# CLINICAL REVIEW

## DIVISION OF GASTROENTEROLOGY PRODUCTS

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| Application Type | NDA |
| Submission Number | 22-101/000 |
| Letter Date | Sept. 27, 2006 |
| Stamp Date | Sept. 29, 2006 |
| PDUFA Goal Date | July 29, 2007 |
| Reviewer Name | Wen-Yi Gao, M.D., Ph.D. |
| Review Completion Date | July 19, 2007 |
| Established Name | Esomeprazole magnesium |
| (Proposed) Trade Name | Nexium |
| Therapeutic Class | Proton Pump Inhibitor |
| Applicant | AstraZeneca |
| Priority Designation | S |
| Formulation | Delayed-Release Granules for Oral Suspension |
| Dosing Regimen | 10 mg once daily for up to 8 weeks |
| Indication | Short-term treatment of symptomatic GERD and erosive esophagitis |
| Intended Population | 1 to 11 years of age |

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# EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

NDA 22-101/000, Nexium Delayed-Release Granules, is recommended for **Approvable** for the short term treatment of pediatric patients 1 to 11 years old with gastroesophageal reflux disease (GERD) and the healing of erosive esophagitis (EE).

The recommendation is based on the demonstrated bioavailability (Study 9614C00099) supported by the safety (Study D9614C00097) and by the similarity of pathogenesis of GERD between 1 to 11 year-old patients and the adult patients.

Imbalanced serious cardiac events were observed in two long-term adult studies (SOPRAN and LOTUS, respectively) with omeprazole or esomeprazole. The recommendation for regulatory action may be modified to **Approval** once the current safety issues regarding the serious cardiac events are resolved.

## 1.2 Recommendation on Postmarketing Actions

### 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

Esomeprazole is a benzimidazole derivative, a compound that inhibits gastric acid secretion of the gastric parietal cells. It belongs to proton pump (the $H^+/K^+$-ATPase) inhibitors (PPI) of the anti-ulcer class. Esomeprazole is the S-enantiomer of omeprazole (a mixture of the S- and R-isomers). The delayed-release granules for oral suspensions were developed for the short-term treatment of pediatric GERD and erosive esophagitis aged 1 to 11 years old.

The primary study to support the proposed indications is entitled "A Phase 3 Multi-center, Randomized, Double-blind Parallel-group Study to Evaluate the Safety and Clinical Out come of Once Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patients 1 to 11 Years of Age, Inclusive" (Study D9614C00097). In total, 109 patients were randomized in 24 study sites. The numbers of evaluable patients were 108 patients in the

safety population, 109 in the intend-to-treat (ITT) population, 98 patients in the per-protocol (PP) population.

### 1.3.2 Efficacy

The major efficacy study was conducted in Study D9614C00097.

The primary efficacy endpoints included:

1) endoscopic healing of erosive esophagitis,
2) daily patient symptom assessment reported by parent/guardian, and
3) physician's global assessment.

Problems with this efficacy study include:

1) no study control for these efficacy endpoints;
2) insufficient subjects (53 in 109 subjects) with erosive esophagitis;
3) insufficient subjects (2 in 109 subjects) with moderate or severe erosive esophagitis; and
4) self-healing of mild erosive esophagitis not ruled out.

The sponsor AstraZeneca proposes to extrapolate the adult controlled efficacy data to the pediatric population age 1 to 11 year old.

**Medical Officer's Comments: In my opinion, the sponsor failed to demonstrate the effectiveness of esomeprazole in the patients 1 to 11 years old. However, the sponsor provided 3 pharmacokinetic studies to support the bioavailability of the product in the pediatric population: 1) a multiple-dose, Phase 1 PK study in pediatric patients 1 to 11 years old (Study D9614C00099), 2) Bioequivalence study between esomeprazole delayed release granules and capsules in healthy adult subjects (Study D9612C00032), and 3) a supportive pediatric PK and pH monitoring study in patients 12 to 24 months (Study SH-NEC-0001).**

**Based on these bioavailability (10 mg and 20 mg) data (Table 1) and the similarity of pathogenesis of GERD in the pediatric patients, it is acceptable to extrapolate the adult efficacy study to this pediatric population. The Case was discussed with the Clinical Pharmacology reviewer, Dr. Tien-Mien Chen, and he concurred (see the Clinical Pharmacology review).**

**Table 1. Comparisons of Exposure among Different Age Groups**

| Age | 1-5 years[a] | | 6-11 years[a] | | 12-17 years[b] | | Adults[c] | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg) | 5 | 10 | 10 | 20 | 20 | 40 | 20 | 40 |
| Dose (mg/kg) | 0.24 | 0.71 | 0.34 | 0.71 | 0.32[d] | 0.64[d] | 0.25[e] | 0.49[e] |
| AUC (μmol·h/L) | 0.74 | 4.8 | 3.7 | 6.3 | 3.7 | 13.9 | 4.2 | 12.6 |

[a] Data derived from Study D9614C00099 CSR, Module 5.
[b] Data derived from Study D9614C00094 CSR, NDA 21-153/S-022.
[c] Data derived from NEXIUM (AstraZeneca, Sweden) Label in Physicians' Desk Reference, 57th edition. Montvale, New Jersey: Thompson PDR. 2003, which was based on data from Astra Hassle Clinical Study Report SH-QBE-0008.
[d] Median weight 62.5 kg (CSR D9614C00094, Table 9).
[e] Median weight 81.0 kg (CSR SH-QBE-0008, Appendix 1 to Statistical Report, Table 1.1).

### 1.3.3 Safety

Safety was assessed in 108 pediatric patients 1 to 11 years old (safety population). The mean daily exposure to esomeprazole was 0.5 mg/kg and the duration of exposure was approximate 8 weeks. The safety profiles were assessed with reports of adverse events (AEs), discontinuation due to adverse events (DAEs), 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 in this study. There were 3 serious adverse events (SAEs), and none of the SAEs were considered treatment related by the investigator. There 4 patients who had DAEs. Three of the 4 patients had DAEs that were not considered treatment related. The treatment-related DAEs (1 patient) were asthenia, nausea, and viral infection, all of which resolved within 1 day of onset, after study drug was stopped.

**Medical Officer's Comments: The narratives of the three SAEs were reviewed and summarized as the following:**

**1) Patient E0027001, a 2 years old female, was treated with esomeprazole 10 mg once daily for 6 days. On day 7, she developed vomiting, and the study discontinued. She was admitted to the emergency room on Day 10 with the diagnosis of bilious vomiting, hypertension, and constipation. The symptoms were resolved in the hospital on Day 15. In the investigator's opinion, it is not esomeprazole treatment related. In the reviewer's opinion, however, the vomiting on Day 7 appears to relate to the esomeprazole treatment.**

**2) Patient E0030012, a 10 years old male, developed laryngospasm during the screening endoscopy prior to the esomeprazole treatment. The patient was treated with oxygen therapy in the hospital, and condition resolved in two days. The reviewer agrees that it is not caused by esomeprazole exposure.**

**3) Patient E0402001, a 4 years old male, developed intractable vomiting 10 days after esomeprazole treatment (10 mg/day for 58 days). The patient was admitted to the hospital. The reviewer agrees that the intractable vomiting may not relate to the treatment.**

A total of 13 treatment-related AEs were reported in 10 patients (9.3%, 10/108 patients). The incidences of these were equally distributed among the 2 weight groups, 5 patients in the <20 kg group and 5 in the ≥20 kg group. The most commonly reported adverse events were vomiting, pyrexia, diarrhea, cough, and headache.

There were no clinically significant findings in hematology, clinical chemistry, and urinalysis.

**Medical Officer Comments: The overall profile of the test agent in this study is safe and well tolerated.**

### 1.3.4 Dosing Regimen and Administration

Esomeprazole doses for this pediatric population were selected based on the analysis of PK and PD data (omeprazole and esomeprazole) and modeling techniques.

Body weight for children ages 1 to 11 years was assumed to be 8 kg to 60 kg. A cut-off weight of 20 kg was selected as the maximum weight for patients 1 to 5 years of age and the minimum weight for patients 6 to 11 years of age.

Patients were randomized based on their weight to receive once daily treatment of 5 mg, 10 mg, or 20 mg doses of esomeprazole.

- Patients who weighed 8 kg to <20 kg received either 5 mg or 10 mg in a 1:1 ratio.
- Patients who weighed ≥20 kg received either 10 mg or 20 mg in a 1:1 ratio.

The parents/guardians were instructed to administer the capsule approximately 1 hour prior to the first morning meal. It was recommended that for all children under the age of 6 years, or any other child who had difficulty swallowing the capsules, that parents/guardians should open the capsule and empty the pellet contents into 1-2 tablespoons of applesauce before oral administration (swallowed). The pellets were not to be chewed or crushed. The applesauce was provided to the sites by AstraZeneca.

**Medical Officer Comments: The dose-selection and dosing regimen are adequate.**

### 1.3.5 Drug-Drug Interactions

Esomeprazole is extensively metabolized in hepatocytes by liver microsomal cytochrome P-450 mono-oxygenase system (CYP2C19 and CYP3A4). The current labeling for esomeprazole 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 will be included in the label of NDA 22-101.**

### 1.3.6 Special Populations

The age range of this submission is 1 to 11 years old. No additional dosage adjustment is recommended.

The AUC and $C_{max}$ values were slightly higher (%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

The current labeling for esomeprazole recommends no dosage adjustment for patients with mild to moderate hepatic insufficiency. The pharmacokinetics of esomeprazole in patients with renal impairment is not expected to be altered relative to those without renal impairment.

# INTRODUCTION AND BACKGROUND

## 1.4 Product Information

The established name of the product is Esomeprazole Magnesium and the trade name is Nexium™. Esomeprazole 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). Esomeprazole is the S-enantiomer of omeprazole (a mixture of the S- and R-isomers). The delayed-release granules for oral suspensions were developed for the treatment of pediatric GERD and erosive esophagitis aged 1 to 11 years old. The proposed treatment regimen is esomeprazole 10 mg or 20 mg P.O. once daily for 8 weeks.

## 1.5 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 listed in the following:

- **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, 2 to 16 years old), esomeprazole (Nexium, 12 to 17 years old), lansoprazole (Prevacid, 1 to 17 years old)

- **Surgical Treatment:** Patients who have severe symptoms such as life-threatening bronchospasm or recurrent aspiration pneumonia and have failed medical therapy.

## 1.6 Availability of Proposed Active Ingredient in the United States

Esomeprazole 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 patients, and combination therapies for the eradication of *Helicobacter pylori*.

## 1.7 Important Issues with Pharmacologically Related Products

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. 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.

### 1.8 Presubmission Regulatory Activity

**April 27, 2000**: AstraZeneca submits a proposed pediatric development plan for esomeprazole to NDA 21-153, and requests deferral of submission of pediatric information, and a partial waiver from studying neonates and infants 0-24 months of age. The pediatric study request is concurrently submitted to IND 53,733 (April 27 2002, SN 084) for Pediatric Exclusivity.

**May 28, 2002**: FDA replies to AstraZeneca's submission of clinical and non-clinical data and states that it is acceptable to bridge data from an omeprazole p53 transgenic mice study.

**July 2, 2002**: FDA reissues the December 31, 2001 Written Request with new provisions in accordance with the Best Pharmaceuticals for Children's Act of 1 April 2002.

**January 7, 2003:** FDA clarifies contents of the letter amending the pediatric Written Request on December 18, 2002, and requests additional non-clinical studies in neonatal rats, dogs and transgenic mice.

**July 7, 2003:** AstraZeneca submits the company's meeting minutes on July 1, 2003 of the discussion and clarification of the Written Request.

**April 24, 2005:** AstraZeneca poses question regarding the submission strategy for the pediatric labeling submission. Nexium (esomeprazole magnesium) Delayed-Release Granules for Oral Suspension NDA 22-101: New Drug Application

**May 18, 2005:** FDA responds to AstraZeneca's question on April 24, 2005 regarding the submission strategy for the pediatric submission, explaining that AstraZeneca can submit the labeling supplement in phases but that it will not be evaluated for exclusivity until labeling for all applicable age groups has been submitted.

**March 9, 2006:** AstraZeneca requests a Type C Meeting to discuss the findings from recently completed neonatal rat and dog toxicity studies (submitted to IND 53,733, Serial No. 351, dated March 6, 2006) with the intent to reach agreement that AstraZeneca may initiate clinical studies in pediatric patients less than 1 year of age.

**April 28, 2006:** FDA approves NDA 21-153/S-022 providing for the revision to the pediatric section of the package insert to add information regarding the use of Nexium Delayed-Release Capsules in adolescent patients, 12 to 17 years of age, inclusive for the short-term treatment of GERD.

**June 2, 2006:** FDA responds to AstraZeneca's meeting questions. FDA will amend the Written Request to allow AstraZeneca to start clinical studies for pediatric patients less than 1 year of age, to allow AstraZeneca to use a 26-week carcinogenicity study of omeprazole in p53(±) transgenic mice as bridging information for esomeprazole and to delete the requirement for a single dose PK study in neonates and infants. The June 5 2006 meeting was canceled.

**June 5, 2006:** FDA responds to AstraZeneca's request for a "submission strategy" for a pediatric labeling supplement to NDA 21-153. FDA recommends a separate efficacy supplement to NDA 21-957 (once it has been approved by the Agency) for the desired pediatric population. Reference to the original submission for CMC information for the dosage strength is acceptable and the information will be reviewed at the time the efficacy supplement is submitted. An alternative strategy is to submit a new original NDA (before NDA 21-957 is approved) for use of this product in the pediatric population.

**July 5, 2006:** AstraZeneca proposes a submission strategy for the 1-11 year old pediatric submission. This strategy includes submitting an Original New Drug Application containing clinical and CMC data for use of a 10 mg Sachet formulation in the 1-11 year old pediatric population.

**August 15, 2006:** FDA accepts AstraZeneca's proposed strategy on July 5, 2006 to submit an Original NDA for the use of the 10 mg sachet formulation in the 1–11 year old population, to a 6-month review clock, and to the possibility of merging the two NDAs (NDA 21-957 and NDA 22-101) following approval of both applications.

### 1.9 Other Relevant Background Information

Esomeprazole 10 mg capsule is not marketed in any foreign country by the applicant. No information regarding pending market applications in foreign countries is identified. Esomeprazole tablets (20 and 40 mg) are currently marketed in 96 foreign countries/areas, and its capsules (20 and 40 mg) are marketed in the United States.

Esomeprazole (20 mg and 40 mg tablets or capsules) has not been withdrawn for reasons related to safety of efficacy in any country where they have been marketed.

## 2 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 2.1 CMC

Esomeprazole delayed-release capsules (20 mg and 40 mg) have been approved for patients 12 years or older. The sponsor proposed to add 10 mg dose form in the labeling for pediatric patients 1 to 11 years old. No significant CMC issues that affected clinical interpretation of the data were identified.

### 2.2 Animal Pharmacology/Toxicology

Esomeprazole delayed-release capsules (20 mg and 40 mg) have been approved. On June 2, 2006, FDA responded to AstraZeneca to allow AstraZeneca to use a 26-week carcinogenicity study of omeprazole in p53(±) transgenic mice as bridging information for esomeprazole. No additional pharmacology and toxicology issues were identified in this submission.

## 3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 3.1 Sources of Clinical Data

The sources of clinical data were summarized in Table 2. AstraZeneca submitted one primary Phase 3 clinical study **(Study D9614C00097)** to support the safety and efficacy of esomeprazole for the short term treatment of pediatric patients 1 to 11 years old with gastroesophageal reflux disease (GERD) and the healing of erosive esophagitis.

In addition, AstraZeneca submitted 3 clinical pharmacology studies:
1) **Study D9614C00099** characterized esomeprazole (5, 10, and 20 mg oral capsules) in 31 subjects 1 to 11 years old;

2) **Study SH-NEC-0001** characterized esomeprazole pellets (0.25 mg/kg and 1 mg/kg) in 7 subjects 12 to 24 months old;

3) **Study D9612C00032** characterized bioequivalence of esomeprazole tablet, capsule, and sachet in healthy adult subjects.

**Table 2. Summary of clinical studies**

| Study Number | Study Design | Primary Objective | Dosing Regimen | N | Study Population | Duration |
|---|---|---|---|---|---|---|
| D9614C00097 | Phase 3, randomized, double-blind, multicenter, no control | To evaluate safety of once daily regimen | Nexium 5, 10, and 20 mg, oral capsules | 108 | Pediatric subjects age 1 to 11 years old with GERD diagnosed by endoscopy | 8 weeks |
| D9614C00099 | Phase 1, open-label, randomized, no control | To determine AUC | Nexium 5, 10, and 20 mg oral capsules | 30 | Pediatric subjects age 1 to 11 years old with GERD or symptoms of GERD | 5 days |
| SH-NEC-0001 | Phase 3, single blind, randomized, no control | To assess PK parameters and gastric pH | Nexium 0.25, 1 mg/kg | 7 | Pediatric subjects 12 to 24 months old with GERD symptoms diagnosed by 24-hour pH-monitoring | 1 week |
| D9612C00032 | Phase 1, open-label, randomized, 3-way crossover | To evaluate bioequivalence (PK parameters) of pellet based sachet, capsule and tablet | Nexium<br>40 mg tablet<br>40 mg capsule<br>40 mg sachet | 96 | Healthy adult volunteers | 3 days, separated by washing-out periods of ≥6 days |

### 3.2 Review Strategy

All of four clinical studies (D9614C00097, D9614C00099, SH-NEC-0001, and D9612C00032) 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 (D9614C00097). The study also contained exploratory data described the burden of pediatric GERD on the parent/guardian from a psychological, social, and economic perspective. Since the data did direct support the pediatric indication, they are not included in this review.

The rest three studies (D9614C00099, SH-NEC-0001, and D9612C00032) were pharmacokinetic or bioequivalent studies. 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.

### 3.3 Data Quality and Integrity

An audit of Studies D9614C00097, D9614C00099, SH-NEC-0001, and D9612C00032 was not performed by the Division of Scientific Investigations or the review team.

### 3.4 Compliance with Good Clinical Practices

According to the sponsor, Studies D9614C00097, D9614C00099, SH-NEC-0001, and D9612C00032 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).

### 3.5 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:**
**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.**

## 4 CLINICAL PHARMACOLOGY

### 4.1 Pharmacokinetics

The pharmacokinetic parameters (AUC and $C_{max}$) of esomeprazole (5 mg, 10 mg, and 20 mg) were studied in patients 1 to 11 year olds, with GERD or symptoms of GERD. The results were as follows:

- The AUC, $AUC_{0-t}$, and $C_{max}$ were several-fold higher for 10 mg esomeprazole compared with 5 mg esomeprazole in children aged 1 to 5 years, while the same parameters were approximately twice as high for 20 mg esomeprazole compared with 10 mg esomeprazole in children aged 6 to 11 years.

- The t½ (terminal) was approximately twice as long for the 10 mg dose compared with the 5 mg dose in children aged 1 to 5 years, while the t½ (terminal) was similar for 20 mg dose compared with 10 mg dose in children aged 6 to 11 years.

- Overall, children aged 1 to 5 years seemed to have a higher apparent clearance than those aged 6 to 11 years in terms of per kilogram of body weight (CL/F/kg).

**Table 3. Summary of PK results (Study D9614C00099)**

| Age | 1-5 years | | | | | | 6-11 years | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Esomeprazole treatment | 5 mg | | | 10 mg | | | 10 mg | | | 20 mg | | |
| Statistic | N | Geo. mean | SD | N | Geo. mean | SD | N | Geo. mean | SD | N | Geo. mean | SD |
| AUC (µmol*h/L) | 5 | 0.74 | 0.36 | 8 | 4.83 | 2.56 | 7 | 3.70 | 2.05 | 6 | 6.28 | 2.71 |
| $AUC_{(0-t)}$ (µmol*h/L) | 6 | 0.63 | 0.37 | 8 | 4.67 | 2.23 | 7 | 3.55 | 1.90 | 6 | 6.09 | 2.64 |
| $C_{max}$ (µmol/L) | 6 | 0.62 | 0.38 | 8 | 2.98 | 0.69 | 7 | 1.77 | 0.96 | 6 | 3.73 | 1.21 |
| $t_{1/2\lambda z}$ (h) | 5 | 0.42 | 0.13 | 8 | 0.74 | 0.36 | 7 | 0.88 | 0.35 | 6 | 0.73 | 0.21 |
| CL/F/kg (L/h/kg) | -- | -- | -- | 8 | 0.40 | 0.19 | 7 | 0.25 | 0.21 | -- | -- | -- |

AUC is area under the plasma concentration-time curve from 0 to infinity; $AUC_{(0-t)}$ is area under the plasma concentration-time curve from 0 to t; CI is confidence interval; $C_{max}$ is maximum plasma (peak) drug concentration; Geo. mean is geometric mean; $t_{½\lambda z}$ is half life associated with terminal slope ($\lambda z$) of a semi-logarithmic concentration-time curve; CL/F/kg is the apparent clearance normalized by body weight (shown only for 10 mg for comparison between 2 different age groups with the same dose).

**Medical Officer's Comments: The PK and bioavailability data were discussed with the Clinical Pharmacology Reviewer. He pointed out that the proposed dosing regimens of 10 mg Q.D. (for all patients aged 1 to 11 years old) and 20 mg Q.D. (for healing of erosive esophagitis in patients weighing ≥20 kg) are reasonable, and are consistent with the known PK data in the adults.**

**The reason why AUC and $C_{max}$ for 10 mg esomeprazole subjects was several fold higher than the 5 mg group is not entirely clear. It appeared that the apparent clearance in the 5 mg group was higher than the 10 mg and the 20 mg groups. The 5 mg dosing regimen is not in the proposed labeling.**

# 5 INTEGRATED REVIEW OF EFFICACY

## 5.1 Indication

The proposed indication for the esomeprazole delayed-release granules is for the short-term treatment of GERD and healing of erosive esophagitis in pediatric patients 1 to 11 years old.

### 5.1.1 Methods

Study D9614C00097 provided the major efficacy data in supporting the pediatric indication. It was a Phase 3, randomized, double-blind design with no control.

The efficacy variables were evaluated with the following endpoints:

1) Assessment of changes from baseline in endoscopic healing of erosive esophagitis;

2) Assessment of changes from baseline in daily patient symptom reported by parent/guardian;

3) Assessment of changes from baseline in Physician's Global Assessment.

In addition, Study D9614C00099 (Phase 1, open-label, age 1 to 11 years) and Study SH-NEC-0001 (Phase 1, single blind, age 12 to 24 months) provided pharmacokinetic (PK) data to support the proposed indication.

Study D9612C00032 (Phase 1 study in healthy adult volunteers) provided the bioequivalent data of tablet, capsule and sachet to support the efficacy studies.

### 5.1.2 General Discussion of Endpoints

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

1) Basis for choosing endoscopic endpoints:

The upper GI endoscopic examination (i.e., esophagus, stomach, duodenum) was performed in each patient during the screening period. The examination was required for diagnosis and grading of erosive or non-erosive esophagitis. The main purpose of the examination was to document the extent of esophagitis, to determine the presence of *H. pylori,* and to rule out exclusionary conditions (i.e., ulcers, bleeding lesions). Endoscopic findings of erosive esophagitis were classified using the Los Angeles (LA) classification (Table 4). At Visit 6 (Day 56), patients with EE at baseline received follow-up endoscopies for the assessment of endoscopic healing. These endpoints were able to help the assessment of clinical benefit.

**Table 4. Los Angeles classification for endoscopic findings**

| Grade | Classification |
|---|---|
| Grade A | One (or more) mucosal break, no longer than 5 mm that does not extend between the tops of 2 mucosal folds |
| Grade B | One (or more) mucosal break more than 5 mm that does not extend between the tops of 2 mucosal folds |
| Grade C | One (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the circumference |
| Grade D | One (or more) mucosal break that involves at least 75% of the circumference |

2) Basis for choosing Physician's Global Assessment and Daily Patient Symptom Assessment by parent/guardian:

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 D9614C00099, SH-NEC-0001, and D9612C00032, the pharmacokinetic parameters AUC and $C_{max}$ were characterized, because they provide the assessment of plasma drug concentrations as functions of treatment time.

### 5.1.3 Study Design

**1. STUDY D9614C00097**

**Title:** A Phase 3 Multicenter, Randomized, double-blind Parallel-group Study to Evaluate the Safety and Clinical Outcome of Once Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patients 1 to 11 Years of AGE, Inclusive

**Study Objective:**
**Primary:** To evaluate the safety of once daily treatment with esomeprazole in relieving GERD-associated symptoms in pediatric patients 1 to 11 years of age

**Secondary:** To evaluate the clinical outcome of once daily treatment with esomeprazole in relieving GERD-associated signs and symptoms in pediatric patients 1 to 11 years of age

**Study Design:** This was a Phase 3, multicenter, double-blind study designed to evaluate the safety and clinical outcome of esomeprazole treatment in pediatric patients with GERD. There was no control group. Patients were stratified based on weight and were randomized in a double-blind 1:1 ratio to receive either of the following treatments (Table 5):

- If weight was <20 kg, once daily treatment with esomeprazole 5 mg or 10 mg
- If weight was ≥20 kg, once daily treatment with esomeprazole 10 mg or 20 mg

**Table 5. Dosing based on patient's weight**

| Age | Weight | Absolute Doses | Expected dose in mg/kg |
|---|---|---|---|
| 1-11 years | ≥8 kg and <20 kg | 5 mg or 10 mg | (0.25 mg/kg-0.6 mg/kg) or (0.5 mg/kg-1.25 mg/kg) |
| | ≥20 kg | 10 mg or 20 mg | (0.5 mg/kg-1.0 mg/kg) for lowest weight patient |

*From the sponsor's Table 2, Section 5.2.1

The duration the study was 8 weeks and consists of a screening period (up to 21 days prior to the first treatment), 8-week treatment periods and follow-up visit (14 days after the last dose). During the treatment period, subjects received 5, 10, or 20 mg esomeprazole P.O. once daily. The efficacy and safety assessments were performed as shown in Table 6.

**Table 6. Summary of study assessments and procedures**

| Assessment/Procedure | Screening Visit 1 (Within 21 days before dosing) | Randomi-zation Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 (Final/ Early Term. Visit) | Follow-up Contact (14 days after last dose of study drug) |
|---|---|---|---|---|---|---|---|
| | Day -21 to Day 0 | Day 0 | Day 14 ±2 Days | Day 28 ±2 Days | Day 42 ±2 Days | Day 56 ± 2 Days | ±2 days |
| Informed Consent/Assent | X | | | | | | |
| Medical History | X | X | | | | | |
| Physical Examination | X | | X | X | X | X | |
| Vital Signs | X | | X | X | X | X | |
| Endoscopic Examination (with biopsy) | X[a] | | | | | X[b] | |
| Laboratory Assessments | X | | | X | | X | |
| Urine Pregnancy Test[c] | X | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | |
| Physician's Global Assessment | X | | X | X | X | X | |
| PGCIQ completed by parent/guardian[d] | | X | | | | X | |
| Dispense Study Drug | | X | | X | | | |
| Study Drug Accountability | | | X | X | X | X | |
| Recall Previous 72 Hours Symptoms Diary | X | | | | | | |
| Collect/Review daily IVRS assessments | | X | X | X | X | X | |
| Review Adverse Events[e] | X[f] | X | X | X | X | X | X[g] |
| Review Serious Adverse Events[e] | X[f] | X | X | X | X | X | X[g] |
| Review Prior/Concomitant Medications | X | X | X | X | X | X | |

[a] Refer to Inclusion Criterion #4 (Section 5.3.1) for endoscopy requirements.
[b] Patients with EE underwent follow up endoscopy to document mucosal healing.
[c] A urine pregnancy test was required for all post-menarchal females at Visit 1.
[d] Only for patients ≤5 years of age.
[e] Weekly telephone contacts with the parent/guardian were made on the weeks that the patient was not seen at the clinic (ie, Days 7, 21, and 35) to assess for AEs/SAEs and compliance with study drug.
[f] Collection of AEs/SAEs began during the screen period once Informed Consent was obtained.
[g] A post-study follow-up (telephone) safety assessment occurred 14 days following administration of the last dose of study drug for each patient.

**Medical Officer's Comments: The study design did not have a comparator, and did not meet the double-blind standard as required by the Guidance.**

**Study Population:**
Inclusion criteria:

1) Patients' parents/guardians must have provided written informed consent prior to starting any study-related procedures.

2) Patients who were able to comprehend their involvement in a clinical study, including risks and benefits, (typically ≥6 years of age) must have had assent documented by study personnel prior to any study-related procedures.

3) Patients were males or females between 1 and 11 years of age, inclusive and must have weight ≥8 kg.

4) Patients must have endoscopically diagnosed GERD by the investigator during the screening period. Patients with a previous (within 2 weeks prior to Visit 1) diagnosis of EE by endoscopy and who were candidates for PPI therapy were not required to have an additional endoscopy at baseline (Visit 1). Patients with extraesophageal and/or atypical symptoms (i.e., failure to thrive, reactive airway disease) who were candidates for endoscopy qualified for inclusion provided they had endoscopic signs of GERD.

5) Patients would be considered for PPI treatment based on symptoms of GER.

6) Postmenarchal females must have had a negative urine pregnancy test at the time of the screening visit.

Exclusion criteria:

1) Patients who had used a PPI within 7 days prior to randomization (Day 0), including over-the-counter (OTC) omeprazole.

2) Patients who had used any prescription or OTC treatment (other than PPIs) for symptoms of GERD, such as $H_2$RAs or prokinetics, within 72 hours prior to randomization (Day 0).

3) Patients who had a history or current need for resectional or reconstructive surgery of the GI tract (e.g., esophagus, stomach, duodenum, jejunum, or colon).

4) Female patients who were taking hormonal contraceptives for medical reasons.

5) Patients who needed to remain on any of the following concomitant medications during the course of the study: bismuth-containing products, barbiturates, anticonvulsants, anticoagulants, narcotics, antineoplastic agents, $H_2$RAs, sucralfate, anti-emetics, systemic steroids (oral and intravenous), pro-motility drugs (e.g., cisapride, metoclopramide, domperidone) or macrolide antibiotics such as erythromycin. Use of topical erythromycin was

permissible. Occasional doses of nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates (≤3 days) to treat acute conditions were permissible.

6) Patients who had the following diseases/conditions: active gastrointestinal bleed, active peptic ulcer disease, eosinophilic gastroenteritis, allergic gastroenteropathies, inflammatory bowel disease, bleeding disorders, seizure disorders, acute pancreatitis, metabolic diseases or meningitis. Patients who had a past history (prior to study enrollment) of EE, Duodenal Ulcers (DU), Gastric Ulcers (GU) and/or *H. pylori* infection were eligible for this study if they satisfied other inclusion/exclusion criteria.

7) Patients with *H. pylori* infection were evaluated on a case-by-case basis. Absolute exclusions were those children with active gastric or duodenal ulceration associated with *H. pylori*. If there was no documentation of active ulceration or recent GI bleed, the principal investigator (PI) could have, at their discretion, planned for their anti-*Helicobacter* antibiotic course after this study was completed, provided the patient's parents/guardian agreed with the course of treatment.

8) The patient's endoscopic findings had evidence of advanced esophageal lesions due to GERD or other severe upper GI tract pathology (e.g., Barrett's, stricture, neoplasm).

9) Patients who had other major clinical pathology or developmental abnormalities (e.g., including but not limited to esophageal atresia, pyloric stenosis), which might have caused gastrointestinal dysmotility as a secondary manifestation.

10) Patients who had acute respiratory distress within 72 hours prior to randomization (Day 0). These patients were eligible for re-evaluation for inclusion once acute symptoms had subsided.

11) Patients who had abnormal screening laboratory values were excluded when the investigator and/or AstraZeneca determined the abnormalities to be unexplained or clinically significant in a way that would put the patient at risk during study participation.

12) Patients who had any condition that might require major surgery during the course of the study.

13) Patients who had a known hypersensitivity, allergy, or intolerance to any component of esomeprazole or omeprazole.

14) Patients who had used any other investigational compound within 28 days prior to the screening visit. Patients who had used investigational devices or products that were not systemically absorbed within 28 days prior to the screening visit were to be discussed with AstraZeneca on a case-by-case basis prior to randomization (Day 0).

15) Patients who had any condition that, in the judgment of the investigator, made performance of any of the study procedures unsafe, or that made it unlikely the patient would complete the

study and all study procedures. These conditions may have included behavioral problems such as Attention Deficit Disorder (ADD) or Pervasive Development Disorders.

16) Parents/guardians who had any condition that, in the judgment of the investigator, made it difficult for the patients to complete the study and all study procedures and visits. Examples would include substance abuse or a serious medical condition.

Statistical population: There were 3 population analyzed: intent-to-treat (ITT) population, per-protocol (PP) population, and safety population (Table 6). The ITT population included patients who had a baseline measurement, at least 1 post-baseline measurement after randomization, and who took at least 1 dose of study medication. The PP analysis was performed in support of the ITT analysis. Patients in the PP population were those who completed the study meeting all criteria of the ITT population 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.

Descriptive statistics were provided for the efficacy outcomes. In total, 109 patients were randomized in 24 study sites. Of these, 101 patients completed the study. The numbers of evaluable patients were 108 patients in the safety population, 109 in the ITT population, and 98 patients in the PP population. As expected, most 1 to 5 year olds weighing <20 kg and most 6 to 11 year olds weighing ≥20 kg. In the total study population, 48.6% of patients had erosive esophagitis. Of the 53 patients who had erosive disease, all but 2 had LA grade A or B. One patient (4.3%) in the <20 kg, 10 mg treatment group had Grade C esophagitis and 1 patient (3.4%) in the ≥20 kg, 20 mg treatment group had Grade D.

**Table 7. Patient population**

| | Esomeprazole dose groups | | | | |
|---|---|---|---|---|---|
| | **5 mg Wt <20 kg** | **10 mg Wt <20 kg** | **10 mg Wt ≥20 kg** | **20 mg Wt ≥20 kg** | **Total** |
| **N Randomized** | 26 | 23 | 31 | 29 | 109 |
| Biopsy urease test *(H. pylori)* | | | | | |
| Negative | 16 (61.5) | 12 (52.2) | 8 (25.8) | 10 (34.5) | 46 (42.2) |
| Positive | 0 | 1 (4.3) | 0 | 0 | 1 (0.9) |
| Unknown | 10 (38.5) | 10 (43.5) | 23 (74.2) | 19 (65.5) | 62 (56.9) |
| Erosive disease [n (%)] | 12 (46.2) | 12 (52.2) | 16 (51.6) | 13 (44.8) | 53 (48.6) |
| LA Grade A[a] | 6 (23.1) | 6 (26.1) | 11 (35.5) | 9 (31.0) | 32 (29.4) |
| LA Grade B[a] | 6 (23.1) | 5 (21.7) | 5 (16.1) | 3 (10.3) | 19 (17.4) |
| LA Grade C[a] | 0 | 1 (4.3) | 0 | 0 | 1 (0.9) |
| LA Grade D[a] | 0 | 0 | 0 | 1 (3.4) | 1 (0.9) |
| **Disposition** | | | | | |
| N (%) of completed patients | 24 (92.3) | 22 (95.7) | 26 (83.9) | 29 (100.0) | 101 (92.7) |
| N (%) of discontinued patients | 2 (7.7) | 1 (4.3) | 5 (16.1) | 0 | 8 (7.3) |
| N (%) analyzed for safety | 25[b] (96.2) | 23 (100.0) | 31 (100.0) | 29 (100.0) | 108 (99.1) |
| N (%) analyzed for efficacy (ITT) | 26 (100.0) | 23 (100.0) | 31 (100.0) | 29 (100.0) | 109 (100.0) |
| N (%) analyzed for efficacy (PP) | 25 (96.2) | 22 (95.7) | 26 (83.9) | 25 (86.2) | 98 (89.9) |

Wt is weight; N is number; ITT is Intention-to-treat; PP is Per-protocol.

[a] Erosive disease LA score classification: Grade A is 1 (or more) mucosal break no longer than 5 mm that does not extend between the tops of 2 mucosal folds; Grade B is 1 (or more) mucosal break more than 5 mm that does not extend between the tops of 2 mucosal folds; Grade C is 1 (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the circumference; D is 1 (or more) mucosal break that involves at least 75% of the circumference.

[b] One patient was not evaluable for safety because he did not have any post-baseline safety data. Some post-baseline diary (clinical outcomes) data was available for this patient so he was included in the ITT population.

## 5.1.4 Efficacy Findings

**1) Changes from baseline in endoscopic healing of EE**

The outcomes for the assessments of endoscopic healing of EE were summarized in Table 8. Patients were considered to be improved if their esophageal erosions at their final endoscopy were 1 or more LA grades better than they were at baseline. Patients were resolved if their final endoscopy showed no signs of erosions. Overall, most of the patients who had EE at baseline and a follow-up endoscopy were improved at their follow-up endoscopy. In most of these patients, the EE was resolved and their erosions had healed. The positive results in improvement and resolution were observed across all treatment groups. PP population results were similar to those of the ITT population.

In this study, there were 3 patients who did not show any improvement. Two of these patients had Grade B erosive esophagitis (Patients E0027007 and E0205001) and 1 had a single ulcer described in the cardiac region (Patient E0042012). It is unclear whether or not this last patient had true EE. These 3 patients received esomeprazole doses of 0.17, 0.55, and 0.60 mg/kg/day.

**Table 8. Summary of outcome for patients who had EE at baseline and had a follow-up endoscopy-ITT population**

| | Esomeprazole dose groups | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5 mg Wt <20 kg (N=11) | | 10 mg Wt <20 kg (N=11) | | 10 mg Wt ≥20 kg (N=10) | | 20 mg Wt ≥20 kg (N=13) | | Total (N=45) | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Improved | 11 | (100.0) | 9 | (81.8) | 9 | (90.0) | 13 | (100.0) | 42 | (93.3) |
| Improved but not resolved | 0 | | 0 | | 0 | | 2 | (15.4) | 2 | (4.4) |
| Resolved | 11 | (100.0) | 9 | (81.8) | 9 | (90.0) | 11 | (84.6) | 40 | (88.9) |
| No improvement (same as baseline) | 0 | | 2 | (18.2) | 1 | (10.0) | 0 | | 3 | (6.7) |
| Worsened | 0 | | 0 | | 0 | | 0 | | 0 | |

Wt is weight.

**Medical Officer's Comments: Interpretation of the results is difficult, because of the lack of moderate to severe EE (Grades C and D) and comparator in the study. The confounding effects of self healing of mild EE can not be ruled out (see Table 9).**

**Table 9. Summary of baseline esophageal endoscopic data**

| | Esomeprazole dose groups | | | | |
|---|---|---|---|---|---|
| | 5 mg Wt<20 kg (n=26) | 10 mg Wt<20 kg (n=23) | 10 mg Wt≥20 kg (n=31) | 20 mg Wt≥20 kg (n=29) | Total (n=109) |
| **Erosive esophagitis** | 12 (46.2%) | 12 (52.2%) | 16 (51.6%) | 13 (44.8%) | 53 (48.6%) |
| **Grade A** | 6 (23.1%) | 6 (26.1%) | 11 (35.5%) | 9 (31.0%) | 32 (29.4%) |
| **Grade B** | 6 (23.1%) | 5 (21.7%) | 5 (16.1%) | 3 (10.3%) | 19 (17.4%) |
| **Grade C** | 0 | 1 (4.3%) | 0 | 0 | 1 (0.9%) |
| **Grade D** | 0 | 0 | 0 | 1 (3.4%) | 1 (0.9%) |

*From the sponsor's Table 17, Section 6.5.1

**2) Changes from baseline in daily patient symptom assessments as reported by parent/guardian**

On a daily basis, the parent/guardian called into the Interactive Voice Response System (IVRS) and reported the presence and severity of their child's GERD symptoms for the prior 24-hour period. The reported GERD symptoms and signs were derived from the NASPGHAN guidelines.

Symptoms assessed included:

**Heartburn:** A burning feeling, rising from the stomach or lower part of the chest towards neck.

**Acid regurgitation:** Perception of unpleasant-tasting fluid backing up into the throat and/or mouth.

**Epigastric pain:** Perception of discomfort located in the central upper portion of the abdomen.

**Vomiting:** Occurs when gastric contents are forcefully brought up to and out of the mouth. Additionally, the number of times the child vomits was captured via the IVRS.

**Difficulty swallowing:** Difficulty in passing anything through the pharynx or esophagus.

**Feeding difficulties:** Food refusal, choking with food/drink and or poor weight gain.

The severity of the symptoms was graded by the parent/guardian using the 4-point scale presented in Table 10.

**Table 10. 4-point scale used in parent/guardian-reported assessment of patient's GER symptoms**

| Severity | Score | Description |
|---|---|---|
| None | 0 | No symptoms |
| Mild | 1 | Symptoms present but not interfering with daily activities |
| Moderate | 2 | Symptoms present and somewhat interfering daily activities |
| Severe | 3 | Symptoms present and greatly interfering or preventing daily activities |

In addition to the above symptoms, the following extraesophageal symptoms were assessed daily via the IVRS:

**Hoarseness:** Rough or harsh quality to the voice.

**Cough:** A sudden explosive forcing of air through the vocal cords, usually triggered by mechanical or chemical irritation of the airways.

**Gagging:** A throat spasm that makes swallowing or breathing difficult.

**Wheezing/Stridor:** A whistling, squeaking, musical, or puffing sound made on the exhalation by air passing through the glottis or narrowed tracheobronchial airways.

Table 11 shows the mean changes from baseline for those patients who reported the symptoms of heartburn, acid regurgitation, or epigastric pain in the ITT population. The symptoms of vomiting, feeding difficulties, and difficulty swallowing were not analyzed in this way, as these symptoms were not reported as occurring in the majority of patients at baseline.

The GERD symptoms of heartburn, acid regurgitation, and epigastric pain were significantly reduced after treatment with esomeprazole in all treatment groups. The p-values for all of these symptoms were <0.0032 regardless of the weight stratum (<20 kg, =20 kg) or esomeprazole dose (Table 11).

**Table 11. Summary of patient diary assessments of GERD symptoms as reported by parent/guardian: mean severity change from baseline at final week for patients who had symptoms at baseline (ITT population)**

| | | | Baseline (72-hour recall) | | Final week in study | | Change from baseline | | |
|---|---|---|---|---|---|---|---|---|---|
| Treatment | Symptom | N[a] | Mean | SD | Mean | SD | Mean | SD | p-value vs baseline[b] |
| 5 mg Wt <20 kg (N=26) | Heartburn | 14 | 1.50 | 0.65 | 0.35 | 0.61 | -1.15 | 0.93 | 0.0005 |
| | Acid regurgitation | 17 | 1.71 | 0.69 | 0.52 | 0.70 | -1.18 | 0.81 | <0.0001 |
| | Epigastric pain | 16 | 1.69 | 0.87 | 0.27 | 0.52 | -1.42 | 0.61 | <0.0001 |
| 10 mg Wt <20 kg (N=23) | Heartburn | 10 | 1.70 | 0.82 | 0.61 | 0.97 | -1.09 | 0.86 | 0.0032 |
| | Acid regurgitation | 11 | 1.64 | 0.81 | 0.31 | 0.41 | -1.32 | 0.93 | 0.0008 |
| | Epigastric pain | 13 | 1.38 | 0.65 | 0.36 | 0.87 | -1.02 | 0.69 | 0.0002 |
| 10 mg Wt ≥20 kg (N=31) | Heartburn | 19 | 1.42 | 0.61 | 0.11 | 0.20 | -1.32 | 0.67 | <0.0001 |
| | Acid regurgitation | 20 | 1.50 | 0.51 | 0.26 | 0.42 | -1.24 | 0.56 | <0.0001 |
| | Epigastric pain | 15 | 1.53 | 0.52 | 0.23 | 0.32 | -1.30 | 0.65 | <0.0001 |
| 20 mg Wt ≥20 kg (N=29) | Heartburn | 13 | 1.46 | 0.66 | 0.24 | 0.40 | -1.22 | 0.85 | 0.0002 |
| | Acid regurgitation | 11 | 1.55 | 0.69 | 0.17 | 0.35 | -1.38 | 0.81 | 0.0002 |
| | Epigastric pain | 15 | 1.67 | 0.72 | 0.30 | 0.42 | -1.37 | 0.67 | <0.0001 |

Wt is weight; ITT is intent-to-treat; SD is standard deviation.
a N is the number of patients who had diary data for baseline and their final week in study.
b paired t-test.
Data derived from Table 11.2.3.3.

Extraesophageal GERD symptoms were assessed and are summarized in Table 12.

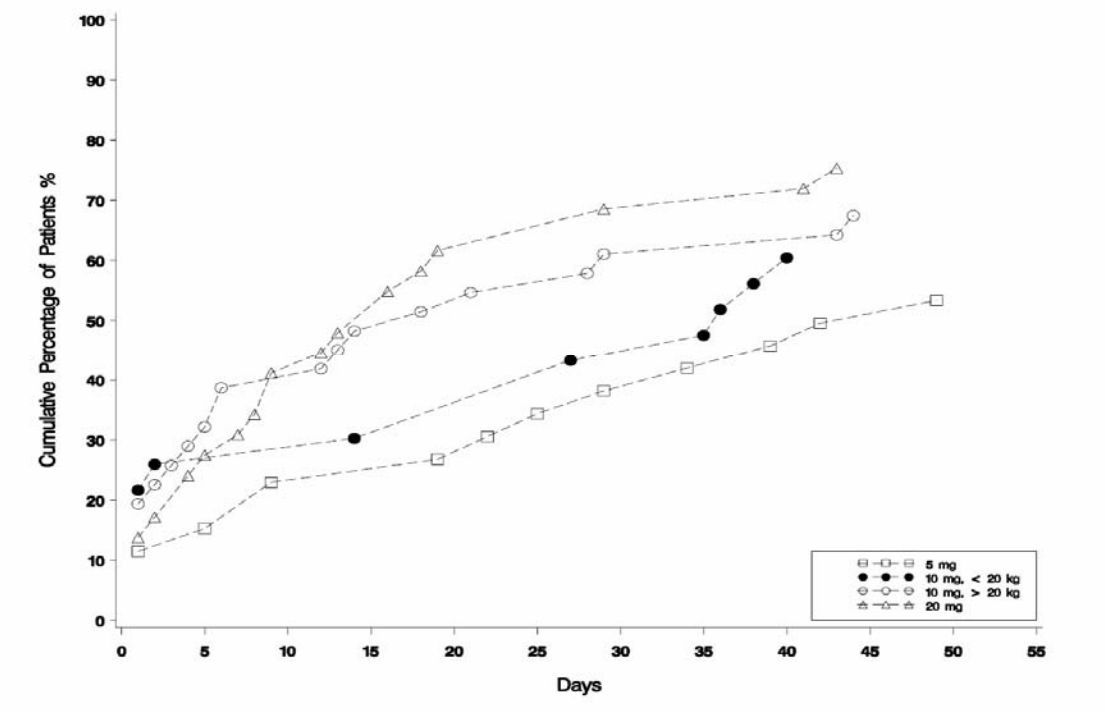
**Table 12. Number of patients having extraesophageal symptoms at base line and at final visit (ITT population)**

| | | Baseline | | Final visit | |
|---|---|---|---|---|---|
| **Treatment** | **Symptom** | **Anytime N[1]** | **Nighttime N** | **Anytime N (%)** | **Nighttime N (%)** |
| Esomeprazole 5 mg Weight <20 kg | Hoarseness | 7 | 2 | 1 (14.3) | 0 |
| | Cough | 20 | 11 | 11 (55.0) | 4 (36.4) |
| | Gagging | 12 | 2 | 6 (50.0) | 0 |
| | Wheezing | 6 | 4 | 3 (50.0) | 2 (50.0) |
| Esomeprazole 10 mg Weight <20 kg | Hoarseness | 10 | 5 | 3 (30.0) | 1 (20.0) |
| | Cough | 13 | 7 | 7 (53.8) | 4 (57.1) |
| | Gagging | 11 | 6 | 1 (9.1) | 1 (16.7) |
| | Wheezing | 3 | 3 | 1 (33.3) | 1 (33.3) |
| Esomeprazole 10 mg Weight ≥20 kg | Hoarseness | 7 | 5 | 1 (14.3) | 1 (20.0) |
| | Cough | 13 | 6 | 7 (53.8) | 2 (33.3) |
| | Gagging | 5 | 2 | 0 | 0 |
| | Wheezing | 2 | 1 | 2 (100.0) | 1 (100.0) |
| Esomeprazole 20 mg Weight ≥20 kg | Hoarseness | 9 | 4 | 2 (22.2) | 0 |
| | Cough | 12 | 6 | 3 (25.0) | 2 (33.3) |
| | Gagging | 7 | 2 | 0 | 0 |
| | Wheezing | 0 | 0 | 0 | 0 |
| Total | Hoarseness | 33 | 16 | 7 (21.2) | 2 (12.5) |
| | Cough | 58 | 30 | 28 (48.3) | 12 (40.0) |
| | Gagging | 35 | 12 | 7 (20.0) | 1 (8.3) |
| | Wheezing | 11 | 8 | 6 (54.5) | 4 (50.0) |

[1]N is the number of patients who had diary data for baseline and their final week in study
*From the sponsor's Table 11.2.4.5

Time to first resolution and time to first sustained resolution were assessed for the GERD symptoms heartburn, acid regurgitation, and epigastric pain. First sustained resolution was defined as the first day of the first string of 7 consecutive entries of "none" for all 3 symptoms in the diary (IVRS). First sustained resolution was achieved faster in the higher weight children (=20 kg) than in the lower weight children (<20 kg) (Figure 1). The median time to reach first sustained resolution was 42 days in the esomeprazole 5 mg (<20 kg) treatment group, 36 days in the 10 mg (<20 kg) group, 18 days in the 10 mg (=20 kg) group, and 16 days in the 20 mg (=20 kg) group. The cumulative percentage of patients achieving first sustained resolution each day is presented graphically in Figure 1. In this figure, it appears that lower percentages of patients in the 5 mg esomeprazole treatment group experienced first sustained resolution of GERD symptoms than in the other treatment groups.

**Figure 1. First sustained resolution of the combined GERD symptoms heartburn, acid regurgitation, and epigastric pain (ITT population)**




### 3) Changes from baseline in Physician's Global Assessment

To complete the global assessment, the physician/investigator recorded the overall clinical impression of the patient's GERD-related symptoms over the last 7 days. The impression was grouped as "None (no symptoms); Mild (symptoms present but not interfering with daily activities); Moderate (symptoms present and somewhat interfering with daily activities); or Severe (symptoms present and greatly interfering or preventing daily activities)." Answers were recorded in the case report form.

Table 13 summarizes the results of the Physician Global Assessments at baseline and the final visit for the ITT population. A significant reduction in overall GERD-related symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition, a significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups. Similar results were seen in the PP population.

**Table 13. Summary of Physician Global Assessment scores (ITT population)**

| Treatment | Timepoint | Assessment | n | (%) | p-value[a] |
|---|---|---|---|---|---|
| Esomeprazole 5 mg Weight <20 kg (N=26) | Baseline | None | 0 | | |
| | | Mild | 10 | (38.5) | |
| | | Moderate | 15 | (57.7) | |
| | | Severe | 1 | (3.8) | |
| | | Missing | 0 | | |
| | Final visit | None | 12 | (46.2) | <0.0001 |
| | | Mild | 11 | (42.3) | |
| | | Moderate | 2 | (7.7) | |
| | | Severe | 0 | | |
| | | Missing | 1 | (3.8) | |
| Esomeprazole 5 mg Weight <20 kg (N=26) | Baseline | None | 2 | (8.7) | |
| | | Mild | 6 | (26.1) | |
| | | Moderate | 15 | (65.2) | |
| | | Severe | 0 | | |
| | | Missing | 0 | | |
| | Final visit | None | 9 | (39.1) | =0.0004 |
| | | Mild | 11 | (47.8) | |
| | | Moderate | 3 | (13.0) | |
| | | Severe | 0 | | |
| | | Missing | 0 | | |
| Esomeprazole 5 mg Weight <20 kg (N=26) | Baseline | None | 1 | (3.2) | |
| | | Mild | 14 | (45.2) | |
| | | Moderate | 14 | (45.2) | |
| | | Severe | 2 | (6.5) | |
| | | Missing | 0 | | |
| | Final visit | None | 18 | (58.1) | <0.0001 |
| | | Mild | 12 | (38.7) | |
| | | Moderate | 0 | | |
| | | Severe | 1 | (3.2) | |
| | | Missing | 0 | | |
| Esomeprazole 5 mg Weight <20 kg (N=26) | Baseline | None | 2 | (6.9) | |
| | | Mild | 15 | (51.7) | |
| | | Moderate | 11 | (37.9) | |
| | | Severe | 1 | (3.4) | |
| | | Missing | 0 | | |
| | Final visit | None | 19 | (65.5) | <0.0001 |
| | | Mild | 10 | (34.5) | |
| | | Moderate | 0 | | |
| | | Severe | 0 | | |
| | | Missing | 0 | | |

[a]Mantel-Haenszel chi-square statistic testing change from baseline
Data derived from Table 11.2.1.1 of the study report.

At the end of the study (final visit), 88% (23/26) of the patients (in the group of body weight <20 kg and esomeprazole 5 mg), 87% (20/23) of patients (in the group <20 kg and esomeprazole 10 mg), 96% (30/31) of patients (in the group ≥20 kg and esomeprazole 10 mg), and all of patients (in the group ≥20 kg and 20 mg) had "none" or "mild" symptoms (Table 13). Similar results were observed in the PP population.

**Medical Officer's Comments: The percentages calculated in Table 13 may not clinically meaningful, because these were 7 days-recalls, and the numbers of subjects were small.**

The numbers of patients who had symptomatic improvements (defined as an improvement by at least 1 grade in the Physician's Global Assessment score) from baseline to their final visit are summarized in Table 14. In the <20 kg weight stratum (approximate age: 1 to 5 years old), 69% of patients receiving 5 mg esomeprazole and 65% of patients receiving 10 mg had reduced symptom severity. Slightly higher numbers were observed in the ≥20 kg weight stratum (approximate age: 6 to 11 years old), with 80% of patients receiving 10 mg and 79% of patients receiving 20 mg having reduced symptom severity (Table 14). In addition, of the 58 patients who reported moderate to severe symptoms at baseline and who had follow-up diary data, 91% experienced symptomatic improvement after esomeprazole treatment.

**Table 14. Physician Global Assessment score improved from baseline at their final visit (ITT population)**

| Esomeprazole dose | Improvement[a] n (%) |
|---|---|
| 5 mg, Weight <20 kg (N=26) | 18 (69.2) |
| 10 mg, Weight <20 kg (N=23) | 15 (65.2) |
| 10 mg, Weight ≥20 kg (N=31) | 25 (80.6) |
| 20 mg, Weight ≥20 kg (N=29) | 23 (79.3) |
| Total (N=109) | 81 (74.3) |

[a]Improvement defined as a reduction in the Physician's Global Assessment score by at least 1 grade from baseline to their final visit
*From sponsor's Table 11.2.1.5

## 5.1.5 Clinical Microbiology

Not applicable.

## 5.1.6 Efficacy Conclusions

1) Changes from baseline in endoscopic healing of EE

According to the sponsor, of the 45 patients who had EE at baseline and had a follow-up endoscopy, 93.3% were improved at their follow-up endoscopy. In most of the improved

patients (88.9%), the EE was resolved and their erosions had healed. Three patients (6.7%) have no improvement (same as baseline).

2) Changes from baseline in daily patient symptom assessment as reported by parent/guardian

The GERD symptoms of heartburn, acid regurgitation, and epigastric pain were significantly reduced after treatment with esomeprazole for 8 weeks in all treatment groups ($p<0.0032$).

Time to first sustained resolution: Sustained resolution was achieved faster in the higher weight children (≥20 kg) than in the lower weight children (<20 kg). The median times were 16 to 18 days in the ≥20 kg, 10 and 20 mg groups versus 36 to 42 days in the <20 kg, 5 and 10 mg groups.

3) Changes from baseline in Physician's Global Assessment

The GERD-related symptom scores, as assessed by the physician/investigators, were significantly reduced at each study visit (Week 2, Week 4, and Week 6, and final visit) for all treatment groups.

At the final visit, 69.2% of patients (<20 kg) receiving 5 mg esomeprazole and 65.2% of the patients receiving 10 mg had reduced symptom severity. For the group with body weight ≥20 kg, 80.6% of patients receiving 10 mg and 79.3% of patients receiving 20 mg had reduced symptom severity.

**Medical Officer Comments: The statistical significance of these results was discussed with Dr. Wen-Jen Chen (the Statistical Reviewer) on May 9, 2007. He commented that the lack of control hampers the interpretation of efficacy outcomes, and I agreed with his comments.**

# 6 INTEGRATED REVIEW OF SAFETY

## 6.1 Methods and Findings

The safety and tolerability of esomeprazole in patients age 1 to 11 years old were assessed based on Study D99614C00097. The safety variables included adverse events (AE), clinical laboratory results and physical examinations.

There were no deaths in this study. There were 2 serious adverse events (SAEs) that occurred during the treatment period and 1 SAE that occurred during the Screening endoscopy, prior to randomization. All SAEs were considered not treatment related by the investigator. There were 4 DAEs (adverse event leading discontinuation of a patient from study), 1 of which was also an SAE. Three of the 4 DAE patients had AEs that were considered not treatment related. One DAE patient had AEs considered as possibly treatment related (asthenia, nausea, viral infection)

and these resolved within 1 day of onset. The most common AEs reported by this population were consistent with the known safety profile of esomeprazole. The occurrence and frequency of treatment-related AEs were similar across treatment groups.

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 esomeprazole treatment groups.

### 6.1.1 Deaths

No patients died during the study.

### 6.1.2 Other Serious Adverse Events

Three patients experienced serious adverse events (SAEs) that listed in Table 15. They were not attributed to the study drug by the investigator. Two patients had SAEs during the treatment period and 1 patient (E0030012) had an SAE before randomization during the Screening period.

**Table 15. Listing of serious adverse event other than death (Safety population)**

| Esomeprazole dose and treatment group (body weight stratum) | Study site | Patient number | Sex (M/F) | Age (y) | Adverse event (preferred term) | Adverse event (investigator text) | Time from start of treatment to SAE onset (days) | Hospitalization | Life-threatening | Action taken with respect to investi-gational product | Causality (as assessed by the investigator) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 mg, <20 kg | 27 | E0027001 | F | 2 | Vomiting | Intractable/ bilious vomiting | 10 | Yes | No | Permanently stopped | None |
| 20 mg, ≥20 kg | 30 | E0030012 | M | 10 | Airway complication of anaesthesia | Laryngospasm/ bronchospasm | -12[a] | Yes | Yes | None | None |
| 10 mg, ≥20 kg | 402 | E0402001 | M | 4 | Vomiting | Intractable vomiting | 68[b] | Yes | No | None | None |

**Medical Officer's Comments: The narratives of 3 SAEs were reviewed. Patient E0027001, a 2 year old female, was treated with esomeprazole 10 mg once daily for 6 days. On Day 7, she developed vomiting, and the study drug was discontinued. She was admitted to the emergency room on Day 10 with the diagnosis of bilious vomiting, hypertension, and constipation. The symptoms were resolved in the hospital on Day 15. The investigator reported this SAE as no-causally related (Page 95, Study D9614C00097 Report). It appeared to the reviewer that the vomiting on Day 7 related to esomeprazole treatment. The other 2 SAEs appeared to be not related.**

### 6.1.3 Dropouts and Other Significant Adverse Events

A total of four patients discontinued from the study because of adverse events (Table 16). One discontinuation (patient E0018001) was considered possibly treatment related. The adverse events included asthenia, weakness, nausea, and viral infection, which resolved in one day after study drug was stopped. The remaining 3 discontinuations were not attributed to the study drug by the investigator. No other significant adverse events were identified in this submission.

**Table 16. Patients with discontinued treatment due to adverse events**

| Dose | Patient | M/F | Age | AE (Preferred term) | AE (Investigator term) | Start day | Causality assessed | Intensity |
|---|---|---|---|---|---|---|---|---|
| 10 mg, <20 kg | E0027001 | F | 2 | Vomiting<br>Hypertension | Intractable/bilious vomiting<br>Hypertension | 10 | No | Moderate |
| 10 mg, ≥20 kg | E0018001 | M | 8 | Asthenia<br>Nausea<br>Viral infection | Weakness<br>Nausea<br>Viral syndrome | 3 | Possibly treatment related | Moderate |
| 10 mg, ≥20 kg | E0038003 | M | 5 | Urticaria<br>Erythema multiforme<br>Eye swelling | Hives<br>Erythema multiforme<br>Swollen eyes | 13 | No | Severe |
| 10 mg, ≥20 kg | E0042009 | F | 9 | Nausea | Nausea | 36 | No | Moderate |

*From sponsor's Table 11.3.3.1

**Overall profile of dropouts**

The overall profile of dropouts consists of 3 discontinuations due to adverse events, and 1 discontinuation due to treatment failure. This patient (E0042009) had "lack of therapeutic response" recorded as reason for withdrawal on termination CRF page. On the AE CRF page, this patient also had an AE that was recorded as causing discontinuation (Table 16). Upon query by the sponsor, the investigator noted that "lack of therapeutic response" was the correct reason for withdrawal and the AE was not reason for discontinuation.

No additional dropouts from other Phase 2 and Phase 3 studies.

**Adverse events associated with dropouts**

The adverse events associated with dropouts included nausea, vomiting, asthenia, viral infection, hypertension, urticaria, erythema multiforme, and eye swelling (Table 15).

**Other significant adverse events**

No additional significant adverse events were identified in this submission.

### 6.1.4 Other Search Strategies

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

### 6.1.5 Common Adverse Events

The most common adverse events were gastrointestinal disorders (38% of safety population). The adverse events with a frequency ≥5% are included in Table 17. In general the AEs reported were consistent with the known safety profile of esomeprazole in adult population. No new safety signals were identified in the pediatric population of 1 to 11 year old.

**Table 17. Most Common Adverse Event (Study D99614C00097)**

| Most common Adverse event | Safety Population (N=108) | |
|---|---|---|
| | N | % |
| Vomiting | 20 | 18.5 |
| Pyrexia | 15 | 13.9 |
| Diarrhea | 13 | 12.0 |
| Cough | 13 | 12.0 |
| Headache | 12 | 11.1 |

*From sponsor's Table 11.3.2.1 and Table 11.3.2.2

**Eliciting adverse events data in the development program**

Adverse event data was obtained on a fixed schedule as outlined in the study plan. General AE assessment was made through 8-week study period on each visit. Laboratory assessment was conducted at screening period and was on monthly basis. Endoscopic examination (with biopsy) was performed at baseline and at the end of study.

**Incidence of common adverse events**

As Table 18 showed, the most common adverse events reported were vomiting (18.5%), pyrexia (13.9%), diarrhea (12.0%), cough (12.0%), and headache (11.1%).

**Identifying common and drug-related adverse events**

A total of 13 treatment-related AEs were reported (Table 18). Dose-relationship was not identified. The incidences of treatment-related AEs were distributed in a similar fashion among the 2 weight groups.

**Table 18. Treatment-related adverse events (safety population)**

| | Esomeprazole dose groups | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| System organ class/ Preferred term | 5 mg Wt <20 kg (N=25) | | 10 mg Wt <20 kg (N=23) | | 10 mg Wt ≥20 kg (N=31) | | 20 mg Wt ≥20 kg (N=29) | | Total (N=108) | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Gastrointestinal disorders | | | | | | | | | | |
| Diarrhoea | 3 | (12.0) | 0 | | 0 | | 0 | | 3 | (2.8) |
| Flatulence | 1 | (4.0) | 0 | | 0 | | 0 | | 1 | (0.9) |
| Nausea | 0 | | 0 | | 1 | (3.2) | 0 | | 1 | (0.9) |
| Vomiting | 0 | | 0 | | 0 | | 1 | (3.4) | 1 | (0.9) |
| General disorders and administration site conditions | | | | | | | | | | |
| Asthenia | 0 | | 0 | | 1 | (3.2) | 0 | | 1 | (0.9) |
| Infections and infestations | | | | | | | | | | |
| Viral infection | 0 | | 0 | | 1 | (3.2) | 0 | | 1 | (0.9) |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | |
| Arthralgia | 0 | | 0 | | 1 | (3.2) | 0 | | 1 | (0.9) |
| Nervous system disorders | | | | | | | | | | |
| Somnolence | 1 | (4.0) | 1 | (4.3) | 0 | | 0 | | 2 | (1.9) |
| Headache | 0 | | 0 | | 2 | (6.5) | 0 | | 2 | (1.9) |

Wt is weight.

## 6.1.6 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.**

## 6.1.7 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.

### 6.1.8 Electrocardiograms (ECGs)

ECGs were not conducted in this study.

## 6.2 Adequacy of Patient Exposure and Safety Assessments

### 6.2.1 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 (D9614C00097). Patients were between 1 and 11 years of age, and had weighed ≥8 kg. Patients had been diagnosed with endoscopically proven GERD by the investigator during the screening period.

**Study type and design/patient enumeration**

This was a Phase III, multicenter, randomized, double-blind study to evaluate the safety and clinical outcome of once daily esomeprazole for the treatment of GERD in pediatric patients 1 to 11 years of age. All subjects across the study are summarized in Table 19.

**Table 19. Summary of patient groups**

| | Esomeprazole dose groups | | | | |
|---|---|---|---|---|---|
| | **5 mg Wt < 20 kg (N=26)** | **10 mg Wt < 20 kg (N=23)** | **10 mg Wt ≥ 20 kg (N=31)** | **20 mg Wt ≥ 20 kg (N=29)** | **Total (N=109)** |
| **Patients evaluable for safety** | 25 | 23 | 31 | 29 | 108 |
| **Patients evaluable for ITT** | 26 | 23 | 31 | 29 | 109 |
| **Patients evaluable for PP** | 25 | 22 | 26 | 25 | 98 |

*From sponsor's Appendices 12.2.2.1 to 12.2.2.3

**Demographics**

There was an equitable distribution of males (51.4%) and females (48.6%) and most patients were Caucasian (81.7%). The distributions of these demographic characteristics were similar

across the weight/dose groups. In addition, within each weight stratum (<20 kg, ≥20 kg), the mean body mass indices (BMIs) of these children were similar between the 2 dose groups.

In the total study population, 48.6% of patients had erosive esophagitis while 51.4% of patients had nonerosive esophagitis (Table 20).

**Table 20. Demographic and baseline characteristics of the full data set**

| | Esomeprazole dose groups | | | | |
|---|---|---|---|---|---|
| | **5 mg Wt < 20 kg (N=26)** | **10 mg Wt < 20 kg (N=23)** | **10 mg Wt ≥ 20 kg (N=31)** | **20 mg Wt ≥ 20 kg (N=29)** | **Total (N=109)** |
| **Male** | 12 (46.2%) | 9 (39.1%) | 17 (54.8%) | 18 (62.1%) | 56 (51.4%) |
| **Female** | 14 (53.8%) | 14 (60.9%) | 14 (45.2%) | 11 (37.9%) | 53 (48.6%) |
| **1 to 5 years** | 25 (96.2%) | 22 (95.7%) | 2 (6.5%) | 3 (10.3%) | 52 (47.7%) |
| **6 to 11 years** | 1 (3.8%) | 1 (4.3%) | 29 (93.5%) | 26 (89.7%) | 57 (52.3%) |
| **Erosive esophagitis** | 12 (46.2%) | 12 (52.2%) | 16 (51.6%) | 13 (44.8%) | 53 (48.6%) |
| **Non-erosive esophagitis** | 14 (53.8%) | 11 (47.8%) | 15 (48.4%) | 16 (55.2%) | 56 (51.4%) |

***From sponsor's Table 11.1.2.1.1**

**Extent of exposure (dose/duration)**

The ranges of daily dose and duration are summarized in Table 21 (from Study D9614C00097).

**Table 21. Summary of dose and treatment duration**

| | Esomeprazole dose groups | | | |
|---|---|---|---|---|
| | **5 mg Wt < 20 kg (N=26)** | **10 mg Wt < 20 kg (N=23)** | **10 mg Wt ≥ 20 kg (N=31)** | **20 mg Wt ≥ 20 kg (N=29)** |
| **Weight based dose** | 0.25-0.6 mg/kg | 0.5-1.25 mg/kg | 0.5 mg/kg for lowest weight patient | 1.0 mg/kg for lowest weight patient |
| **Duration (mean)** | 54 days | 54 days | 50 days | 56 days |

***From sponsor's Table 11.1.2.1.1**

### 6.2.2 Adequacy of Overall Clinical Experience

**Medical Officer's Comments: The patient population consisted of 108 subjects in 24 study sites. Among them, 101 patients completed the study. Three dose levels, 5 mg, 10 mg, and 20 mg once daily for 8 weeks were studied. The proposed market dose is 10 mg once daily for up to 8 weeks. The overall clinical experiences appeared adequate to assess safety for the intended use.**

### 6.2.3 Assessment of Quality and Completeness of Data

**Medical Officer's Comments: The safety data base included 108 pediatric subjects age 1 to 11 years old with GERD diagnosed by endoscopy (Study D9614C00097). The study report included investigator comments, serious adverse event analysis, and summarization of frequent adverse event. The explanations by the investigators helped the review. The overall quality and completeness of the data were acceptable.**

## 6.3 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 esomeprazole in pediatric patients 1 to 11 years old is similar to that of 12 to 18 years old and adults. Gastrointestinal disorders (vomiting and diarrhea) were the most common treatment-related adverse events (see Table 18, Treatment Related Adverse Events).**

# 7 ADDITIONAL CLINICAL ISSUES

## 7.1 Dosing Regimen and Administration

Esomeprazole capsules (5 mg, 10 mg, and 20 mg once daily for 8 weeks) were studied in pediatric patients 1 to 11 years old with GERD.

- The results support the recommended doses and dosing regimen.
- The mean exposures of ITT population (N=109) were 53 days.
- Dose-toxicity relationship at the range of 5 to 20 mg was not identified.

### 7.2 Drug-Drug Interactions

Esomeprazole 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 esomeprazole was recently identified, and should be added to the proposed labeling. No new data in the pediatric submission were identified.

### 7.3 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.

### 7.4 Pediatrics

Esomeprazole delayed-release capsules are approved for pediatric patients 12 to 17 years old with GERD. The current submission supports the indication for pediatric patients 1 to 11 years old with GERD.

## 8 OVERALL ASSESSMENT

### 8.1 Conclusions

In this submission, esomeprazole was generally safe and well tolerated in pediatric GERD patients aged 1 to 11 years old (Study D9614C00097). There was no death. There were one treatment-related serious adverse event and four dropouts due to adverse events. The most common adverse events reported from this population were consistent with the known adverse events of esomeprazole. In addition, there were no clinically important findings or trends in hematology, clinical chemistry, vital signs, or physical examination observed across treatment groups.

The comparable bioavailability (Study 9614C00099) between 1 to 11 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 22,101 is recommended for **Approvable**.

### 8.2 Recommendation on Regulatory Action

The clinical recommendation is **approvable** for the treatment of pediatric patients 1 to 11 years old with GERD and the healing of erosive esophagitis.

The recommendation is based on the demonstrated bioavailability (Study 9614C00099) supported by the safety (Study D9614C00097) and by the similarity of pathogenesis of GERD between 1 to 11 year-old patients and the adult patients.

Imbalanced serious cardiac events were observed in two long-term adult studies (SOPRAN and LOTUS, respectively) with omeprazole or esomeprazole. The recommendation for regulatory action may be modified to **Approval** once the current safety issues regarding the serious cardiac events are resolved.

### 8.3 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**<br>Use of NEXIUM in pediatric and adolescent patients 1 to 17 years of age for short-term treatment of GERD is supported by a) extrapolation of results, already included in the currently approved labeling, from adequate and well-controlled studies that supported the approval of NEXIUM for adults, and b) safety and pharmacokinetic studies performed in pediatric and adolescent patients. [*See Clinical Pharmacology, Pharmacokinetics, Pediatric* for pharmacokinetic information.(12.3)] The safety and effectiveness of NEXIUM for the treatment of symptomatic GERD in patients <1 year of age have not been established. The safety and | **8.4 Pediatric Use**<br>Use of NEXIUM in pediatric and adolescent patients 1 to 17 years of age for short-term treatment of GERD is supported by a) extrapolation of results, already included in the currently approved labeling, from adequate and well-controlled studies that supported the approval of NEXIUM for adults, and b) safety and pharmacokinetic studies performed in pediatric and adolescent patients. [*See Clinical Pharmacology, Pharmacokinetics, Pediatric* for pharmacokinetic information.(12.3)] The safety and effectiveness of NEXIUM for the treatment of symptomatic GERD in patients <1 year of age have not been established. The safety and |

effectiveness of NEXIUM for other pediatric uses have not been established.

**1 to 11 Years of Age**
**GERD**
In a multicenter, parallel-group study, 109 pediatric patients with endoscopically-proven GERD (1 to 11 years of age; 53 female; 89 Caucasian, 19 Black, 1 Other) were treated with NEXIUM once daily for up to 8 weeks to evaluate safety and tolerability. Dosing by patient weight was as follows:

weight <20 kg: once daily treatment with esomeprazole 5 mg or 10 mg
weight > 20 kg: once daily treatment with esomeprazole 10 mg or 20 mg

Patients were endoscopically characterized as to the presence or absence of erosive esophagitis.

Fifty-three patients had erosive esophagitis at baseline. [redacted] patients who had follow-up endoscopy, [redacted] 8 weeks.

[redacted]

**12 to 17 Years of Age**
**GERD**
In a multicenter, randomized, double-blind, parallel-group study, 149 adolescent patients (12 to 17 years of

effectiveness of NEXIUM for other pediatric uses have not been established.

**1 to 11 Years of Age**
**GERD**
In a multicenter parallel-group study, 109 pediatric patients with history of endoscopically-proven GERD (1 to 11 years of age; 53 female; 89 Caucasian, 19 Black, 1 Other) were treated with NEXIUM once daily for up to 8 weeks to evaluate safety and tolerability. Dosing by patient weight was as follows:

weight <20 kg: once daily treatment with esomeprazole 5 mg or 10 mg
weight > 20 kg: once daily treatment with esomeprazole 10 mg or 20 mg

Of the 109 patients, 53 had erosive esophagitis at baseline (51 had mild, 1 moderate, and 1 severe esophagitis). Although most of the patients who had a follow up endoscopy at the end of 8 weeks of treatment healed, spontaneous healing cannot be ruled out because these patients had low grade erosive esophagitis prior to treatment, and the trial did not include a concomitant control.

[redacted]

**12 to 17 Years of Age**
**GERD**
In a multicenter, randomized, double-blind, parallel-group study, 149

| | |
|---|---|
| age; 89 female; 124 Caucasian, 15 Black, 10 Other) with clinically diagnosed GERD were treated with either NEXIUM 20 mg or NEXIUM 40 mg once daily for up to 8 weeks to evaluate safety and tolerability. Patients were not endoscopically characterized as to the presence or absence of erosive esophagitis.<br>  | adolescent patients (12 to 17 years of age; 89 female; 124 Caucasian, 15 Black, 10 Other) with clinically diagnosed GERD were treated with either NEXIUM 20 mg or NEXIUM 40 mg once daily for up to 8 weeks to evaluate safety and tolerability. Patients were not endoscopically characterized as to the presence or absence of erosive esophagitis.<br>  |

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