CLINICAL REVIEW

DIVISION OF GASTROENTEROLOGY PRODUCTS

Application Type	NDA
Submission Number	20-973/SE5-022
Letter Date	December 28, 2007
Stamp Date	December 31, 2007
PDUFA Goal Date	June 30, 2008
Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	June 19, 2008
Established Name	Rabeprazole Sodium
Trade Name	Aciphex®
Therapeutic Class	Proton Pump Inhibitor
Applicant	Eisai Medical Research Inc.
Priority Designation	P
Formulation	Delayed-Release Tablets
Dosing Regimen	(b) (4) 20 mg once daily for up to 8 weeks
Indication	Short-term treatment of symptomatic GERD
Intended Population	12 to 16 years of age

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 20-973/SE5-022, Aciphex 20 mg Delayed-Release Tablets, is recommended for **Approval** for the short-term treatment of pediatric patients 12 years of age and older with gastroesophageal reflux disease (GERD).

The recommendation is based on:

1) Extrapolation of previous adult placebo-controlled efficacy data to the proposed pediatric population;
2) Similarity of pathogenesis of GERD between the 12 to 16 year-old patients and the adult patients;
3) Following 20 mg qd dosing (Study E3810-A001-119), the systemic exposure in adolescent patients with GERD 12 to 16 years of age was within the range observed in healthy adult volunteers for the same dosing regimen (Clinical Pharmacology Review by Dr. David Gortler)
4) Safety data in the adolescent population (Study E3810-A001-202).

(b) (4)

[redacted]

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor, Eisai Medical Research Inc., submitted the results of Studies E3810-A001-202 and E3810-A001-119 (Table 1) (b) (4) regarding the effectiveness and safety of 10 mg and 20 mg Delayed-Release Tablets in the treatment of symptomatic GERD in pediatric patients 12 to 16 years old.

Table 1: Summary of clinical studies

Study Number	Study Design	Objective	Dosing Regimen	N	Study Population	Duration
E3810-A001-202	Phase 2, open-label, no control, no randomization	To evaluate safety & efficacy	Aciphex 10, & 20 mg	111	Pediatric subjects age 12 to 16 years old with clinical GERD	8 weeks
E3810-A001-119	Phase 1, open-label	To determine PK parameters	Aciphex 10, & 20 mg	24	Pediatric subjects age 12 to 16 years old with clinical GERD	5 to 7 days

From the sponsor's NDA 20-973/S-022 submission

Rabeprazole is a benzimidazole derivative, a compound that inhibits gastric acid secretion of the gastric parietal cells. It belongs to the proton pump (the H^+/K^+-ATPase) inhibitor (PPI) class. The delayed-release Tablets of rabeprazole were developed for the short-term treatment of pediatric GERD aged 12 to 16 years old.

The primary study to support the proposed indications is entitled "Safety and Efficacy of Rabeprazole in the Treatment of Gastroesophageal Reflux Disease in 12 to 16 Year Old Patients" (Study E3810-A001-202).

In total, 111 patients were enrolled (Intent-To-Treat population, patients who had a baseline measurement, at least 1 post-baseline measurement, and who took at least 1 dose of study medication), and 107subjects completed the study (Per-Protocol population,

patients who completed the study and met all criteria pre-stipulated in the protocol). Data for safety analysis originated from the 111 patients who received at least 1 dose of study treatment (safety population).

In addition, Study (E3810-A001-119) was a pharmacokinetic study with 24 pediatric GERD patients 12 to 16 years old. Patients were exposed to two dose levels (10 mg or 20 mg) for 5 to 7 days.

1.3.2 Efficacy

This submission did not include adequate information for an efficacy evaluation. The study (Protocol E3810-A001-202) was poorly designed.

The "efficacy endpoints" of the protocol included:

1) Changes in frequency of GERD symptoms at 8 weeks and 10 weeks as compared with baseline; changes in frequency at 10 weeks as compared with at 8 weeks.

   GERD symptoms include five primary symptoms (i.e. heartburn, regurgitation, nausea, vomiting, and epigastric pain, and two additional subject-selected symptoms if present). Symptoms were assessed using Gastroesphageal Reflux Disease Symptom Assessment Scale (GSAS).

2) Changes in severity of GERD symptoms as compared with baseline

3) Changes in antacid use as compared with baseline

4) Changes in quality of life (QOL) as compared with baseline

   QOL assessments included the Psychological General Well-Being Index (PGWBI) and the Medical Outcomes Study 10-item (SF-10) questionnaire for children.

5) Exploration of relationship of dose received with symptom response

The sponsor proposes to extrapolate the adult placebo-controlled efficacy data to the pediatric population age 12 to 16 years old.

Medical Officer's Comments: Deficiencies of the efficacy data include:

1) **No study control for these efficacy endpoints;**

2) **No randomization for assignment to 10 mg or 20 mg dose;**

3) **Statistically, it was not stipulated what was expected of the 10 mg and 20 mg rabeprazole (i.e. the 20 mg superior to 10 mg? or 10 mg not inferior to 20 mg?);**

4) **The protocol did not provide adequate endpoints and methods for assessment. In April 2008, DGP requested the sponsor resubmit responder analysis (e.g., the percentage of patients who had complete relief of GERD symptoms at the end of the study);**

5) **Most of the patients only had very mild GERD symptoms at baseline and had less than one episode (such as heartburn) per day. Thus, no clinically meaningful improvement at the end of the study was demonstrated.**

6) **PGWBI and SF-10 are generic instruments that do not specifically reflect the impact of GERD on patient functioning. The instruments cannot be effectively utilized to support the efficacy claims.**

Based on the six deficiencies, the sponsor failed to demonstrate the effectiveness of rabeprazole in the proposed pediatric patients.

The amended Written Request for pediatric study was conveyed to the sponsor on June 27, 2007. The Written Request (Study 5: Pharmacokinetic and Safety Study in Pediatric Patients 12 to 16 Years of Age) did not ask to conduct controlled efficacy study in patients 12 to 16 years old.

In this submission, the sponsor provides the requested Pharmacokinetic and Safety Studies, and expects approval based on the extrapolation of adult efficacy data.

In my opinion, the extrapolation is acceptable for the following three reasons:

1) The pathogenesis of GERD is not different between the 12 to 16 years old and the adults. In general, irrespective of whether the patients are adults or adolescents, the contributing factors include defective lower esophageal sphincter (LES), hiatal hernia, impaired esophageal peristalsis, delayed gastric emptying, gastric acid production and bile reflux. The common central pathogenic events are gastric acid in contact with esophageal epithelium breaking down the tissue.

2) The Clinical Pharmacology team Drs. David Gortler and Sue Chih Lee also believe that extrapolation is appropriate at the review team meeting on May 28, 2008. Bioavailability data (Study E3810-A001-119) were summarized in Table 2.

Table 2: Summary of mean PK parameters of rabeprazole on Day 5 in 12 to 16 year old subjects compared with healthy adults in previous studies*

PK Parameter	Rabeprazole (10 mg)		Rabeprazole (20 mg)	
	Adolescents (range)	Adults (study code)	Adolescents (range)	Adults (study code)
AUC_{0-t} (ng•hr/mL)	228 (61.6-425.9) (n=11)	315 (001)	731 (137.9-1864) (n=11)	545 (001)
		326 (002)		435 (002)
		445 (012)		845 (009)
C_{max} (ng/mL)	184 (28.3-354.3) (n=11)	184 (001)	460 (88.6-999) (n=12)	294 (001)
		215 (002)		253 (002)
		272 (012)		594 (009)

*From the sponsor's report: Module 2, Section 2.7.2, Table 3

3) Study E3810-A001-202 provides acceptable safety information.

1.3.3 Safety

Study E3810-A001-202: Safety was assessed in 111 pediatric patients 12 to 16 years old (safety population). Of the 111 subjects, 52 (96.3%) subjects in the 10 mg rabeprazole and 55% (96.5%) subjects in the 20 mg rabeprazole groups completed the 8 weeks of treatment. The safety profile was assessed with reports of adverse events (AEs), clinical laboratory evaluations (including hematology, clinical chemistry, and urinalysis), changes to medical history, vital signs, and physical examinations. These assessments were consistent with standard of care in pediatric medical practice.

There were no deaths and no subject discontinued from the study due to adverse event. There was one serious adverse event (SAE), mood swings, that was considered not related to rabeprazole by the investigator.

Medical Officer's Comments: The narrative of SAE was reviewed and summarized as the following:

Patient (185/(b) (4) R301474-201-USA), a 12 years old female with a history of anxiety disorder, sexual assault, attention deficit disorder, and persistent sinusitis received rabeprazole (20 mg once daily) for gastroesophageal reflux disease during this clinical study. The subject was hospitalized for mood swings and behavioral problems after 40 days of exposure to rabeprazole.

The reviewer agrees that mood swings may not be related to the treatment.

Adverse event were reported in 31 of the 54 subjects (57.4%) in the 10 mg dose group and in 35 of the 57 subjects (61.4%) in the 20 mg dose group. Most of the events were mild to moderate.

Treatment-related or possibly-related adverse events included diarrhea, nausea, abdominal pain, and headache, and occurred in 4 of the 54 subjects (7.4%) in the 10 mg dose group and 8 of the 57 subjects (14.0%) in the 20 mg dose group.

Adverse events reported in ≥2% of the subjects in the treatment groups were pharyngolaryngeal pain, headache, cough, upper respiratory tract infection, nasal congestion, nasopharyngitis, diarrhea, nausea, bronchitis, pharyngitis, abdominal pain, chest pain, otitis media, and sinusitis.

Medical Officer's Comments: the adverse events reported were consistent with the most common adverse events in this pediatric age group (such as upper respiratory tract infection, otitis, and sinusitis) and disease-related events (such as nausea and abdominal pain). The possible treatment-related adverse events may include headache, nausea, diarrhea, and abdominal pain.

No clinically significant findings in hematology, clinical chemistry, and urinalysis were reported.

Study E3810-A001-119 (Pharmacokinetic study): Safety was also assessed in 24 pediatric subjects with GERD 12 to 16 years old. No deaths or SAEs were reported, and no subjects were discontinued from the study due to AEs. Headache was the most frequently treatment-emergent AE (4 subjects, 16.7%), followed by nausea (2 subjects, 8.3%). No dose-relationship of AEs was identified. Five subjects (3 subjects in 10-mg group and 2 subjects in 20- mg) reported adverse events that were considered to be related to study drug. These were mild or moderate diarrhea, headache, nausea, periorbital edema, and proteinuria.

Medical Officer Comments: The periorbital edema and proteinuria were not reported in the 8-week pediatric safety study (see Table 11, Study E3810-A001-202), but in adult study (1064 patients), peripheral edema was reported (Aciphex label). The causal relationship of periorbital edema and proteinuria to rabeprazole is not clear at the present time. In my opinion, the overall profile of rabeprazole in the two adolescent studies was that of a safe and well tolerated drug.

1.3.4 Dosing Regimen and Administration

The sponsor selected rabeprazole doses (10 mg or 20 mg once per day) for this adolescent population based on the analysis of PK parameters and safety data (Study E3810-A001-119).

Medical Officer Comments: The dose-selection and dosing regimen was based on the controlled adult data and the PK study in the adolescent patients. It appeared to be appropriate.

1.3.5 Drug-Drug Interactions

Rabeprazole is extensively metabolized in hepatocytes by liver microsomal cytochrome P-450 (CYP3A and CYP2C19). The current labeling for rabeprazole provides details with respect to drug interactions. No new drug interaction data were submitted in this submission.

1.3.6 Special Populations

The age range of this submission is 12 to 16 years old. No additional dosage adjustment for the proposed patients is recommended.

The current labeling for rabeprazole recommends no dosage adjustment for patients with mild to moderate hepatic insufficiency. The pharmacokinetic parameters of a single 20 mg dose in patients with stable renal impairment (creatinine clearance $\leq$5 mL/min/1.73 m^2) were not clinically different to those of healthy subjects.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the product is rabeprazole Magnesium and the trade name is Aciphex®. Rabeprazole 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). The delayed-release (b) (4) tablets were developed for the short-term treatment of pediatric GERD aged 12 to 16 years old. The proposed treatment regimen is rabeprazole (b) (4) 20 mg P.O. once daily for up to 8 weeks.

2.2 Currently Available Treatment for Indications

The currently available treatment for pediatric patients with GERD and erosive esophagitis include medical therapy and surgical treatment (such as fundaplication).

- **Histamine-2 Receptor Antagonists (H_2-RAs):** Ranitidine (Zantac, 1 month to 16 years old), and famotidine (Pepcid, 3 months to 16 years old), and nizatidine (Axid, 2 to 18 years old).

- **Proton Pump Inhibitors (short term treatment):** Omeprazole (Prilosec, 1 to 16 years old), esomeprazole (Nexium, 1 to 17 years old), lansoprazole (Prevacid, 1 to 17 years old)

- **Surgical Treatment:** Only for 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

Rabeprazole is currently marketed in the United States for the treatment of symptomatic GERD, healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of pathological hypersecretory conditions such as Zollinger-Ellison syndrome, and combination therapies for the eradication of *Helicobacter pylori* in adult patients.

2.4 Important Issues with Pharmacologically Related Products

1) ECL cell hyperplasia and development of carcinoid

Long-term treatment of PPI in animals may result in gastric enterochromafin-like (ECL) cell hyperplasia and development of gastric carcinoid (such as rats). However, in human, only dose- and exposure time-dependent ECL cell hyperplasia was observed. PPI-related development of dysplasia, or malignancy was not evident.

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.

One year treatment of rabeprazole (10 or 20 mg/day) increased of the incidence of ECL cell hyperplasia. No patient developed the adenomatoid, dysplastic or neoplastic changes in the gastric mucosa.

2) Non-malignant change

Patients with long-term omeprazole treatment and *Helicobacter pylori* infection may develop gastric intestinal metaplasia Type I.

Medical Officer's Comments: Intestinal metaplasia Type I is not a pre-malignant condition. 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 accepted that only incomplete intestinal metaplasia (*i.e.* Types II and III) is associated with pre-malignant condition of gastric adenocarcinoma.

2.5 Other Relevant Background Information

No information regarding pending market applications in foreign countries is available. Rabeprazole delayed-release tablets (20 mg P.O.) have been marketed in the United States since 1999.

Rabeprazole (20 mg tablets) has not been withdrawn for reasons related to safety of efficacy in any country where they have been marketed.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Rabeprazole delayed-release tablets (20 mg) have been approved for patients 18 years or older. (b) (4)

(b) (4) No significant CMC issues that affected clinical interpretation of the data were identified.

Medical Officer's Comment: In my opinion, (b) (4) dosing regimen should not be approved.

3.2 Animal Pharmacology/Toxicology

The sponsor provided responses (final study reports) to Pediatric Written Request - Amendment #5 for pediatric studies with aciphex dated June 27, 2007. In the written request, the sponsor was asked to conduct 1) a 4-week repeated dose toxicity study in neonatal rats, and 2) a 90-day repeated dose toxicity study in neonatal dogs with aciphex.

In the 5-week juvenile rat study (282 male and 282 female, Study 900948), Sprague-Dawley rat from Days 7 to 41 post-partum were exposed to 5, 25, or 150 mg/kg rabeprazole by oral gavage for 5 weeks. Treatment increased the serum gastrin concentrations and stomach weight. Histopathological examination revealed a dose-related increase of cytoplasmic eosinophilia of chief cells in gastric mucosa. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg or higher and females at 25

mg/kg or higher. The changes were reversible. The NOAEL of the 5-week study in rats was 25 mg/kg.

In the 90-day oral toxicity study in neonatal dogs, rabeprazole was given by oral gavage to 7 days old dogs (31 male and 32 female Beagle dog pups) at 0, 3, 10, and 30 mg/kg/day (Study 900949). Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness. Histopathological examination revealed degeneration /necrosis of parietal cells and mucosal hypertrophy/ hyperplasia at the fundus of the stomach in a dose-related manner. The changes were reversible. The NOAEL of the 90-day study in dogs was 3 mg/kg.

In a previous 104-week carcinogenicity study in Sprague-Dawley rats, rabeprazole at 5 mg/kg/day induced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats. At the same dose level, rabeprazole also induced ECL cell carcinoid tumors in female rats (Aciphex label).

The Pharmacology and Toxicology reviewer Dr. Ke Zhang commented that the 5-week oral toxicity study in the neonatal rats and the 90-day oral toxicity in neonatal dogs are acceptable, and that there were no new toxicities or target organ of toxicity identified in these studies as compared to the adult animals. Completion of these studies in neonatal rats and dogs satisfied the requirements of the Pediatric Written Requests (in Amendment #5 dated June 27, 2007).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data were from 1) the previous adult studies and 2) the pediatric studies summarized in Table 1.

1) GERD studies in adults: In two multi-center, placebo-controlled adult studies, 316 patients with daytime and nighttime heartburn were treated with 20 mg P.O. qd for 4 weeks. The percentage of heartburn free daytime and /or nighttime periods was greater with rabeprazole 20 mg compared to placebo in Study RAB-USA-2 (47% vs. 23%) and Study RAB-USA-3 (52% vs. 28%). The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for rabeprazole 20 mg as compared to placebo at Week 4.

In addition, the combined analysis of these two studies showed rabeprazole 20 mg significantly improved other GERD-associated symptoms (regurgitation, belching and early satiety) by Week 4 compared with placebo (all p values< 0.005).

2) GERD studies in 12 to 16 years old: Eisai submitted results of one Phase 2 clinical study **(Study E3810-A001-202)** to support the safety of rabeprazole for the short-term treatment of pediatric patients 12 to 16 years old with gastroesophageal reflux disease (GERD).

In addition, Eisai submitted one clinical pharmacology study **(Study E3810-A001-119)** to support the bioavailability in the pediatric patients.

Medical Officer's Comment: The two clinical trials plus the efficacy data from the controlled adult studies are adequate.

4.2 Review Strategy

The two clinical studies (**E3810-A001-202** and **E3810-A001-119**) were reviewed. As a Medical Officer, my review of this NDA laid an emphasis on the safety and efficacy data of the Phase 2 study (**E3810-A001-202**).

Stud E3810-A001-119 was a pharmacokinetic study. 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.

4.3 Data Quality and Integrity

A study site inspection (**E3810-A001-119)** was requested by the clinical pharmacology reviewer, and will be conducted by the Division of Scientific Investigations.

4.4 Compliance with Good Clinical Practices

According to the sponsor, **Studies E3810-A001-202** and **E3810-A001-**202 were conducted based on 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 Comment:
Eisai has adequately disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up concerns which would possibly jeopardize the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetic parameters of rabeprazole (10 mg and 20 mg) were studied in 7 centers in patients 12 to 16 year olds with symptoms of GERD. The results were as follows:

- The AUC and C_{max} values of Day 5 or 7 were not significantly higher than that of Day 1, suggesting that no accumulation of rabeprazole occurred.
- $T_{½}$ values of 10 mg and 20 mg on Day 1 and Day 5 to 7 were in a similar range.
- Overall, the rabeprazole treatment in children aged 12 to 16 years was safe and well tolerated.

Table 3: Summary of PK results (Study E3810-A001-119)

Study Day/PK Parameters	E3810 10 mg (n=12)	E3810 20 mg (n=12)
Day 1		
AUC (ng•hr/mL)	305.0 ±37.9	557.8 ±109.8
C_{max} (ng/mL)	186.6 ±25.4	319.0 ±43.4
T_{max} (hr)	3.3 ±0.3	3.9 ±0.2
T½ (hr)	0.54 ±0.04	1.04 ±0.27
CL/F/Wt (mL/min/kg)	NA	NA
Day 5 or 7		
AUC (ng•hr/mL)	249.8 ±31.4	828.0 ±176.1
C_{max} (ng/mL)	184.1 ±26.6	460.4 ±85.82

T_{max} (hr)	3.4 ±0.5	4.1 ±0.5
T½ (hr)	0.54 ±0.04	0.97 ±0.19
CL/F/Wt (mL/min/kg)	12.58 ±1.83	10.14 ±2.30

From the sponsor's Table on Page 6 of Volume 1; E3810: rabeprazole

Medical Officer's Comments: The bioavailability data were discussed with Drs. Sue-chih Lee and David Gortler, the Clinical Pharmacology Review team. They pointed out that the proposed dosing regimen of 20 mg Q.D. is reasonable, and is consistent with the known PK data in adults. In addition, they also pointed out that the mean value of AUC in 10 mg group on Days 5 and 7 is apparently lower than that of the 20 mg.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the rabeprazole delayed-release tablets is for the short-term treatment of GERD and healing of erosive esophagitis in pediatric patients 12 to 16 years old.

6.1.1 Methods

Study E3810-A001-202 provided inadequate efficacy data to support the pediatric indication. It was a Phase 2, open-label design with no control or randomization.

Study objectives: The primary objective was to collect safety information on rabeprazole 10 mg and 20 mg in the treatment of GERD in children 12 to 16 years old.

The secondary objective was to assess the efficacy of rabeprazole on the improvement of symptoms of GERD.

The efficacy variables were evaluated with the following endpoints:
1) Assessment of changes in frequency and severity of GERD symptoms from baseline based on daily patient report (Statistic tests were conducted for Weeks 2, 4, 6, 8 or 10 vs. baseline);

2) Assessment of changes in antacid (Mylanta® for children) use from baseline;

3) Assessment of changes in quality of life (QOL) from baseline via PGWBI (Psychological Well-Being Index) and SF-10 (Medical Outcomes Study 10-Item Short Form questionnaire for children)

6.1.2 General Discussion of Endpoints

Basis for choosing Daily Patient Symptom Assessment:

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.

6.1.3 Study Design

1. STUDY E3810-A001-202

Title: Safety and Efficacy of Rabeprazole in the Treatment of Gastroeophageal Reflux Disease in 12 to 16 Year Old Patients

Study Objective:
Primary: To evaluate the safety of once daily treatment with rabeprazole in the treatment of GERD in pediatric patients 12 to 16 years of age

Secondary: To assess the efficacy of once daily treatment with rabeprazole in improvement of GERD-associated symptoms, based on symptom frequency and severity, antacid use and quality of life (QOL) measures.

Study Design: This was a Phase 2, open-label, multicenter study designed to evaluate the safety and "efficacy" of rabeprazole treatment in pediatric patients with GERD aged 12 to 16 years old. The duration of the treatment was 8 weeks. There was no control group, nor randomization.

Assessments included full physical examinations at Screening, Baseline and Week 8. Vital signs were taken at the biweekly study center visits. Phone contact to check compliance, symptom diary, and adverse event assessments in the weeks when there were no study center visits. Clinical laboratory samples (hematology, clinical chemistry, and urinalysis) were collected at Screening and Week 8.

Subjects recorded the frequency and severity of 5 predetermined GERD symptoms (heartburn, regurgitation, nausea, vomiting, and epigastric pain; Appendix 4 GERD Symtom Assessment on Page 694 to 697 of the submission). In addition, 2 other patient-selected GERD symptoms were chosen during the Screen Visit from a list such as cough, belching, fullness, abdominal pain, anorexia, hoarseness, dysphagia, abdominal distension, painful swallowing, wheezing, choking chest pain, flatulence constipation, and diarrhea. Symptom severity was determined through a 5-point Likert scale (Table 6) (see Appendix 5 Pain Faces on Page 698 of the submission).

At the biweekly study center visit, a QOL assessment was conducted using the Psychological General Well-Being Index (PGWBI) and the Medical Outcomes Study 10-item Short form questionnaire (SF-10) scales. Gastroesophageal reflux disease symptoms were evaluated at the biweekly study center visits by having the subjects answer the GERD Symptom Assessment questionnaire (GSAS, version 4) along with a Visual Analog Scale.

The GSAS Assessment asked the following questions:
I. During the past week, did you have any of the symptoms listed below:
1) heartburn or burning pain inside your chest, 2) a feeling of pressure or discomfort inside your chest, 3) food coming back into your mouth, 4) an acid or sour taste in your mouth, 5) frequent gurgling in your stomach, 6) feeling of pressure or lump in the throat, 7) nausea or feeling like you were going to vomit, 8) burning pain in your throat, 9) bloating or feeling like you had to loosen your belt or unbutton your pants/skirt, 10) belching, 11) flatulence or passing gas from below, 12) feeling full after eating a little, 13) bad breath, 14) coughing, 15) hoarseness, & 16) Overall, how would you rate the severity of your symptoms during the past 2 weeks?

II. How many times in the past week did you have this symptom?

III. If you have this symptom, how much did it distress or bother you in the past week?

Subjects were asked the following overall symptom assessment question on symptomatic response to treatment at the end of active study drug treatment (Week 8, or when the subject prematurely discontinued the study).

Table 4: Summary of study assessments and procedures

Assessments	Screening[a]	Baseline[a]									Stop study drug[b]		Discharge
Week of study[c]	-2 to 0	Day -1	Day 0 to 2	1	2	3	4	5	6	7	8	9	10
Visit study site[e]	X	X	X		X		X		X		X		X
Written Informed Consent and Assent	X												
Medical history	X												
Telephone contact	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	
Symptom assessment (Diary and questions from Investigator)	X	X		X	X	X	X	X	X	X	X[e]	X	
QOL and GSAS assessments	X[a]	X[a]			X		X		X		X		X
Vital signs (BP, HR, temp)	X	X			X		X		X		X		X
Physical examination[f,g]	X[f,g]	X[g]									X[f,g]		X[g]
Laboratory evaluation (hem, chem., UA)	X[a]	X[a]									X		
Drug screen	X[h]	X[h]											
β-hCG pregnancy test (post-pubertal females only)	X[h]	X[h]									X		
Antacids dispensed	X[i]	X[i]			X[i]		X[i]		X[i]		X[b]		
Study drug dispensed			X[i]		X[i]		X[i]		X[i]				
Dispense diaries[j]	X[j]	X			X		X		X		X		
Review completed diaries		X			X		X		X		X		
Adverse events assessment	X	X		X	X	X	X	X	X	X	X	X	X
Compliance		X		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X

From the sponsor's report (Study E3810-A001-202) on Page 639 of the submission.

Medical Officer's Comments: The deficiencies of the study design included:

1) **No study control for these efficacy endpoints;**

2) **No randomization for assignment to 10 mg or 20 mg dose;**

3) **It was not statistically stipulated what was expected of the 10 mg and 20 mg rabeprazole (i.e. the 20 mg superior to 10 mg? or 10 mg not inferior to 20 mg?);**

4) **The protocol did not provide adequate endpoints and methods for assessment. In April 2008, DGP requested the sponsor to resubmit responder analysis (e.g., the percentage of patients who had complete relief of GERD symptoms at the end of the study);**

5) **Most of the patients only had very mild GERD symptoms at baseline and less than one episode (such as heartburn) per day. Thus, no clinically meaningful improvement at the end of the study was demonstrated.**

6) **PGWBI and SF-10 are generic instruments that do not specifically reflect the impact of GERD on patient functioning. The instruments cannot be effectively utilized to support the efficacy claims.**

Thus, the efficacy of this submission has not been established.

Study Population:
In total, 111 patients were studied. Of these, 107 patients completed the study.

Inclusion criteria:
1) Males and females aged 12 to 16 years with a clinical diagnosis of symptomatic GERD or suspected or endoscopically proven GERD.

2) Patients who have ever been treated with, or currently receiving PPIs, H2 blockers, or antacids were eligible (as long as they could go off PPIs and H2 blockers for three days prior to dosing, except for cimetidine, which had to discontinued for at least seven days prior to dosing). Also, patients were able to go off PPI therapy for two weeks at the end of test drug treatment.

3) Children with stable asthma/reactive airways disease on stable treatment regimens were eligible.

4) Children on stable doses of allergy, antiepi1eptic, antidepressant, and attention deficit disorder medicines were eligible.

5) Patients must be able and willing to swallow the test drug tablet intact. The ability of the child to swallow an intact tablet must be confirmed by the site at Screening.

6) The patient was willing and able to give assent to participate.

7) The patient's parent or guardian gave written informed consent.

8) Post-pubertal females were required to be abstinent during the course of the study.

9) Clinically insignificant laboratory findings.

Exclusion criteria:
1) Evidence of significant hepatic, renal, respiratory, endocrine, immune, infectious, hematologic, neurologic, psychiatric, or cardiovascular system abnormalities that would interfere with the conduct of the study, the interpretation of study results, or the health of the patient during the study.

2) History of primary esophageal motility disorders or systemic condition affecting the esophagus (e.g., scleroderma, esophageal infections).

3) History of eosinophilic esophagitis, persistent milk protein allergy, or allergic gastroenteropathy. History or current presence of peptic ulcers; current presence of *Helicobacter pylori.*

4) History of definitive acid-lowering surgery, previous esophageal surgery, or esophageal stricture was disallowed. History of fundop1ication or feeding tube insertion is allowed.

5) Treatment with full therapeutic doses of H2-receptor antagonists or sucra1fate within three days prior to dosing (or a shorter washout if agreed to by Investigator and Sponsor), except for cimetidine, which must be discontinued for at least seven days prior to dosing.

6) Treatment with a proton pump inhibitor within three days prior to dosing (or a shorter washout if agreed to by Investigator and Sponsor).

7) Inability to have 2-week PPI therapy-free period at end of test drug treatment.

8) Pregnancy or lactation.

9) Known or suspected drug addiction or alcohol abuse and/or a positive urine drug screen not explained by medication list; occasional alcohol or tobacco use was not an exclusion criterion.

10) Unwilling or unable to abide by the requirements of the study or violating the prohibitions and restrictions of the study defined in Section 9.4.

11) Any condition which would make the patient, in the opinion of the Investigator or Sponsor, unsuitable for the study.

12) Participation in another investigational drug study within one month prior to dosing.

13) A history of allergy/sensitivity to proton pump inhibitors or to their inactive ingredients.

Statistical population: Only descriptive statistics were conducted. There were 3 population analyzed: intent-to-treat (ITT) population, per-protocol (PP) population, and safety population. The ITT population included patients who had a baseline measurement, at least 1 post-baseline measurement, and who took at least 1 dose of study medication. Patients in the PP population were those who completed the study meeting all criteria pre-stipulated in the protocol and who did not have a major protocol violation

or deviation. The safety population included all patients who took at least 1 dose of study medication and had at least 1 post-baseline safety data value.

The safety analysis was conducted in safety population, and the efficacy in ITT population. Descriptive statistics were provided for the efficacy outcomes of Weeks 2, 4, 6, 8, and 10 vs. baseline.

Table 5: Demographic Profile of Study E3810-A001-202

Parameter	Treatment Groups	
	Rabeprazole 10 mg N =54	Rabeprazole 20 mg N =57
Age (years)		
Mean ± SD	14.2 ± 1.29	14.1 ± 1.49
Range	12 –16	12 –16
Groups		
12	7 (13.0%)	13 (22.8)
13	9 (16.7%)	8 (14.0%)
14	15 (27.8%)	10 (17.5%)
15	13 (24.1%)	13 (22.8%)
16	10 (18.5%)	13 (22.8%)
Sex		
Female	27 (50%)	26 (45.6%)
Male	27 (50%)	31 (54.4%)
Race		
Asian	0	0
Black	4 (7.4%)	1 (1.8%)
Caucasian	47 (87.0%)	53 (93%)
Hispanic	1 (1.9%)	2 (3.5%)
Other	2 (3.7%)	1 (1.8%)

Source: Clinical Study Report E3810-A001-202 Table 14.1.2.1

6.1.4 Efficacy Findings

Drug Exposure: Compliance was calculated as the following: Compliance = (total number of tablets taken / 56) × 100%.

Mean compliance (percent ± SD) was 94.7% ± 16.9% in the 10-mg dose group and 90.8% ± 17.7 % in the 20-mg dose group (The mean daily drug exposure was 9.47 mg ± 1.7 mg in the 10-mg dose group and 18.16 mg ± 3.54 mg in the 20-mg dose group).

Approximate 96% of the subjects (52 of 54) in the 10-mg group took at least 80% of study drug, and 84% (48 of 57) in the 20-mg group took at least 80% of study drug.

1) No clinically significant changes of frequency and severity of GERD from baseline based on analysis of daily patient symptom reports. This is taken as a lack of demonstration of efficacy.

On a daily basis, the patients called to report the presence and severity of their GERD symptoms for the prior 24-hour period.

Symptoms assessed included:
Heartburn: Burning behind breastbone.
Regurgitation: Sensation of food coming back into throat.
Nausea
Vomiting
Epigastric pain: Pain in stomach or the area around the stomach.
Other GERD symptom: two additional symptoms chosen by the patient during the screening visit from list of symptoms (see Study Design).

The severity of the symptoms was graded using the 5-point Likert scale presented in Table 6.

Table 6: Likert scale used in patient-reported assessment of GERD symptoms

Severity	Score	Symptoms
None	0	No symptoms
Mild	1	Mild symptoms present, causing little discomfort
Moderate	2	Annoying, but not interfering daily activities
Severe	3	Marked discomfort, interfering daily activities
Very severe	4	Disabling, greatly interfering daily activities, unable to sleep

From the sponsor's Study E3810-A001-202 protocol on Page 657.

No clinically significant changes of the frequency and severity of GERD symptoms are identified (Tables 7 and 8)

Table 7: Changes of Frequency of GERD Symptoms between Baseline and Week 8 (ITT Population)

	Nighttime		Daytime	
Symptom	**10mg Rabeprazole Mean (± SD)**	**20 mg Rabeprazole Mean (± SD)**	**10mg Rabeprazole Mean (± SD)**	**10mg Rabeprazole Mean (± SD)**
Heartburn Week 8-Baseline	-0.21 ±0.50	-0.48 ±0.73	-0.54 ±1.10	-0.88 ±1.15
Regurgitation Week 8-Baseline	-0.10 ±0.33	-0.21 ±0.61	-0.30 ±0.96	-0.42 ±1.16
Nausea Week 8-Baseline	-0.19 ±0.69	-0.24 ±0.45	-0.55 ±0.98	-0.41 ±0.70
Vomiting Week 8-Baseline	-0.07 ±0.36	-0.04 ±0.28	-0.09 ±0.46	-0.04 ±0.25
Epigastric Pain Week 8-Baseline	-0.21 ±0.92	-0.29 ±0.52	-0.50 ±0.87	-0.54 ±0.81

From the sponsor's Table 14.2.2.17, Study E3810-A001-202

Medical Officer's Comments: The sponsor calculated p-values in the NDA submission (Table 14.2.2.17 and 14.2.2.18). These p-values were meaningless, because the study was not designed for assessing efficacy endpoints (no randomization at baseline, and no pre-specified comparison).

Table 8: Changes of Severity of GERD Symptoms between Baseline and Week 8 (ITT Population)

Symptom	**10 mg Rabeprazole Mean (± SD)**	**20 mg Rbeprazole Mean (± SD)**
Heartburn Week 8-Baseline	-0.57 ±0.82	-0.87 ±0.77
Regurgitation Week 8-Baseline	-0.39 ±0.70	-0.42 ±0.75
Nausea Week 8-Baseline	-0.41 ±0.71	-0.55 ±0.70
Vomiting Week 8-Baseline	-0.13 ±0.52	-0.09 ±0.35
Epigastric Pain Week 8-Baseline	-0.40 ±0.57	-0.59 ±0.68

From the sponsor's Table 14.2.2.18, Study E3810-A001-202

Medical Officer's Comments: DGP requested the sponsor conduct responder analysis on April 4, 2008, because the Tables 7 and 8 did not demonstrate the effectiveness. The sponsor submitted the responder analysis in Table 9.

Table 9 showed that there were approximately 30% to 50% of patients that had complete relief of GERD symptoms at Week 8. Complete relief was defined as no symptoms for the preceding 7 days prior to the Week 8 visit according to the subject's diary.

Table 9: Complete Relief of GERD Symptoms at Week 8 (ITT Population)

Symptoms	10 mg Rabeprazole (N=54)	20 mg Rabeprazole (N=57)
Heartburn	18 (33.3%)	23 (40.4%)
Regurgitation	17 (31.5%)	20 (35.1%)
Nausea	18 (33.3%)	26 (45.6%)
Vomiting	23 (42.6%)	30 (52.6%)
Epigastric Pain	17 (31.5%)	22 (38.6%)

From the sponsor's re-submission on April 28, 2008, Study E3810-A001-202

Medical Officer's Comment: In my opinion, the results in Table 9 did not appear to be consistent with the negative results of Tables 7 and 8.

2) No clinically meaningful changes of antacid use as compared with baseline

Children's Mylanta® chewable tablets (calcium carbonate) were pre-specified as the rescue antacid. At bi-weekly study center visits, the subjects were asked "Did you take 6 or fewer antacids per day on average?" Approximate 2% subjects reported taking more than 6 antacid tablets at baseline, and remained this percentage at weeks 6, 8, and 10 in both groups (ITT population).

Medical Officer's Comment: Antacid consumption, under these experimental conditions, provides little information, if any, on the effectiveness of rabeprazole treatment.

3) Changes of QOL score as compared with baseline

PGWBI (Psychological General Wellbeing Index) questionnaire and SF-10 (Medical Outcomes Study 10-Item Short Form) were used to assess the QOL. PGWBI consisted of 22 items which evaluated anxiety, depressed mood, positive well-being, self-control, general health, and vitality. SF-10 consisted of physical and psychological summary scores. The sponsor claimed that some significant improvement was observed from baseline to Week 10.

Medical Officer's Comments: Without a study control, there are no scientific basis for the claim of significant improvement.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

The study failed to demonstrate the effectiveness of rabeprazole in the treatment of symptomatic GERD in pediatric patients 12 to 16 years old.

Medical Officer's Comments: Study E3810-A001-202 was poorly designed for the assessment of effectiveness of rabeprazole. The deficiencies of design include:

1) **No treatment comparator**
2) **No randomization**
3) **Most of the subjects had only mild GERD symptoms at baseline, *i.e.* the average number of daily GERD episodes was less than 1, and the severity of GERD symptoms less than Likert scale Score 1 (Mild symptoms, Table 6). There was no clinically meaningful improvement after 8 weeks treatment.**
4) **The statistical issues were discussed with Dr. Mike Welch (the Statistical Team Leader) on May 8, 2008. He commented that the study was not designed to show efficacy (no control, no randomization, open-label), and that the p-values are quite meaningless. I agreed with his comments.**

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety and tolerability of rabeprazole in patients 12 to 16 years old were assessed based on Study E3810-A011-202. The safety variables included adverse events (AE), clinical laboratory results and physical examinations.

There were no deaths in this study. There was one serious adverse event (SAE), mood swings that occurred during the treatment period, and was considered not related to rabeprazole. There were no adverse events leading to discontinuation of patients from study. The most common treatment-related AEs were diarrhea, nausea, abdominal pain, pharyngeal pain and headache. These AEs were consistent with the known safety profile of rabeprazole.

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

7.1.1 Deaths

No patients died during the study.

7.1.2 Other Serious Adverse Events

There was one serious adverse event, mood swings, that was considered not related to rabeprazole by the investigator:

Patient (185/(b) (4) R301474-201-USA), a 12 years old female with a history of anxiety disorder, sexual assault, attention deficit disorder, and persistent sinusitis received rabeprazole (20 mg once daily) for gastroesophageal reflux disease during this clinical study. The subject was hospitalized for mood swings and behavioral problems after 40 days of exposure to rabeprazole.

Medical Officer's Comments: Based on the narrative of the SAE, I agree that the mood swings may not be related to the rabeprazole treatment.

7.1.3 Dropouts and Other Significant Adverse Events

No patient discontinued from the study because of adverse events. No other significant adverse events were identified in this submission.

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 common adverse events were gastrointestinal disorders (18/111, 16.2% of ITT population). The adverse events with a frequency ≥2% in total are included in Table 10. In general, the AEs reported were consistent with the known safety profile of rabeprazole

in the adult population. No new safety signals were identified in the pediatric population of 12 to 16 years old.

Table 10: Most Common Adverse Event (Study E3810-A001-202)

System Organ Class	Total Patients N=111 (%)
Gastrointestinal Disorders:	
Diarrhea	5 (4.5%)
Nausea	5 (4.5%)
Vomiting	4 (3.6%)
Abdominal Pain	4 (3.6%)
General Disorders:	
Chest Pain	3 (2.7%)
Infections and Infestations:	
Bronchitis	5 (4.5%)
Nasopharyngitis	5 (4.5%)
Otitis Media	4 (3.6%)
Pharyngitis	5 (4.5%)
Sinusitis	5 (4.5%)
Upper Respiratory Tract Infection	7 (6.3%)
Nervous System Disorders:	
Headache	11 (9.9%)
Respiratory & Thoracic Disorders:	
Cough	8 (7.2%)
Nasal Congestion	8 (7.2%)
Pharyngolaryngeal Pain	11 (9.9%)

From the sponsor's E3810-A001-202 Study Report, Table 14.3.1.2

Eliciting adverse events data in the development program

Adverse event data were obtained on a weekly schedule as outlined in the study plan. General AE assessment was made on each clinical visit and phone contact through the 8-week study period. Laboratory assessment was conducted at screening period and at Week 8.

Identifying treatment-related adverse events

The most frequently reported treatment-related adverse event in both treatment groups was headache. Treatment-related adverse events occurring at a frequency of ≥1% that were considered to be possibly or probably related to study drug are presented in Table 11.

Table 11: Treatment-related adverse events (≥1% of subjects, ITT population)

System Organ Class	Total Patients N=111 (%)
Gastrointestinal Disorders	
Diarrhea	1 (0.9%)
Nausea	2 (1.8%)
Abdominal Pain	3 (2.7%)
General Disorders	
Chest Pain	1 (0.9%)
Nervous System Disorders	
Headache	6 (5.4%)

From the sponsor's Table 14.3.1.2 of Clinical Study Report (E3810-A001-202)

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 Comments: 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.

7.1.8 Electrocardiograms (ECGs)

ECGs were not conducted in Study E3810-A001-202. In Study E3810-A001-119, ECG assessments were unremarkable at baseline or at the Day 6 or 8 discharge evaluations.

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 source used in conducting the review was one Phase 2 study with 111 patients (Study E3810-A001-202). Patients were between 12 and 16 years of age.

Patients had clinically diagnosed or suspected or endoscopically proven GERD by the investigators during the screening period.

Demographics

There was an equitable distribution of males (52.2%) and females (47.8%), and most patients were Caucasian (90.1%). The distribution of these demographic characteristics was similar across the dose groups (Table 12). As previous stated, most patients at baseline had mild GERD with average episode of GERD symptoms less than 1 per day.

Table 12: Demographic and baseline characteristics (ITT Population, Study E3810-A001-202)

Parameter	Treatment Groups	
	Rabeprazole 10 mg N =54	Rabeprazole 20 mg N =57
Age (years)		
Mean ± SD	14.2 ± 1.29	14.1 ± 1.49
Range	12 –16	12 –16
Groups		
12	7 (13.0%)	13 (22.8)
13	9 (16.7%)	8 (14.0%)
14	15 (27.8%)	10 (17.5%)
15	13 (24.1%)	13 (22.8%)
16	10 (18.5%)	13 (22.8%)
Sex		
Female	27 (50%)	26 (45.6%)
Male	27 (50%)	31 (54.4%)
Race		
Asian	0	0
Black	4 (7.4%)	1 (1.8%)
Caucasian	47 (87.0%)	53 (93%)
Hispanic	1 (1.9%)	2 (3.5%)
Other	2 (3.7%)	1 (1.8%)

Source: Clinical Study Report E3810-A001-202 Table 14.1.2.1

Extent of exposure (dose/duration)

Subjects were directed to take the study medication once daily. Medication compliance was monitored at Weeks 2, 4, 6, and 8 based on pill counts from returned study drug bottles. In addition, subjects filled out daily medication diaries. Subjects' compliance to study drug treatment over the entire study period (8 weeks) was calculated as follows:

Compliance = (total number of study medication tablets taken by a subject / 56)•100%

Mean compliance (percent ± SD) was 94.7% ± 16.9% in the 10-mg dose group and 90.8% ± 17.7 % in the 20-mg dose group (The mean daily drug exposure was 9.47 mg ± 1.7 mg in the 10-mg dose group and 18.16 mg ± 3.54 mg in the 20-mg dose group). The number of subjects who took at least 80% of their planned study drug in the 10-mg dose group was 96.3% (52 of 54) and 84.2% (48 of 57) in the 20-mg dose group.

7.2.2 Adequacy of Overall Clinical Experience

Medical Officer's Comments: The patient population consisted of 111 subjects in 25 study sites in the United States. Among them, 107 patients completed the study. Two dose levels 10 mg and 20 mg once daily for 8 weeks were studied. The proposed market doses are (b) (4) 20 mg once daily for up to 8 weeks. The previously approved adult dose was 20 mg. The overall clinical data supported the safety of the 20 mg treatment in the proposed adolescent patients.

7.2.3 Assessment of Quality and Completeness of Data

Medical Officer's Comments: The "efficacy" data are inadequate to draw meaningful recommendations. Safety data base include 135 pediatric subjects age 12 to 16 years old (111 subjects in Studies E3810-A001-202 and 24 subjects in E3810-A001-119). The two studies partially fulfilled the Pediatric Written Request. FDA only requested PK and safety studies for 12 to 16 years old. The overall quality and completeness of the safety 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 treatment-related adverse events of rabeprazole in the pediatric patients 12 to 16 years old is similar to that of adult patients. The most common treatment-related adverse events were headache, diarrhea, nausea, vomiting and abdominal pain (Table 11).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Rabeprazole tablets (10 mg, and 20 mg once daily for 8 weeks) were studied in pediatric patients 12 to 16 years old with symptomatic GERD.

- The safety results support the recommended dose and dosing regimen (20 mg once daily).
- The mean exposures of ITT population (N=111) were 56 days.
- Dose-toxicity relationship at the range of 10 to 20 mg was not identified.

8.2 Drug-Drug Interactions

Rabeprazole is extensively metabolized in the liver by the microsomal cytochrome P450 enzyme system. The drug-drug interactions are described in the existing label. Except for a few, listed in the labeling, these drug-drug interactions are not considered to be clinically relevant. No new data in the pediatric submission were identified.

8.3 Special Populations

No dose modification for race and gender is suggested by the sponsor's submission. For pediatric patients with hepatic or renal insufficiency, special dosing was not studied.

8.4 Pediatrics

The current submission supports the indication for treatment of symptomatic GERD of pediatric patients 12 to 16 years old, but for the 20 mg per day dose only. (b) (4)

9 OVERALL ASSESSMENT

9.1 Conclusions

In this submission, rabeprazole was generally safe and well tolerated in pediatric GERD patients aged 12 to 16 years old (Studies E3810-A001-202 and E3810-A001-119). There was no death. There was no treatment-related serious adverse event, nor dropout due to adverse events. The most common adverse events reported from this population were

consistent with the known adverse events of rabeprazole in adult population. In addition, there were no clinically important findings or trends in hematology, clinical chemistry, vital signs, or physical examination observed across treatment groups.

The proposed comparable bioavailability data (Study E3810-A001-119) between 12 to 16 years old and the adult was reviewed by the Clinical Pharmacology reviewer, and was found acceptable.

Based on the comparable bioavailability and the safety in the pediatric patients, NDA 20,973/S-022 (20 mg rabeprazole) is recommended for **Approval**. (b) (4)

9.2 Recommendation on Regulatory Action

The clinical recommendation is **approval** for the treatment (20 mg rabeprazole) of pediatric patients 12 to 16 years old with GERD.

The recommendation is based on the demonstrated bioavailability (Study E3810-A001-119) supported by the safety (Study E3810-A001-202) and by the similarity of pathogenesis of GERD between 12 to 16 year-old patients and the adult patients.

(b) (4)

9.3 Labeling Review

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

(b) (4)

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/s/

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6/19/2008 11:24:59 AM
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