3 Labeling Review

The sponsor's proposed label and the reviewer's proposed labeling changes (single underlined) are as the following:

Sponsor Proposal	FDA Changes
8.4 Pediatric Use	**8.4 Pediatric Use**
[redacted]	[redacted]

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1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

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