

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-957 (b) (4) S005
Priority or Standard	Priority
Submit Date(s)	18 December 2008
Received Date(s)	18 December 2008
PDUFA Goal Date	18 June 2009
Reviewer Name(s)	Aisha E. Peterson MD, MPH, MBA
Review Completion Date	15 June 2009
Established Name	Esomeprazole magnesium
Trade Name	Nexium [®]
Therapeutic Class	Proton-pump Inhibitor
Applicant	AstraZeneca
Formulation(s)	Delayed-release oral suspension
Dosing Regimen	
Indication(s)	Short-term treatment of GERD symptoms (b) (4)
Intended Population(s)	0-11 month olds, inclusive

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1 Recommendation on Regulatory Action	6
1.2 Risk Benefit Assessment	6
1.3 Recommendations for Postmarket Risk Management Activities	8
1.4 Recommendations for Postmarket Studies/Clinical Trials	8
2 INTRODUCTION AND REGULATORY BACKGROUND	9
2.1 Product Information	9
2.2 Tables of Currently Available Treatments for Proposed Indications	9
2.3 Availability of Proposed Active Ingredient in the United States	9
2.4 Important Safety Issues With Consideration to Related Drugs	12
2.5 Summary of Presubmission Regulatory Activity Related to Submission	12
2.6 Other Relevant Background Information	12
3 ETHICS AND GOOD CLINICAL PRACTICES	13
3.1 Submission Quality and Integrity	13
3.2 Compliance with Good Clinical Practices	13
3.3 Financial Disclosures	13
4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	13
4.1 Chemistry Manufacturing and Controls	13
4.3 Preclinical Pharmacology/Toxicology	14
4.4 Clinical Pharmacology	14
4.4.1 Mechanism of Action	14
4.4.3 Pharmacokinetics	15
5 SOURCES OF CLINICAL DATA	16
5.1 Tables of Studies/Clinical Trials	16
5.2 Review Strategy	17
5.3 Discussion of Individual Studies/Clinical Trials, Study D9614C00096	17
5.3.1 Protocol Summary	17
5.3.2 Key Inclusion Criteria	19
5.3.3 Key Exclusion Criteria	19
5.3.4 Treatment	20
5.3.5 Study Visits and Procedures	21
5.3.6 Control Procedures	27
5.3.7 Primary Efficacy Endpoint	27
5.3.7 Secondary Efficacy Endpoint(s)	28
5.3.8 Statistical Information	28
5.3.9 Protocol Amendments	29
6 REVIEW OF EFFICACY	30
6.1 Indication	31
6.1.1 Methods	31
6.1.2 Demographics	31
6.1.3 Subject Disposition	34
6.1.4 Analysis of Primary Endpoint(s)	35
6.1.5 Analysis of Secondary Endpoints(s)	37
6.1.6 Other Endpoints	40
6.1.7 Subpopulations	40

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.....	41
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects	41
6.1.10 Additional Efficacy Issues/Analyses	41
7 REVIEW OF SAFETY	41
7.1 Methods	42
7.1.1 Studies/Clinical Trials Used to Evaluate Safety	42
7.1.2 Categorization of Adverse Events	42
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	42
7.2 Adequacy of Safety Assessments	42
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	42
7.2.2 Explorations for Dose Response.....	43
7.2.3 Special Animal and/or In Vitro Testing	43
7.2.4 Routine Clinical Testing.....	43
7.2.5 Metabolic, Clearance, and Interaction Workup	44
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	44
7.3 Major Safety Results.....	44
7.3.1 Deaths	44
7.3.2 Nonfatal Serious Adverse Events.....	44
7.3.3 Dropouts and/or Discontinuations	47
7.3.4 Significant Adverse Events.....	48
7.3.5 Submission Specific Primary Safety Concerns	48
7.4 Supportive Safety Results	48
7.4.1 Common Adverse Events.....	48
7.4.2 Laboratory Findings.....	50
7.4.3 Vital Signs.....	50
7.4.4 Electrocardiograms (ECGs)	51
7.4.5 Special Safety Studies/Clinical Trials	51
7.4.6 Immunogenicity	51
7.5 Other Safety Explorations.....	51
7.5.1 Dose Dependency for Adverse Events	51
7.5.2 Time Dependency for Adverse Events.....	51
7.5.3 Drug-Demographic Interactions	51
7.5.4 Drug-Disease Interactions.....	51
7.5.5 Drug-Drug Interactions	52
7.6 Additional Safety Evaluations	52
7.6.1 Human Carcinogenicity	52
7.6.2 Human Reproduction and Pregnancy Data	52
7.6.3 Pediatrics and Assessment of Effects on Growth	52
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound	53
7.7 Additional Submissions.....	53
8 POSTMARKET EXPERIENCE.....	53
9 APPENDICES	55
9.1 Literature Review/References	55
9.2 Labeling Recommendations	55
9.3 Advisory Committee Meeting.....	55
9.4 Table of Written Request Studies	56

Table of Tables

Table 1. Clinical Trials Submitted	16
Table 2. Study 96, Patients Enrolled by Country	17
Table 3. Weight-based Nexium® dosing	20
Table 4. Schedule of Study Assessments	22
Table 5. Study 96, Parent and Physician Symptom Severity Assessment Scale.....	23
Table 6. IVRS Symptom Patient Assessment.....	24
Table 7. Study 96, Improvement Guidelines for Randomization	26
Table 8. Study 96, Patient Demographics	32
Table 9. Standardized Growth Parameters.....	33
Table 10. Study 96, Open-Label Screen Failures.....	34
Table 11. Patient Disposition	34
Table 12. Study 96, Treatment Compliance	35
Table 13. Analysis of Primary Endpoint.....	35
Table 14. Total Discontinuations from Study 96	36
Table 15. Proportion of Treatment Successes.....	37
Table 16. IVRS Summary of mean patient symptom severity scores, Open-Label.....	38
Table 17. IVRS Summary of mean patient symptom severity scores, Double-blind	38
Table 18. Summary of PGA Scores, Open-Label, n=95.....	39
Table 19. Summary of PGA Scores, Double-blind	39
Table 20. Primary endpoint, subgroup analysis.....	40
Table 21. Extent of Exposure (Days), Study 96.....	43
Table 22. Summary of Study 96 Safety Results	44
Table 23. Summary of Serious Adverse Events, Study 96.....	47
Table 24. Discontinuations due to Adverse Events, Study 96	48
Table 25. Common Adverse Events, Study 96 Double-blind Treatment Phase.....	49
Table 26. Study NEC-1, Adverse Events by dosage group.....	50
Table 27. PSUR Adverse events reported in patients ≤17 years old.....	54

Table of Figures

Figure 1. Overall Study Design	18
Figure 2. Kaplan-Meier plot of time to discontinuation due to symptom worsening	36

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

(b) (4)

(b) (4)

It is the recommendation of this reviewer that (b) (4) an approval action be taken for S-005 provided agreement is reach on changes in labeling. (b) (4)

(b) (4). The labeling should be amended though an approval action to provide clinical study results of the infant study and pharmacodynamic information to aid providers.

1.2 Risk Benefit Assessment

(b) (4)

Esomeprazole is currently approved for pediatric patients ages 1 to 17. Approvals were based upon pharmacokinetic and pharmacodynamic (PK/PD) studies showing safety and the extrapolation of adult efficacy. Because the pathophysiology of GERD is known to be similar in pediatric patients greater than one year of age and adults, this extrapolation of adult efficacy was appropriate. However, it is not appropriate for infants

(age less than one year) because there is likely a unique pathophysiology responsible for infantile GERD due to the differences in symptoms, duration, and prognosis between the two groups.

Studies for efficacy are necessary to ensure that drugs are treating symptoms of true reflux disease. Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus. This occurs normally in both pediatrics and adults. Uncomplicated GER presents as recurrent vomiting without other symptoms or complications. Infants with GER are often referred to as “happy spitters”. In contrast, gastroesophageal reflux disease (GERD) is defined as symptoms or complications of GER caused by exposure to acid. In pediatric patients, these symptoms could include irritability, poor weight gain, dysphagia, abdominal or substernal pain, esophagitis, and respiratory disorders.¹

Several factors unique to infants are postulated to be responsible for the difference in infantile and adult GERD. First, infants have caloric needs of 120 kcal/kg/day (in contrast to the adult need of 25 kcal/kg/day). Because the infant diet is largely liquid, infants take in a relatively large volume into the stomach each day. It is hypothesized that this results in a pressure build-up that must be relieved by lower esophageal sphincter (LES) opening and resultant GERD symptoms. Second, infants have a lower gastric compliance than older children and adults which could promote LES relaxation at relatively low intragastric volumes. Third, infants lack increased torso tone and upright posture which could make the LES more prone to transient relaxation.²

Because GERD symptoms are so prevalent in the infant population, proton pump inhibitor (PPI) use is continuing to increase despite a lack of documented efficacy. According to a recent retrospective observational study of insurance claims data in patients less than 12 months of age, PPI use increased seven-fold from 1999 to 2004. The mean age of first PPI use in this study was 4 to 5 months of age with treatment being discontinued in most patients by 7 to 8 months of age.³ Uncomplicated GER generally resolves by one year of age. GERD symptoms in infants also spontaneously resolve in more than 95% of patients by 18 months of age.⁴

While clinical studies have failed to show efficacy, pharmacodynamic information showing that PPIs increase pH holds out the possibility that PPIs are, in fact, efficacious in infants despite several negative studies. If this is true, it is important to understand why these clinical studies have failed to show efficacy. Incorrect study design, inappropriate patient selection, and/or improper study endpoints are likely to blame. Dr. Orenstein, a leading pediatric gastroenterologist and developer of the patient symptom assessment tool used in the clinical study submitted in support of this NDA, describes

1 Pediatric GE Reflux Clinical Practice Guidelines

2 Orenstein SR, Izadnia F, Khan S. Gastroesophageal Reflux Disease in Children. *Gastroenterology Clinics of North America*. 1999; 28:947-68.

3 Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton Pump Inhibitor Utilization Patterns in Infants. *Journal of Pediatric Gastroenterology and Nutrition*. 2007; 45:421-27.

4 Orenstein SR, Shalaby TM, Kelsey SF, et al. Natural history of infant reflux esophagitis: symptoms and morphometric histology during on year without pharmacotherapy. *J Gastroenterol* 2006; 101:628-40.

the treatment withdrawal design as “fatally flawed for studying the efficacy of PPIs...”⁵ She explains that rebound acid hypersecretion can occur in patients who abruptly discontinue PPIs leading to worsening of GERD symptoms. If this occurs, placebo patients abruptly discontinued from PPI therapy will do worse than patients who continue on PPI therapy and an artificial treatment effect (in favor of the PPI) could be seen.

Some studies suggest that rebound acid hypersecretion is related to the degree of pH elevation achieved by the PPI.⁶ Others suggest that there is no strong evidence to support clinically relevant rebound acid hypersecretion. Further studies are needed to understand the relationship between PPI use and rebound acid hypersecretion. In the meantime, studies should be designed to minimize the possible impact of rebound acid hypersecretion.

Choosing which patients to treat with PPIs is also important. Treating “happy spitters” with medications to increase pH is unlikely to result in a change in “symptoms”. For efficacy studies it might be necessary to include only patients with GERD diagnosed by a strict set of clinical symptoms and diagnostic evidence of acidic contents in the esophagus.

In addition to determining the correct study design and the appropriate patient population, it will be important to determine the proper study endpoint(s). In the infant population, clinical study endpoints based on symptoms are particularly susceptible to caregiver bias. In addition, symptoms such as irritability, fussing, and crying are vague and could be due to problems other than GERD.

There is still work to do to determine if PPIs are effective in treating pediatric GERD. Important questions remain unanswered. Currently, there is insufficient evidence to recommend the use of PPIs in patients less than one year of age.

1.3 Recommendations for Postmarket Risk Management Activities

None.

1.4 Recommendations for Postmarket Studies/Clinical Trials

None.

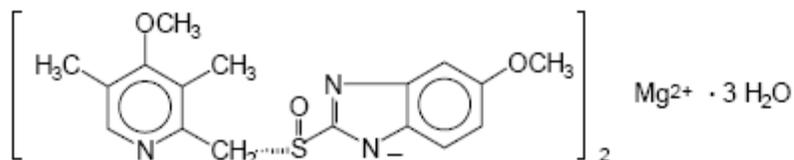
5 Orenstein SR, Hassell E. Infants and proton Pump Inhibitors: Tribulations, No Trials. *Journal of Pediatric Gastroenterology and Nutrition*. 2007;45:395-398.

6 Gillen D, Wirz AA, ARdill JE, McColl KEL. Rebound Hypersecretion After Omeprazole and its Relation to On-treatment acid suppression and Helicobacter pylori Status. *Gastroenterology*. 199;116:239-247.

2 Introduction and Regulatory Background

2.1 Product Information

Nexium™ (esomeprazole magnesium)



Nexium® (esomeprazole magnesium) is the pure S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole (Prilosec®) currently approved for the treatment of GERD adults and pediatric patients greater than one year of age.

Nexium® is currently available in delayed-release capsules (20 mg, 40 mg) and as granules for delayed-release oral suspension (10 mg, 20 mg, and 40 mg).

Patients in the studies submitted in support of this Application used Nexium® granules in capsules in doses of 2.5 mg, 5 mg, and 10 mg. The granules in these capsules were identical to currently approved Nexium® granules.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no PPIs approved for the treatment of GERD symptoms in pediatric patients less than one year of age. Two medications are approved for the treatment of GERD in the intended population—ranitidine and famotidine. Both of these medications are histamine-2 receptor antagonists (H₂RA). Ranitidine is approved for pediatric patients age one month to 16 years and famotidine is approved for neonates to 16 year old pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Nexium® is currently approved for use in pediatric patients greater than one year of age and in adults for various indications. See below for details regarding chronology of approved dosage forms, populations, and indications.

February 20, 2001, NDA 21-153

Population: Adults

Indications:

- Healing of Erosive esophagitis (20 mg or 40 mg once daily for 4 to 8 weeks)
- Maintenance of healing of erosive esophagitis (20 mg once daily)
- Treatment of symptomatic GERD (20 mg once daily for 4 weeks)

February 20, 2001, NDA 21-154 (acted on jointly with the Division of Special Pathogens).

Population: Adults

Indication: *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (40 mg once daily NEXIUM in combination with clarithromycin and amoxicillin for 10 days).

November 22, 2004, NDA 21-153/S-019

New Indication: Risk Reduction of NSAID-associated gastric ulcers (in adults).

March 31, 2005, NDA 021-689

New Formulation: Solution for IV administration

April 28, 2006, NDA 21-153/S-022

New Indication: Short-term treatment of GERD (20 mg or 40 mg once daily for up to 8 weeks).

October 11, 2006, NDA 21-153/S-023

New Indication: Treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

October 20, 2006, NDA 021-957

New Formulation: Delayed-release granules for oral suspension (20 mg and 40 mg).

New Population: Pediatric patients, 12 to 17 years of age.

Indication: Same indications as approved for adults.

February 27, 2008, NDA 22-101

New Dosage: Delayed-release granules for oral suspension (10 mg).

New Population: Pediatric patients 1 to 11 years of age.

Indication: Short-term treatment of GERD symptoms and healing of erosive esophagitis.

MO Comment: The delayed-release granules for oral suspension formulation approval was based on the demonstration of bioequivalence between the capsule and oral suspension. The approvals in the 1 to 11 and 12 to 17 year old populations were based upon the extrapolation of adult efficacy and safety studies.

NDA 22-101 was submitted prior to the approval of NDA 21-957; therefore, it was given a unique NDA number. In general, subsequent submissions for the same dosage form are supplements to the original application for that dosage form. Therefore, had the submission of NDA 22-101 occurred after the approval of NDA 21-957, it would have been a supplement to NDA 21-957 (the original NDA for the delayed-release granules formulation).

With the current submission, the Applicant submitted the final studies as required by a Pediatric Written Request issued 31 December 2001 (final amendment 10 October 2008). The time frame for submitting the studies was 31 December 2008. The Agency's Pediatric Exclusivity Board met 3/3/09 and 4/6/09 and determined that the Applicant fairly met the requirements of the Written Request. Pediatric exclusivity was granted effective May 1, 2009. See Appendix 9.4 for a brief description of Written Request studies.

Due to the fact that esomeprazole is the pure S-enantiomer of omeprazole, this period of exclusivity is actually the second period of exclusivity for the compound (omeprazole was previously granted exclusivity). As such, a second period of exclusivity for a compound is contingent upon positive studies and not just the completion of studies. Therefore, AstraZeneca was granted exclusivity for esomeprazole for pediatric patients ages 1 to 2 years of age.

(b) (4)

[Redacted text block]

2.4 Important Safety Issues With Consideration to Related Drugs

PPIs are widely used and have generally been found to be safe and well-tolerated. Current PPI labeling includes the following as warnings and precautions:

- Symptomatic response does not preclude presence of gastric malignancy.
- Atrophic gastritis has been noted with long-term omeprazole therapy.
- Triple therapy for *H. pylori* – there are risks due to the antibiotics.
- Patients treated with a PPI and Warfarin may need to be monitored for increases INR and prothrombin time due to the risk of abnormal bleeding.

In addition, prescribers should be warned against the concomitant use of certain antiretroviral drugs and drugs for which gastric pH can affect bioavailability. See individual product labeling for further details.

MO Comment: The precaution to monitor patients on concomitant PPI and Warfarin therapy has no PK/PD basis and is based solely on post-marketing reports. This warning/precaution is not present in all PPI labels and is not present in the Nexium® label.

Long-term PPI therapy has been associated with increased risk of hip fracture.⁷ And the concomitant use of PPIs and clopidogrel has been associated with an increased risk of adverse outcomes following acute coronary syndrome.⁸

MO Comment: The strength of these associations is still unknown. Therefore, there is currently no labeling of these subjects.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were no specific pre-submission regulatory activities (meetings, etc.). However, it should be noted that this submission is in response to a Pediatric Written Request issued October 31, 2001.

2.6 Other Relevant Background Information

Since its world-wide launch in Sweden on 10 March 2000, total exposure for Nexium® has been estimated to be approximately (b) (4) patient treatment courses. Nexium® is currently approved in more than 110 countries in both oral and intravenous formulations.

7 Yu-Xiao Y, Lewis JD, Epstein S, Metz DC. Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. *JAMA* 2006 296: 2947-2953.

8 Ho MP, Maddox TM, Wang L, Fihn S, Jesse RL, Peterson ED, Rumsfeld JS. Risk of Adverse Outcomes Associated with Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome. *JAMA* 2009; 301: 937-944.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well-organized and easily navigable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

No Division of Scientific Integrity (DSI) consult was requested due to the lack of demonstrated efficacy in the submitted clinical study.

3.3 Financial Disclosures

Financial disclosure forms were reviewed and all but one Investigator who participated in studies associated with this application reported no financial interests. (b) (6) principal investigator at site (b) (6) in Study (b) (6) disclosed "significant payments" from AstraZeneca. This Investigator screened (b) (6) patients in this study. Of these (b) (6) patients, only (b) (6) entered the randomized portion of the study.

MO Comment:

The possible impact of any financial bias from (b) (6) is very limited. Therefore, the patients randomized by this investigator were included in the primary efficacy analysis.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Nexium® delayed-release granules for oral suspension are currently available in 10 mg, 20 mg, and 40 mg unit dose packets. Each packet contains a fine yellow powder, consisting of white to pale brownish esomeprazole granules and pale yellow inactive granules.

Studies submitted in support of this application used 2.5 mg, 5 mg, and 10 mg esomeprazole doses. Capsules containing the identical enteric-coated esomeprazole granules currently marketed in the US were used. See Section 5.2 for more detailed information on administration of study drug.

The Applicant did not submit any new CMC information, omitting Module 3 and Module 2 CMC QOS sections. (b) (4)



The 10 mg sachet of granules for oral suspension was approved under NDA 22-101 (10 mg, 7/13/07 CMC review by M. Sloan).

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical studies were submitted in support of this efficacy supplement. However, there was a 1-month oral toxicity study in rats and a 3-month oral toxicity study in dogs using esomeprazole previously submitted in response to the Pediatric Written Request. These studies were submitted 6 March 2006 as Amendment #351 to IND 53,733. There were no findings indicating that neonatal juvenile animals are more susceptible to proliferative changes in the gastric mucosa and no unexpected toxicities. Overall, there were no studies indicating any specific risk in the pediatric population.

Dr. Ke Zhang, pharmacotoxicology reviewer, (b) (4)



See the full review by Dr. Zhang in DFS, 20 May 2009. Dr. Zhang recommended against including information on the neonatal rat and dog studies in the label because it would not add any new information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor (PPI) that inhibits gastric acid secretion through irreversible inhibition of the H⁺/K⁺ ATPase in the gastric parietal cell.

4.4.3 Pharmacokinetics

Two pharmacokinetic/pharmacodynamic (PK/PD) studies were submitted in support of this application, NEC-1 and NEC-2. Study NEC-1 was designed to evaluate the PK/PD parameters of repeat dose Nexium® in infants. In this study, neonates received Nexium® 0.25 mg/kg/day or 1 mg/kg/day for 7 days. In this study the geometric mean AUC_{tau} was 0.65 µmol*h/L, (95%CI 0.27 to 1.57 µmol*h/L,) and 3.51 µmol*h/L, (95% CI 1.28 to 9.59 µmol*h/L,) for the 0.25 and 1.0 mg/kg dose groups, respectively. In the 1.0 mg/kg dose group, the mean exposure (AUC) was similar to that observed after 10 mg in 1 to 11 year old, and 20 mg in 12 to 17 year-olds, and adults.

In Study NEC-2, 24 neonates received Nexium® 0.5 mg/kg/day for 7 days. The geometric mean AUC_{tau} was 2.5 µmol*h/L (range 0.2 to 5.5 µmol*h/L). Mean esomeprazole exposure in neonates receiving 0.5 mg/kg/day was less than exposure in infants receiving 1 mg/kg/day, children 1 to 11 years who received 10 or 20 mg/day, adolescents 12 to 17 years old who received 20 or 40 mg/day, and adults who received 20 or 40 mg/day.

While exposure was lower in neonates (0.5 mg/kg/day), there was a similar increase (approximately 40% each) in the percentage of time intragastric pH > 4 over the dosing interval in neonates and infants receiving 1.0 mg/kg. In contrast, infants who received 0.25 mg/kg experienced only a small (14%) increase in the percentage of time intragastric pH >4. The pharmacodynamic endpoint, % time intragastric pH >4 during the 24-hour dosing interval, has been shown to be correlated with clinical efficacy in the treatment of GERD in adults.

For further information see the full Clinical Pharmacology review for this supplement by Dr. Kristina Estes.

MO Comment:

(b) (4)

(b) (4)

it is important to provide PD data in the label for providers. Currently, many providers use esomeprazole (and other PPIs) off-label for the treatment of patients less than one year of age. It is likely that providers will continue to use these medications off-label due to the lack of an approved PPI for

the treatment of GERD in this age group. Any information that we can share with providers will be helpful.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 below summarizes the primary studies used in the review of this NDA to evaluate the efficacy, safety, and PK/PD of Nexium® in patients ages 0 to 11 months, inclusive. Study D9614C00096 was the only pivotal efficacy study submitted in support of this NDA for the indication of treatment of GERD in infants ages 0 to 11 months, inclusive. Studies NEC-1 and NEC-2 were submitted to provide supportive clinical outcomes and PK/PD data.

Table 1. Clinical Trials Submitted

Study Identifier	Objective of Study	Treatment	Study Design	Number of patients	Treatment Duration
D1964C00096 (Study 96)	To assess the safety and efficacy of esomeprazole magnesium for the treatment of GERD in infants aged 1 to 11 months, inclusive.	Esomeprazole magnesium according to body weight at baseline: 3-5 kg→2.5 mg >5-7.5kg→5 mg >7.5-12kg→10 mg	Multicenter, randomized, double-blind, placebo-controlled, parallel group, treatment withdrawal	Open-label: 98 enrolled 80 completed Double-blind: 80 enrolled 53 completed	2-week open label phase followed by a 4-week randomized, treatment withdrawal phase
SH-NEC-0001 (Study NEC-1)	To assess the PK of two doses of esomeprazole and its efficacy in controlling intragastric pH in infants up to 24 months of age.	Esomeprazole magnesium 0.25 mg/kg and 1.0 mg/kg	Single-center, randomized, single-blind, 2-arm, parallel, repeated dose study in infants up to 24 months of age.	Total patients: 50 enrolled 45 completed 0 to 11 month olds: 43 enrolled 39 completed	7 days
SH-NEC-0002 (Study NEC-2)	To assess the PK of esomeprazole and its effect on intragastric pH in preterm infants and neonates.	Esomeprazole magnesium 0.5 mg/kg	Single-center, open, repeated-dose study in preterm infants and neonates. One investigational dose of esomeprazole administered once daily.	26 enrolled 25 completed	7 days

5.2 Review Strategy

The Phase 3 clinical efficacy study, D9614C00096, is reviewed in detail. Detailed review of the supportive pharmacokinetic studies, SH-NEC-001 and SH-NEC-002 was deferred to the Clinical Pharmacology Reviewer, Dr. Kristina Estes. However, the adverse event data from the pharmacokinetic studies SH-NEC-0001 and SH-NEC-0002 are integrated into the safety review of this review.

5.3 Discussion of Individual Studies/Clinical Trials, Study D9614C00096

5.3.1 Protocol Summary

Title

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Treatment-withdrawal Study to Evaluate the Efficacy and Safety of Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Infants Aged 1 to 11 Months, Inclusive.

Study Centers

This study was conducted in 33 centers in four countries—US (16 sites), France (4 sites) Germany (9 sites), and Poland (4 sites). However, of the 33 participating centers, only 25 centers enrolled patients into the study—11 sites in the US, 4 sites in France, 6 sites in Germany, and 4 sites in Poland. There were 103 total patients screened and 98 were found to meet criteria for study entry.

Table 2. Study 96, Patients Enrolled by Country

Country	# of Sites	Patients Screened	Patients Enrolled	Patients Randomized
France	4	16	15	13
Germany	6	16	16	13
Poland	4	31	30	28
USA	11	40	37	26
TOTAL	25	103	98	80

Study Period

12 April 2007 to 4 June 2008

Study Objective

The primary study objective was to assess the efficacy of once daily Nexium® in reducing the esophageal and supraesophageal signs and symptoms of infantile GERD.

The secondary study objective was to evaluate the safety and tolerability of once daily Nexium® in infants aged 1 to 11 months, inclusive, with GERD.

Study Design

The pivotal study, D9614C00096 (Study 96), was a multicenter, randomized, double-blind, placebo-controlled, parallel group, treatment-withdrawal study designed to evaluate the efficacy and safety of Nexium® for the treatment of GERD in infants aged 1 to 11 months, inclusive. See Figure 1 below.

The study consisted of the following periods:

10-day screening period

2-week open-label period

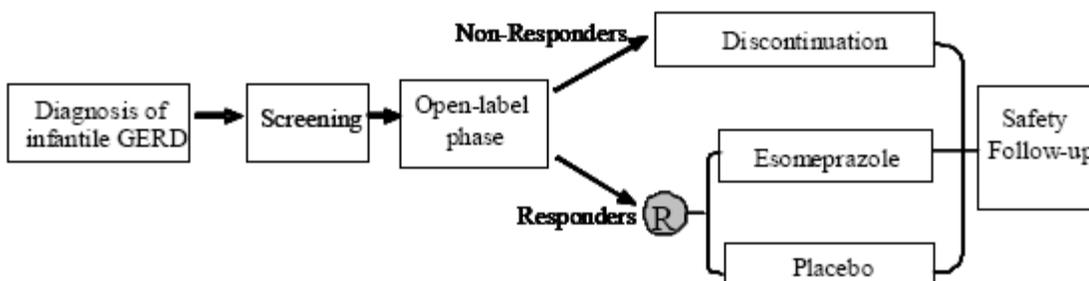
4-week randomized treatment period (involving responders from the open-label period)

2-week safety follow-up period

Efficacy was assessed by comparing the time to study discontinuation due to symptom worsening between the active and placebo treatment groups during the randomized treatment period.

MO Comment: The study design appears adequate to achieve the study objectives. Enriching the randomized population with responders from the open-label period is an acceptable approach.

Figure 1. Overall Study Design



Reproduced from Sponsor's submission, Module 2.5 p. 30.

5.3.2 Key Inclusion Criteria

For inclusion in the study, patients had to meet all of the following criteria:

1. Term or post-term infants beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected gestational age of at least 44 weeks but less than 12 months and weight between 3 kg and 12 kg, inclusive.
2. Clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, made by the investigator based on the following factors: history, physical examination, symptoms identified during the review of systems, laboratory test results, or information from diagnostic testing. Patients with erosive esophagitis were evaluated for study inclusion on a case by case basis.
3. At least one of the symptoms of GERD must be present for at least twice a week for a 4-week duration
4. Failed standard anti-reflux measures (thickened feeds, elimination diet, positioning, etc.).
5. Patients with supraesophageal manifestations of GERD, including wheezing, should present with a clinical picture consistent with GERD.
6. Infants with GERD clinical symptoms and suspected food allergy, who in the opinion of the investigator, have not responded to standard medical interventions (e.g. elimination diet) after a reasonable amount of time (e.g. 1-2 weeks).
7. Patients who, in the judgment of the investigator, would be considered for treatment with an acid suppression agent based on symptoms of pathological GERD.

5.3.3 Key Exclusion Criteria

1. PPI use within 7 days prior to enrollment in the open-label treatment phase (Day 0).
2. Use of any prescription or over-the-counter treatment for symptoms of GERD, such as H2RAs or prokinetics within 24 hours prior to enrollment in the open-label phase (Day 0). Antacids were allowed except for those containing bismuth (e.g. Pepto-Bismol® and Kaopectate®).
3. History or current need for resection or reconstructive surgery of the esophagus, stomach, duodenum, or the jejunum.
4. History of acute life-threatening events, e.g., apnea, near Sudden Infant Death Syndrome (SIDS).
5. History of the gastrointestinal bleed, allergic gastroenteropathies, eosinophilic gastroenteritis bleeding disorders (or a history of these disorders), pyloric stenosis, active seizure disorder, acute pancreatitis, or meningitis.
6. History of any acute or chronic illness that, in the opinion of the investigator, would place the patient at risk because of his/her participation in the study or potentially confound the study results.
7. History of acute respiratory distress within 72 hours prior to enrollment in the open-label phase (Day 0).
8. History of any condition likely to require surgery during the study period.

9. History of known hypersensitivity, allergy, or intolerance to any component of esomeprazole, omeprazole, or MAALOX[®] or equivalent age-appropriate non-Bismuth containing liquid antacid.
10. Use of any investigational compound within 28 days prior to the screening visit.

MO Comment: The inclusion and exclusion criteria are appropriate for the study.

5.3.4 Treatment

Upon enrollment (Visit 2, Day 0), parent's were provided with enough Nexium[®] for four weeks along with an appropriate number of single-use sachets containing an inactive granulate. Nexium[®] was provided in capsules of 2.5, 5, or 10 mg. To prepare a dose of study drug for administration, each parent was instructed to open the excipient granules sachet into a syringe or cup containing 5 mL of water. The mixture was then to be shaken or stirred and left for a couple of minutes to thicken. Next, the capsule of Nexium[®] or matched placebo was to be opened and emptied into the mixture. The mixture was to be administered before 30 minutes had elapsed. If patients were unable to tolerate the suspension, the contents of the capsule could have been mixed with 1 to 2 tablespoons of cold or room temperature applesauce (provided by the Applicant or an external service provider). Once mixed, the pellet/applesauce mixture was to be given immediately and not stored for future use.

Patients were to be treated once daily (first dose on Day 1) with Nexium[®] according to body weight obtained at enrollment (see Table 3 below for weight-based Nexium[®] doses). The weight-based doses used in this study were in the dose range of 0.5 to 1.3 mg/kg. This dose range was chosen based on comprehensive pharmacokinetic and analyses done in adults and older pediatric patients.

Each dose was to be given approximately 30 to 60 minutes before breakfast or a morning feeding. Parents were also instructed to attempt administer the study medication at the same time each day.

Table 3. Weight-based Nexium[®] dosing

Weight	Dose of Nexium [®]
3-5 kg	2.5 mg
>5-7.5 kg	5 mg
>7.5- 12 kg	10 mg

Patients who experienced symptoms of GERD during the study were to use the rescue medication provided by the Applicant. The rescue medication provided was MAALOX[®] liquid (aluminum hydroxide/magnesium 225/200 mg per 5 mL) or an equivalent, age appropriate liquid antacid.

Parents/guardians were instructed to administer the rescue medication according to the product labeling or as prescribed by the physician. The parent was instructed to contact the site if the child required rescue medication more than four times daily, so the investigator could re-evaluate the patient for symptom control and/or worsening. Rescue medication usage was documented at each study visit and daily through the Interactive Voice Response System (IVRS).

During the double-blind treatment phase, patients identified as showing symptom worsening were discontinued from the study so that they could receive other appropriate therapies.

The dose, duration, and indication for all concomitant medications were recorded in each patient's file and CRF. Medications considered necessary for the patient's safety and well-being were allowed at the discretion of the investigator.

Prohibited concomitant medications were as follows:

- Anticholinergics
- Bismuth-containing products
- Barbiturates
- Anti-convulsants
- Warfarin
- Narcotics
- Antineoplastic agents
- H2RAs
- Sucralfate
- Anti-emetics
- Prokinetics (cisapride, metoclopramide, domperidone, levosulpirida, macrolide antibiotics)
- Medications requiring the presence of gastric acid for optimal absorption (e.g., ketoconazole, digoxin, iron salts, ampicillin esters)
- Systemic corticosteroids (short courses for asthma permitted)

Treatment compliance was assessed at each visit. Parents were instructed to return the previously dispensed medication package along with any unused medication. The number of capsules returned was verified against the number dispensed.

5.3.5 Study Visits and Procedures

All study visits occurred in an outpatient setting. The study visits and related safety assessments are summarized in Table 4 below.

Table 4. Schedule of Study Assessments

	Screening	Open-label Phase		Double-blind Phase		Post-study
	Visit 1 Day -10 to 0	Visit 2 Day 0	Visit 3 Day 14±2	Visit 4 Day 28±2	Visit 5 Day 42±2	
Assessment/procedure	Screening	Enrollment	Follow-up	Follow-up	Final/early termination	Follow-up
Informed Consent	X					
Incl/Excl criteria	X	X				
Medical History	X					
Prior/Con Meds	X	X	X	X	X	X
Physical exam	X	X	X	X	X	
Vital signs	X	X	X	X	X	
Laboratory evaluation	X		X		X	
PGA		X	X	X		
Provide IVRS instructions	X					
Review IVRS responses		X	X	X	X	
Enroll in open-label phase		X				
Randomization			X			
Adverse event collection	X	X	X	X	X	X

The study consisted of a 10-day screening period (Visit 1: Day -10 to Day 0). During this screening period, patients underwent physical examination, laboratory testing, and other procedures as outlined in Study Procedures table below. Parents were also taught how to use the study’s interactive voice response system (IVRS) to report patient symptoms. Adverse events collection began during Visit 1 (Day -10 to Day 0) and continued throughout the study and the post-study follow-up period.

Using the IVRS, parents were to provide a daily rating of patient symptoms during the screening and treatment phases in each of four symptom classes—vomiting/regurgitation, irritability, supraesophageal and respiratory disturbances, and feeding difficulties. The IVRS tool was based upon the validated Orenstein’s Infant Gastroesophageal Reflux Questionnaire (I-GERQ). See the IVRS questionnaire in Table 6 below.

If parent’s missed a day of reporting symptoms, it was possible to call the IVRS to reports symptoms over the previous 48 hours. However, in order to minimize recall bias, parents could not report symptoms older than 48 hours.

In addition to noting the presence of symptoms, parents were also asked to give a once-daily assessment of symptom *severity* for each of the 4 symptoms using a 4-point scale (none (0) to severe (3)). See Table 5 below.

Table 5. Study 96, Parent and Physician Symptom Severity Assessment Scale

Severity	Score	Description
None	0	No symptoms
Mild	1	Symptoms present but not interfering with daily activities (feeding, sleeping, bathing, etc.)
Moderate	2	Symptoms present and somewhat interfering with daily activities
Severe	3	Symptoms present and greatly interfering with or preventing daily activities

Patients who passed the screening phase were enrolled into the open-label phase of the study during Visit 2 (Day 0). Investigator's ensured that all inclusion /exclusion criteria were met. Patients also underwent physical examination. In addition, laboratory results from the screening period were reviewed. Adverse events reported using the IVRS were also reviewed along with concomitant medications.

Using IVRS information along with in-person assessment, investigator's gave a Physician's Global Assessment (PGA) of the patient's GERD-related symptoms over the previous seven days. This global, 4-point severity scale was the same one used by parents, see Table 5 above.

During Visit 2 (Day 0), patients were dispensed study medication. Study drug administration began on Study Day 1.

Table 6. IVRS Symptom Patient Assessment

Rescue Medication Usage	Question	Response options
	Did your baby require any rescue medication within the last 24 hours? If yes: How many total teaspoons of rescue medication did you give your baby over that 24 hour period?	Yes or no
Symptom class	Question	Response options
Vomiting/ regurgitation	How many times did the baby spit up?	Number will be entered
	How much did the baby usually spit up?	A teaspoonful to a tablespoonful or 5-15 mL of feed; A tablespoonful to an ounce or 15-30 mL of feed; More than an ounce or >30 mL of feed
	Did the spitting up seem to be painful/uncomfortable for the baby?	Yes or no
Irritability	What was the overall severity of the spitting up?	None, mild, moderate, or severe
	Do you think the baby cried or fussed more than normal?	Yes or no
	How many hours did the baby cry or fuss?	Less than 1 hour, 1 to 3 hours, or more than 3 hours
	Did the baby cry during or after feedings?	Yes or no
Supraesophageal and respiratory disturbances	What was the overall severity of the crying or fussing?	None, mild, moderate, or severe
	Did the baby have spells of arching back during or after feeds?	Yes or no
	Did the baby have a persistent cough, without a cold, sometime during the previous 24 hours?	Yes or no
	If yes, did the coughing occur during the night?	Yes or no
	Did the baby have wheezing or labored breathing sometime during the previous 24 hours?	Yes or no
	If yes, did the wheezing or labored breathing occur during the night?	Yes or no
	Did the coughing, wheezing, or labored breathing typically occur during or following feedings?	Yes or no
What was the overall severity of the coughing, wheezing, or labored breathing?	None, mild, moderate, or severe	
Feeding difficulties	Did the baby refuse feedings even when hungry?	Yes or no

Did the baby choke or gag on a feeding?	Yes or no
Do you think the baby hiccups more than 1 hour per day?	Yes or no
What was the overall severity of the feeding difficulties?	None, mild, moderate, or severe

Study Visit 3 (Day 14±2) occurred at the end of the open-label period. Patients underwent physical examination and laboratory testing. During this visit, patients whose symptoms resolved by a pre-determined amount were randomized into the double-blind phase of the study. All other patients were discontinued from the study. Rescue medication use was recorded. Each patient's primary caregiver completed the PGCIQ. A PGA score was also calculated during this visit. Study medication (Nexium® and placebo) for the four-week, double-blind phase was dispensed.

For patients to continue into the double-blind treatment period, the Physician's Global Assessment score of patient symptomatology must have improved by at least one category when compared with baseline. In addition, the investigator must have judged that there were no severe symptoms of any duration present that might require medical intervention during the study and therefore cause the patient to be discontinued from the study. It was also recommended that there was improvement in at least one or more of the symptom classes as listed in Table 7 below.

Table 7. Study 96, Improvement Guidelines for Randomization

Symptom class	Improvement in a symptom class may be determined by any of the following (compared to baseline):
Vomiting/ regurgitation	<p>Reduction by 50% (or improvement by 1 category in frequency as noted below OR amount of vomiting/regurgitation)</p> <ul style="list-style-type: none"> • None • One to three times a day • Three to five times a day • More than five times a day <p>Improvement by 1 category (or reduction in number of vomiting/regurgitation episodes as noted above)</p> <ul style="list-style-type: none"> • A teaspoonful to a tablespoonful or 5-15 mL of feed • A tablespoonful to an ounce or 15-30 mL of feed • More than an ounce or >30 mL of feed <p>Resolution of vomiting or residual mild symptoms with no painful vomiting</p>
Irritability	<p>Cries less than 1 hour per day, does not seem irritable</p> <p>Minimal to no crying with feedings</p> <p>No arching back during or following feedings</p>
Supraesophageal and respiratory disturbances	<p>No persistent cough, wheezing, labored breathing for the last 24 hours</p> <p>No respiratory symptoms triggered by feedings</p>
Feeding difficulties	<p>No feeding refusal</p> <p>No choking or gagging with feedings</p> <p>Minimal to no hiccups</p>

Study Visit 4 (Day 28±2) occurred midway through the double-blind treatment phase. A PGA score was also calculated during this visit. Additionally, each patient underwent physical examination.

Study Visit 5 (Day 42±2) occurred at the end of the double-blind treatment phase. During this visit, patients underwent a physical examination and laboratory evaluation.

A post-study follow-up safety assessment occurred via telephone two weeks after the last dose of study drug for each patient. During this assessment, concomitant medication and adverse event data were collected.

At each visit, prior and concomitant medications were assessed and recorded in each patient's CRF. IVRS responses were also reviewed at each visit as were adverse event data.

5.3.6 Control Procedures

Randomization

Patients were randomized in blocks of four, strictly sequentially as they became eligible for entry into the double-blind treatment withdrawal phase of the study. Randomization was stratified by weight group (3-5kg, >5-7.5 kg, or >7.5-12 kg) at enrollment (Visit 2) to ensure similar treatment breakdowns in each weight group.

The randomization schedule was computer-generated. If a number or treatment was allocated incorrectly, no attempt was made to remedy the error once study medication had been dispensed in the double-blind portion of the study.

Placebo Control

Each placebo capsule was matched to the appropriate dose Nexium[®] capsule. The contents of placebo capsules were mixed in the excipient suspension or mixed with applesauce similar to the active drug. Both the active and placebo capsules were manufactured by AstraZeneca R&D in Mölndal Sweden. All of the excipient granules in sachet were manufactured by AstraZeneca Operations in Södertälje, Sweden.

Blinding

In the double-blind portion of the study, all study site personnel were blinded to the patient treatment assignment. The treatment codes were to be broken by an investigator only in cases of medical emergency. The investigators were to document and report to AstraZeneca any breaking of the blind. AstraZeneca reserved the right to break the blind for serious adverse events requiring expedited reporting to regulatory authorities. There were no reported episodes of breaking the blind prior to locking the data.

5.3.7 Primary Efficacy Endpoint

The primary efficacy variable for this study was the time from randomization to discontinuation due to symptom worsening in the randomized, treatment-withdrawal phase of the study. At each visit, the Investigator made a global assessment of the patient's symptoms and compared this PGA category to the patient's presentation at randomization. If the PGA had worsened by at least one category, the patient was discontinued from the study. If the PGA remained unchanged, it was up to the Investigator's discretion of whether the patient should be discontinued due to the severity of symptoms. See Table above 5 and following text for PGA score assessment details.

5.3.7 Secondary Efficacy Endpoint(s)

1. Time to study discontinuation due to any cause.
2. Proportion of treatment successes at the end of the 4-week double-blind treatment phase.

Treatment success was defined as patients who maintained symptom throughout the double-blind phase, without discontinuing from the study for any reason.

3. Parent's assessment of patient's symptoms grouped by 4 classes.
 - a. Vomiting/regurgitation
 - i. Frequency
 - ii. Volume
 - b. Irritability
 - i. Frequency of irritability/fussing/crying symptoms
 - ii. Presence or absence of irritability/fussing/crying symptoms during or following feedings
 - iii. Back arching assess as present or absent during or following feedings
 - c. Supraesophageal and respiratory disturbances
 - i. Presence or absence of cough and whether it occurred during or following feedings
 - ii. Presence or absence of wheezing/stridor and whether it occurred during or following feedings and whether it occurred at night
 - d. Feeding difficulties
 - i. Food refusal
 - ii. Choking with food/drink
 - iii. Hiccups for >1 hour per day

See Table 5 above for parent severity assessment scale.

4. Physician's global assessment (PGA) of patient's GERD-related symptoms over the previous 7 days.

See Table 5 above for physician severity assessment scale.

5.3.8 Statistical Information

The sample size for Study 96 was determined based on an assumption of 80% active and 40% placebo success rates. Using Fisher's exact test, 90% power to detect this difference, at a 2-sided significance level of 5%, would require 76 patients (38 per treatment arm).

The intent-to treat (ITT) population was used for the primary analysis. The ITT population for the analysis of the primary endpoint included all randomized patients with available data for a particular endpoint and who took at least 1 dose of the study medication during the double-blind phase. For the open-label analyses, the ITT population included all patients who enrolled in the open-label phase, had available data for a particular endpoint, and took at least 1 dose of study medication.

The primary endpoint of time from randomization to discontinuation due to symptom worsening during the double-blind phase of the study was analyzed using the Cox proportional hazards model, adjusting for treatment. All formal analyses were conducted at the 2-sided 5% significance level.

Because of the time windows allowed around the protocol-specified visits, it was possible for patients to be in the double-blind portion of the study for longer than 28 days. To control the size of the risk sets in the Kaplan-Meier plots and Cox proportional hazards regression, the Applicant decided that any patient with an uncensored time to discontinuation greater than 28 days would have that time truncated to 28 days. And any patient completing the double-blind phase without experiencing an event would have their time right-censored at 28 days.

No adjustments for multiplicity were made in the analysis of the secondary endpoints. To analyze the time from randomization to discontinuation due to any reason (secondary endpoint number 1) and the proportion of treatment successes at the end of the double-blind phase (secondary endpoint number 2) a Chi-square test was used to compare treatment groups.

The presence and severity of symptoms reported daily by the parent/guardian of the child (secondary endpoint number 3) and the Physician's Global assessments (secondary endpoint number 4) during the open label phase were summarized descriptively. While the Cochran-Mantel-Haenszel test (stratifying by baseline score) was used to assess treatment differences in the end of study Physician Global Assessment (secondary endpoint number 4) as compared with PGA upon entering the double-blind phase of the study.

Because there was only one clinical study in this submission, all efficacy results are present in Section 6, Review of Efficacy, below.

5.3.9 Protocol Amendments

The protocol was finalized 14 November 2006.

Protocol Change 1 was finalized 16 March 2007. This date is before the study began. The change was introduced for the following primary reasons:

1. To clarify the inclusion criteria and specify that patients with GERD and suspected food allergies must first undergo a trial of an elimination diet to see if symptoms resolve before being allowed to enroll in the study.
2. To add text to clarify that increased rescue medication, regardless of whether or not symptoms worsen, during the double-blind treatment phase should not be permitted. Instead, these patients should be removed from the study.

Protocol Change 2 was finalized 11 June 2007. This date is after the study began, but before study completion. The change was introduced for the following primary reason:
To restrict the analysis of the stool hemocult to the study center only.

Protocol Change 3 was finalized 09 November 2007. This date is after the study began, but before study completion. The change was introduced for the following reason:
To clarify that daily entry into the Interactive Voice Response System by parents is a recommendation and not a requirement for study participation.

Local Protocol Amendments in Germany (15 November 2006) and France (09 November 2007) were introduced to allow patients to begin study medication during Visit 2 before results of screening labs from Visit 1 were available.

An additional Local Protocol Amendment in France was finalized 27 February 2007. The Amendment was introduced per the request of the French Regulatory Authorities and included excluding the following groups:

1. Patients with known hypersensitivity to substituted benzimidazoles.
2. Patients taking atazanavir.
3. Patients with known intolerance to fructose, with glucose or galactose malabsorption syndrome or with sucrase-isomaltase deficiency.

6 Review of Efficacy

Study 96, the single efficacy study submitted in support of this supplement, (b) (4)



(b) (4)

6.1 Indication

The Applicant is proposing that Nexium® receive an indication for the short-term treatment of GERD (b) (4)

6.1.1 Methods

A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, treatment-withdrawal study was used to evaluate the safety and efficacy of once-daily treatment with Nexium® in infants ages 0 to 11 months for reducing the signs and symptoms of infantile GERD. The primary efficacy endpoint for the study was the time to study discontinuation due to symptom worsening during the double-blind treatment phase.

Section 5.3 contains a discussion of the study; Section 6 contains the study results.

6.1.2 Demographics

Baseline demographic characteristics are summarized below in Table 8. Overall, there were more males than females in both treatment phases. Most patients were White and were >5 to 7.5 kg and therefore received 5 mg esomeprazole once daily.

The patients who entered the double-blind treatment phase were not significantly different from the open-label patients as a whole. That is, the RCT population was not significantly older or larger (weight, height, head circumference) than the open-label population.

Overall in the RCT population, the esomeprazole and placebo groups did not vary significantly with regard to demographic characteristics. In both treatment groups, the majority of patients were White race (90% Nexium® and placebo) with a mean age of approximately 5 months. While the number of non-white patients was small, there is no reason to believe efficacy would be different in these groups.

Table 8. Study 96, Patient Demographics

		RCT Population		
Demographic Subgroup	Open Label (n=98)	Esomeprazole (n=39)	Placebo (n=41)	Total (n=80)
Weight Group (n,%)				
3 kg - 5 kg	11 (11%)	3 (8%)	5 (12%)	8 (10%)
>5kg - 7.5 kg	61 (62%)	26 (67%)	22 (54%)	48 (60%)
>7.5 -12 kg	26 (27%)	10 (26%)	14 (34%)	24 (30%)
Weight (kg) (n,%)				
Mean (SD)	6.6 (1.5)	6.9 (1.6)	6.7 (1.4)	
Median (min,max)	7 (3,11)	7 (4,11)	7 (4,10)	
Height (cm)				
Mean (SD)	64.2 (5.8)	64.6 (5.4)	64.5 (6.0)	
Median (min,max)	64 (49,75)	64 (57,75)	64 (49,74)	
Head Circumference (cm)				
Mean (SD)				
Median (min,max)				
Sex (n,%)				
Male	63 (64%)	30 (76%)	27 (65%)	57 (71%)
Female	35 (35%)	9 (23%)	14 (34%)	23 (29%)
Race (n,%)				
White	86 (88%)	35 (90%)	37 (90%)	72 (90%)
Black	4 (4%)	2 (5%)	0	2 (4%)
Asian	3 (3%)	1 (3%)	1 (2%)	2 (4%)
Other	5 (5%)	1 (3%)	3 (7%)	4 (8%)
Age (months) (n,%)				
Mean (SD)	4.8 (2.9)	4.9 (2.6)	4.9 (3.2)	
Median (min,max)	4 (1,11)	4 (1,11)	3 (1,11)	

To fully understand the information provided in the demographics table, it is important to see how Study 96 patients compare with standardized growth parameters for children in the USA (the proposed marketing country). Study 96 patients were smaller, on average, than the general population as evidenced by growth parameters all less than the 50th percentile. While the mean values were low, the study was successful in recruiting a wide range of patient sizes with ranges for all parameters including patients less than the 5th and greater than the 95th percentiles. See Table 9 below.

Table 9. Standardized Growth Parameters

(derived from the US CDC growth charts (2000))

Growth Parameter	RCT POPULATION		
	Open Label (n=98)	Esomeprazole (n=39)	Placebo (n=41)
Percentile length for age			
Mean (SD)	44.0 (31.0)	42.4 (31.4)	46.7 (33.2)
Range	0, 100.0	1.0, 95.5	0, 100.0
Percentile weight for age			
Mean (SD)	33.5 (29.9)	35.0 (31.9)	35.7 (30.3)
Range	0, 100.0	1.0, 99.1	0.6, 98.1
Percentile weight for length			
Mean (SD)	37.0 (31.9)	42.3 (31.2)	37.7 (33.4)
Range	0, 100.0	0, 99.5	0, 100.0
Percentile head circumference			
Mean (SD)	43.9 (31.2)	45.6 (35.2)	44.3 (27.3)
Range	0, 99.4	0.5, 99.4	0.1, 98.9

Patients were eligible for inclusion into the study if they had a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically-proven GERD. Most patients underwent at least one diagnostic study (pH probe, x-ray, endoscope, or other) in the work-up of a possible GERD diagnosis (67% of open-label patients and 70% of randomized patients). A total of 20 (20%) study patients had endoscopy performed. Of these patients, only six were found to have erosive esophagitis.

MO Comment:

Endoscopy at the end of the study was not required (even for patients who had erosive esophagitis on endoscopy at the beginning of the study). This is a limiting factor in demonstrating the effectiveness of Nexium® in healing erosive esophagitis.

6.1.3 Subject Disposition

In Study 96, 103 patients were screened for participation. Of these patients, 98 were enrolled in the open-label phase of the study. Of these patients, 80 were randomized into the double-blind, treatment-withdrawal phase of the study. During this phase, an additional 27 patients discontinued from the study. Most patients were discontinued due to lack of therapeutic response.

Table 10. Study 96, Open-Label Screen Failures

Screened for study entry	103
Screen failures	5
Discontinuation by parent/guardian	4
Non-compliance	1

Table 11. Patient Disposition

	OPEN-LABEL N=98 (%)	RCT POPULATION N=80	
		Eso N=39	Placebo N=41
Disposition			
Enrolled in open-label phase	98 (100%)		
Discontinued from open-label phase	18 (18%)		
Adverse event	5		
Lack of therapeutic response	9		
Withdrew consent	4		
Entered randomized, double-blind phase	80 (82%)	39 (100.0)	41 (100.0)
Discontinued from randomized phase		10 (25.6)	17 (41.5)
Lack of therapeutic response		8	17
Adverse event		2	0
Completed the Study		29 (74.4)	24 (58.5)

There were 8 major protocol deviations during the open-label period. Two were due to non-compliance with study medication, four were due to concomitant use of prohibited medication, and two were due to the patient receiving the wrong dose of the study medication.

In the double-blind phase, 3 patients experienced major protocol deviations. One patient was incorrectly randomized according to weight group. The patient was randomized to the placebo group; therefore, there is no potential impact from this violation. Another patient was randomized despite a lack of PGA score improvement from baseline. The other major protocol deviation was caused by a patient having a compliance of less than 80%.

Overall, treatment compliance throughout both phases of the study was quite high. In the double-blind treatment phase of the study, compliance in each treatment group was greater than 97%.

MO Comment: The protocol deviations had the potential for very little impact on the efficacy analysis.

Table 12. Study 96, Treatment Compliance

Study Period	Compliance	Open-label	Double-blind Treatment	
			Esomeprazole n= 39	Placebo n=41
Open Label	<80%	1 (1%)		
	80%-120%	96 (98%)		
	>120%	1 (1%)		
	Unknown	0		
Double-blind	<80%		1 (3%)	0
	80%-120%		38 (97%)	41 (100%)
	>120%		0	0
	Unknown		0	0

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of this study was the time from randomization to discontinuation due to symptom worsening in the randomized, treatment-withdrawal phase of the study. At each visit, the Investigator made a global assessment of the patient's symptoms and compared this PGA category to the patient's presentation at randomization. If the PGA had worsened by at least one category, the patient was discontinued from the study. If the PGA remained unchanged, it was up to the Investigator's discretion as to whether the patient should be discontinued due to the severity of symptoms.

A Cox proportional hazards analysis of the primary endpoint indicates a 31% lower risk of discontinuing due to symptom worsening in the esomeprazole group compared with placebo (hazard ratio=0.69). However, this difference was not statistically significant (p=0.2751).

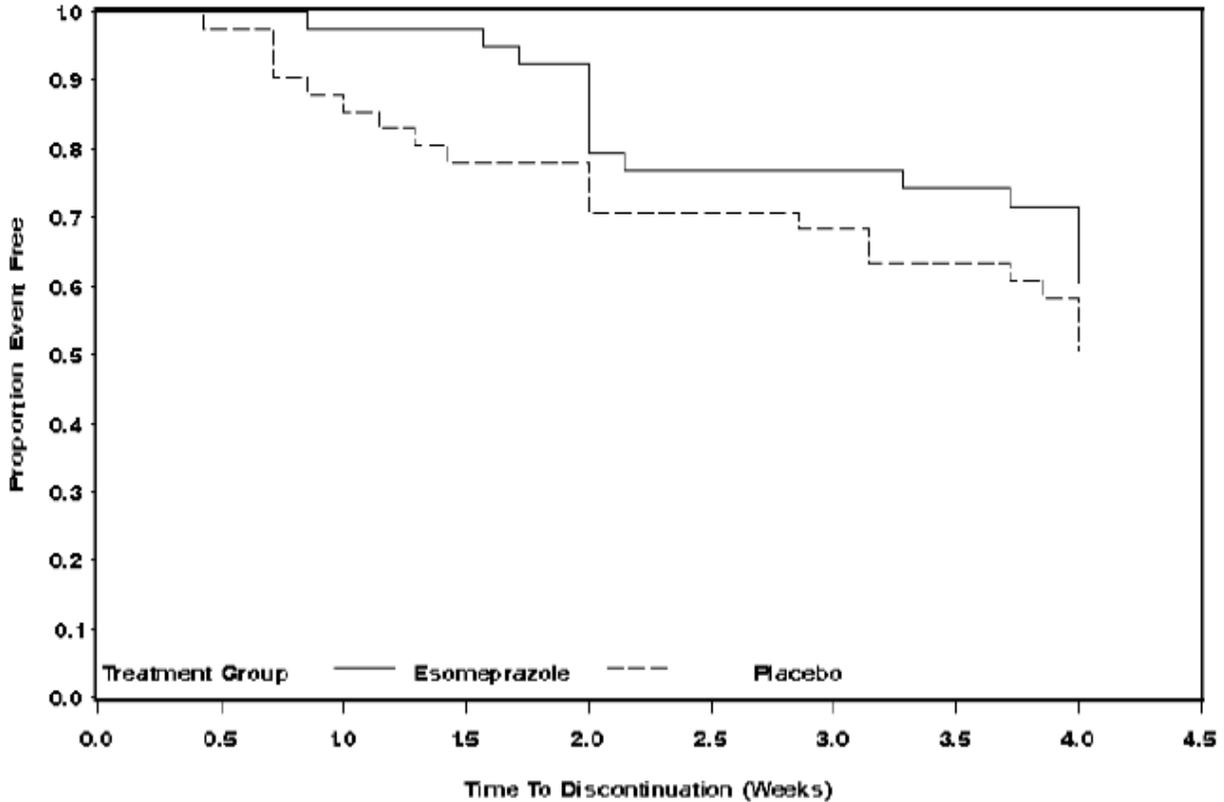
Table 13. Analysis of Primary Endpoint

Hazard ratio	95% CI	p-value
0.69	0.35 to 1.35	0.2751

A Kaplan-Meier plot of the time-to-withdrawal shows that the discontinuation events in both the active and placebo groups were similar. See Figure 2 below.

Figure 2. Kaplan-Meier plot of time to discontinuation due to symptom worsening

(reproduced from Applicant submission, clinical Study Report, p. 67)



An additional pre-specified Cox proportional hazards analysis was done adjusting for treatment and weight group. This analysis revealed a 30% lower risk of discontinuing due to symptom worsening in the esomeprazole group compared with the placebo group (hazard ratio=0.70). However, as with the primary analysis, this difference was not statistically significant (p=0.296).

Table 14. Total Discontinuations from Study 96

Treatment	Patients Discontinuing Due to Symptom Worsening		
	N	%	N
Esomeprazole	39	38.5 %	15
Placebo	41	48.8 %	20

MO Comment:

(b) (4)

(b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

Four secondary endpoints were defined *a priori* as described in Section 5.3.1 above.

(b) (4)

1. Time to study discontinuation due to any cause.

The result for the analysis of the first secondary endpoint was identical to the result of the primary endpoint analysis. This occurred because the only two patients who discontinued the study for adverse events (AEs) were also found to have symptom worsening.

2. Proportion of treatment successes at the end of the 4-week double-blind treatment phase.

Patients were classified as treatment success if they maintained the improvement in their symptoms throughout the double-blind phase, without reaching a threshold for discontinuation or discontinuing for any reason. (b) (4)

Patients were considered treatment responders if they maintained their improvement in symptoms throughout the study without reaching a threshold for discontinuation. See Table 15 below.

Table 15. Proportion of Treatment Successes

Treatment	Successes		Summary Statistics	
	%	N	Odds Ratio	1.524
Esomeprazole (N=39)	62%	24	95% CI	0.626 to 3.709
Placebo (N=41)	51%	21	p-value	0.3524

3. Parent's assessment of patient's symptoms grouped by 4 classes—vomiting/regurgitation, irritability, supraesophageal and respiratory disturbances, and feeding difficulties.

Mean severity scores were calculated based on parent IVRS responses for each of the four symptom classes. Symptoms were assessed by parents on a scale of 0 (none) to 3 (severe symptoms present, and greatly interfering with or preventing daily activities). For scoring details see Table 5 in Section 5.3.6 above.

Table 16 below reveals that from screening to Week 2 (end of open-label period) the mean symptom scores in each of the four symptom classes decreased.

MO Comment: (b) (4)

Table 16. IVRS Summary of mean patient symptom severity scores, Open-Label

Symptom Class	Screening n=84*	Week 2 n=79^	Change
Vomiting/Regurgitation	1.42	1.00	-0.42
Irritability (fussing/crying)	1.50	1.02	-0.48
Supraesophageal/respiratory disturbances (coughing/wheezing/labored breathing)	0.54	0.44	-0.10
Feeding Difficulty	1.16	0.83	-0.33

*n=83 for Feeding Difficulty at screening, ^ n=78 for Feeding Difficulty at Week 2

Table 17. IVRS Summary of mean patient symptom severity scores, Double-blind

Symptom Class	Treatment Group	Screening	Change
Vomiting/Regurgitation	Eso *	0.89	-0.04
	Placebo^	0.86	-0.09
Irritability (fussing/crying)	Eso	1.0	-0.06
	Placebo	0.80	-0.19
Supraesophageal/respiratory disturbances (coughing/wheezing/labored breathing)	Eso	0.32	-0.12
	Placebo	0.35	-0.03
Feeding Difficulty	Eso	0.75	-0.09
	Placebo	0.67	-0.10

* n=37, ^ n=40

MO Comment:

(b) (4)

(b) (4)

4. Physician’s global assessment (PGA) of patient’s GERD-related symptoms over the previous 7 days.

Investigators completed the PGA at Visits 2 (Day 0, enrollment visit) through 5 (Final/early termination visit). To complete the PGA, providers responded to the following instruction: “Please provide your overall clinical impression of the patient’s GERD-related symptoms over the last 7 days 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).”

During the open-label period PGA scores improved overall. From Visit 2 to Visit 3, the percentage of patients with none or mild symptoms increased from 7.4% to 79%. The percentage of patients with moderate or severe symptoms decreased from 93% to 21%. See Table 18 below.

Table 18. Summary of PGA Scores, Open-Label, n=95

PGA	Visit 2 (Study Day 0)	Visit 3 (Study Day 14)	Change
None	0	11%	↑11%
Mild	7%	68%	↑61%
Moderate	74%	16%	↓58%
Severe	19%	5%	↓14%

During the double-blind treatment period, patient symptoms as measured by PGA scores worsened overall. Because non-responders were not continued into the double-blind treatment phase, there were no patients with severe symptoms at the beginning of this phase. In addition, only 12.8% of esomeprazole patients and 9.8% of placebo patients had moderate symptom PGA scores. However 38.4% of esomeprazole patients and 46.3% of placebo patients had moderate or severe symptom PGA scores recorded as their worst post-randomization assessment scores. See Table 19 below.

Table 19. Summary of PGA Scores, Double-blind

PGA	Esomeprazole (n=39)		Placebo (n=41)	
	Visit 3 (Randomization)	Worst post-randomization assessment	Visit 3 (Randomization)	Worst post-randomization assessment
None	13 %	10%	10%	5%
Mild	74%	51%	81%	49%
Moderate	13%	26%	10%	32%
Severe	0	13%	0	15%

6.1.6 Other Endpoints

There were no other efficacy endpoints presented related to the efficacy of esomeprazole in the target population.

6.1.7 Subpopulations

All subpopulation analyses were done after database lock and unblinding. These analyses were not pre-planned and no adjustments have been made for multiplicity. Therefore, these analyses should be interpreted as exploratory and treated with caution.

Primary endpoint analyses were completed by the Applicant for the following subpopulations: age < 6 months, age ≥6 months, pre-treated for GERD, not pre-treated for GERD, verified GERD, unverified GERD. All p-values for these subpopulations were greater than the primary analysis p-value of 0.2751 except for the p-value associated with the subpopulation of patients with an unverified GERD diagnosis. The diagnosis of GERD could have been verified by any modality (e.g. x-ray, endoscope, pH probe, etc.). For this subpopulation of 18 esomeprazole patients and 18 placebo patients, the p-value was significant at 0.0145. Subpopulation analyses of the primary endpoint were also conducted for race and sex by Dr. Freda Cooner, statistical reviewer. No differences were seen.

Table 20. Primary endpoint, subgroup analysis

Subgroup [n(eso/placebo)]	Hazard Ratio	Confidence Interval	p-value
Age < 6 months (26/27)	0.68	0.31 - 1.50	0.3404
Age ≥ 6 months (13/14)	0.68	0.19 - 2.40	0.5455
Pre-treated for GERD (16/17)	0.79	0.30 – 2.05	0.6273
Not pre-treated for GERD (23/24)	0.60	0.23 – 1.54	0.2885
Verified GERD (21/23)	1.39	0.56 – 3.46	0.4799
Unverified GERD (18/18)	0.24	0.08 – 0.75	0.0145
Vomiting episodes ≥ 5	0.62	0.23 – 1.72	0.3591
Vomiting episodes <5	0.90	0.32 – 2.56	0.8420
Vomiting Med to large Volume	0.54	0.19 – 1.58	0.2623
Vomiting None-Small Volume	0.90	0.34 – 2.42	0.8353
Crying ≥1 episodes/hour	0.48	0.19 – 1.22	0.1231
Crying <1 episode/hour	1.27	0.39 – 4.18	0.6885
Crying ≥1 episodes/hour AND Vomiting Medium to large volume	0.31	0.09 – 1.03	0.0564

MO Comment:

(b) (4)

(b) (4)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dosing recommendations for patients aged less than one year will be provided in the labeling. (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable, Study 96 did not show efficacy.

6.1.10 Additional Efficacy Issues/Analyses

Currently, no PPI is labeled for the treatment of patients aged less than one year for the treatment of GERD. Pharmacokinetic and pharmacodynamic data in this age group shows that the medication does, in fact, raise gastric pH. However, this has failed to translate into a clinical reduction in GERD symptoms. Given this information, it is possible to infer that clinical trials have not shown efficacy due to a lack of correct endpoint selection, patient population, and/or trial design. For further discussion, see Section 1.2.

7 Review of Safety

Overall, Nexium[®] was found to be relatively safe and well-tolerated in patients age 0 to 11 months, inclusive. There were no deaths seen in either the clinical or PK/PD studies. There were no clinically important findings or trends noted in hematology, clinical chemistry, urinalysis, vital signs, or physical examinations. There was a difference in the number of serious adverse events (SAEs) reported in the Nexium (3 events) and placebo groups (0 events) in the clinical study. However, these numbers were very small. Subjects in the PK/PD studies did not reports any SAES during the study period.

Adverse events reported during the studies were similar between treatment groups and not unexpected for the target population.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from primary efficacy Study 96. This study provided the primary safety information given that it was the only double-blind, placebo controlled efficacy study submitted in support of this Application. Supportive safety information was obtained from the pharmacokinetic studies SH-NEC-0001 and SH-NEC-0002.

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 11.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from three studies: Efficacy Study 96, Pharmacokinetic Study NEC-1, and Pharmacokinetic Study NEC-2. The two pharmacokinetic studies were seven or eight days in length with safety populations totaling 76 patients. Efficacy Study 96 provided the majority of the safety data given that it contained a double-blind treatment portion which allowed for comparisons between esomeprazole and placebo groups.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination including growth parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population. A total of 98 patients from Study 96, 50 patients from Study NEC-1, and 26 patients from Study NEC-2 were included in the safety populations.

Prior to the submission of this supplement, the Applicant submitted the results of a 1-month oral toxicity study in neonatal rats and a 3-month oral toxicity study in neonatal dogs. These studies did not reveal any unexpected toxicity.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The doses and durations of esomeprazole studied were adequate to assess safety and to support the proposed duration of “up to six weeks.” Study 96 had a duration of six weeks and a two week study follow-up period. During the open-label portion of the study, patients received esomeprazole for a mean duration of 14.3 days. During the

double-blind treatment phase, patients received esomeprazole for a mean duration of 24.6 days. PK/PD studies NEC-1 and NEC-2 were of a significantly shorter duration, 7 or 8 days.

Table 21. Extent of Exposure (Days), Study 96

Study period	Open-label	Double-blind	
	n=98	Esomeprazole n=39	Placebo n=41
Open-label			
Mean (SD)	14.3 (2.6)	14.3 (1.7)	14.9 (1.7)
Median	14	14	14
Range	4 to 21	11 to 19	12 to 19
Double-blind			
Mean		24.6 (8.0)	21.7 (9.5)
Median		27	27
Range		5 to 42	2 to 30

The demographic make-up of the pooled safety population was adequate. Most patients were white race and male. For further information regarding Study 96 patient demographics, see Section 6.1.2.

7.2.2 Explorations for Dose Response

All patients in primary efficacy Study 96 were dosed according to weight to receive 0.5 mg/kg to 1.3 mg/kg. Therefore no dose response safety analyses were performed.

In PK Study NEC-1, patients were treated with esomeprazole 0.25 mg/kg or 1.0 mg/kg. No difference in AE occurrence was noted between dose groups.

Exposure in patients receiving 0.5 mg/kg/day was lower than in patients receiving 1.0 mg/kg/day and in older patients taking up to 40 mg/day. However, the exposure in patients taking 1.0 mg/kg/day was similar to that seen in older populations. In efficacy Study 96, patients were given 0.5 to 1.3 mg/kg/day this dose range was adequate to assess both safety and efficacy at different levels of exposure.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this NDA. See section 4.3 for information regarding previously submitted juvenile animal studies.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

Nexium® is extensively metabolized by the cytochrome P450 enzymes. Pediatric patients less than 2 years of age show increased clearance (CL/F) with age.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Proton-pump inhibitors are a well-known drug group. Like other PPIs, esomeprazole inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, iron salts, and digoxin). The concomitant use of these medications was prohibited during the study. See Section 5.3.1 for the full list of prohibited concomitant medications.

7.3 Major Safety Results

The major safety data regarding the use of esomeprazole in patients less than one year of age are provided by Study 96. This study contained a double-blind treatment phase, which allowed for the comparison of adverse event data between patients taking esomeprazole and patients taking placebo. During the double-blind treatment period, 59% of esomeprazole patients experienced adverse events compared with 66% of placebo patients. However, all SAEs and AEs leading to discontinuations were experienced by esomeprazole patients. Specifically, 8% of esomeprazole patients experienced SAEs and 5% experienced discontinuations due to AEs compared with 0% of placebo patients.

Table 22. Summary of Study 96 Safety Results

	Open-label	Double-blind	
	n=98	Esomeprazole n=41	Placebo n=39
Any Adverse Event	47 (48%)	23 (59%)	27 (66%)
Serious Adverse Event (SAE)	4 (4%)	3 (8%)	0
Discontinuation due to Adverse Event (DAE)	5 (5%)	2 (5%)	0
Deaths	0	0	0

7.3.1 Deaths

There were no deaths during any phase of this study.

7.3.2 Nonfatal Serious Adverse Events

Study 96, Open-Label Period

The open-label period at the beginning of the study was two weeks long. A total of 98 patients were enrolled in this period and all patients were treated with esomeprazole in weight based doses of 2.5 mg, 5 mg, or 10 mg per day. During this portion of the study, 4 patients (4.1%) experienced serious adverse events—failure to thrive, rotavirus infection, recurrent urinary tract infection, and chlamydia pneumonia. Details of these serious adverse events are described below.

Patient E2001002 (5mg/day)

This seven month old female patient with a past medical history of failure to thrive (FTT), cranial trauma, and acute gastroenteritis received open-label medication 24 July 07 to 07 August 07. The patient was not randomized into the double-blind treatment period. (b) (6) days after stopping treatment, the patient was hospitalized ((b) (6)) for continued FTT.

Patient E3008001 (10 mg/day)

This 10 month old male with a past medical history of patent ductus arteriosis received esomeprazole 12 January 08 to 25 January 08. After (b) (6) days on the study drug, the patient began to have symptoms of vomiting and diarrhea and was admitted to the hospital on (b) (6) for presumptive rotavirus infection. On 25 January 08, the patient was prematurely discontinued from the open-label portion of the study.

Patient E4002012 (5 mg/day)

This three month old male with a past medical history of recurrent urinary tract infections (UTI) received five days of open-label esomeprazole before he started having symptoms of a recurrent UTI. The patient was admitted to the hospital and symptoms resolved after seven days. The patient subsequently completed both the open-label and double-blind phases of the study.

Patient 4005006 (5 mg/day)

This three month old male with a past medical history of recurrent pneumonia started open-label therapy on 26 February 08. After five days of therapy, the patient began having symptoms of coughing and wheezing. On 3 March 08, the patient was diagnosed with chlamydia pneumonia. The episode resolved and the patient continued into the double-blind treatment phase. Fifteen days into the double-blind treatment phase, the patient began having pneumonia symptoms again. The patient was subsequently diagnosed with a second case of chlamydia pneumonia.

Study 96, Double-blind Period

The double-blind period of the study was four weeks in length. A total of 80 patients were randomized into the double-blind treatment phase. Patients were treated with esomeprazole in weight based doses of 2.5 mg, 5 mg, or 10 mg per day or matched placebo. During this portion of the study, 3 patients (7.7% of patients randomized to the esomeprazole group) experienced serious adverse events. All patients experiencing

SAEs were in the esomeprazole treatment group. Details of these serious adverse events are described below.

Patient E1018001 (esomeprazole 5 mg/day)

SAE 1: RSV Bronchiolitis

SAE 2: Bronchospasm

SAE 3: Poor Peripheral Circulation

This 4 month old male, with a past medical history of eczema, started open label esomeprazole on 12 January 08. The patient was randomized to double blind study drug on 25 January 08 and discontinued the study drug on 07February08 due to worsening GERD symptoms. (b) (6) days after the last dose of double blind study drug, the patient began experiencing bronchiolitis symptoms of congestion, cough, and bronchospasm (wheezing). These symptoms worsened and were accompanied by signs of poor peripheral circulation, resulting in an overnight hospital admission. The patient was hospitalized for one day.

Patient E2002005 (esomeprazole 2.5 mg/day)

This 3 month old female with a past medical history of vomiting, acute diarrhea, bronchiolitis, and rhinopharyngitis began having vomiting and diarrhea began before the open-label phase. During the double-blind phase, the patient was discontinued from the study drug due to worsening GERD symptoms.

Patient E3005001 (esomeprazole 5 mg/day)

This 6 month old male with no past medical history completed the open-label and double-blind phases of the study. On the day of the last dose of study drug, the patient had an episode of apnea lasting 10 to 30 seconds. The patient was hospitalized for two days. There were no further episodes of apnea.

Study NEC-1

There were no SAEs reported during this study.

Study NEC-2

During Study NEC-1, no SAEs occurred during the 7-day treatment period. However, one SAE occurred during the 14-day follow-up period.

Patient 4

This 5 week old male born at 33 weeks gestation was noted to be lethargic with partial refusal of feedings on day 10 of the 14 day follow-up period. The patient was seen by a provider and became flaccid and blue. The baby was oxygenated and admitted to a pediatric intensive care unit and was diagnosed eventually diagnosed with pertussis. The patient completed the follow-up period.

Table 23. Summary of Serious Adverse Events, Study 96

Dose (mg)	Preferred Term	Days from start of phase to SAE	Investigator's Relatedness Assessment
Open-label			
5	Failure to thrive	18	Not related
10	Rotavirus infection	13	Not related
5	Recurrent UTI	5	Not related
5	Chlamydia pneumonia ^a	5	Not related
Double-blind			
5	RSV bronchitis, bronchospasm, poor peripheral circulation	16	Not related
2.5	Gastroenteritis	-16 ^b	Not related
5	Apnea	29	Not related
5	Chlamydia pneumonia	16	Not related

^a The same patient experienced different cases of Chlamydia pneumonia, one in the open-label phase, one in the double-blind phase.

^b The episode of gastroenteritis started before the open-label phase and continued into double-blind phase.

MO Comment:

The adverse events reported are not unexpected in the target population (neonates and infants). The investigator's assessment of relatedness seems appropriate given that most SAEs were infectious. The biologic plausibility of PPIs causing infection is unlikely. In addition, there was no clear association between dose and onset of SAE. However, the fact that no SAEs occurred in placebo during the double-blind phase does make it necessary to continue to monitor this trend in future studies.

The 7/8 day PK/PD studies involved 76 patients in the target age group all receiving esomeprazole. Of these patients, none experienced a SAE. In contrast, 6 (6%) of the 98 patients who received esomeprazole in Study 96 experienced a SAE. Study 96 was six weeks in length and this raises the concern that prolonged use of esomeprazole may be associated with SAEs.

7.3.3 Dropouts and/or Discontinuations

During Study 96, five patients discontinued during the open-label period. At the end of the open-label period an additional 18 patients were not allowed to enter the double-blind treatment phase due to symptom worsening or failure to improve by a pre-specified amount. During the double-blind treatment phase, two patients were discontinued from the study due to adverse events.

Table 24. Discontinuations due to Adverse Events, Study 96

Dose (mg)	Preferred Term	Days from start of phase to discontinuation
Open-label Phase		
5	Abdominal pain	6
5	Otitis Media, Sinusitis	21
5	Failure to thrive	15
10	Rotavirus infection	14
2.5	Respiratory syncytial virus (RSV)	10
Double-blind Phase		
5	Abdominal pain, vomiting	8
10	Gastroenteritis	9

MO Comment:

During the double-blind portion of the study, all discontinuations due to adverse events occurred in patients taking esomeprazole. This suggests that the use of esomeprazole may be associated with adverse events serious enough to lead to discontinuation. Further study is needed given the relatively small number of randomized patients.

During Study NEC-1, one patient discontinued due to an adverse event. The patient began having extreme irritability on Day 1 and was discontinued from the study on Day 4. The patient was randomized to the 0.25 mg/kg treatment group. There were no discontinuations due to adverse events in Study NEC-2.

7.3.4 Significant Adverse Events

There were no other significant adverse events in Study 96, Study NEC-1, or Study NEC-2 other than SAEs and AEs associated with discontinuations.

7.3.5 Submission Specific Primary Safety Concerns

A review of safety information from clinical trial and post-marketing use of esomeprazole in other age groups has not prompted any submission-specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported adverse events during the double-blind treatment period were in the System Order Classes of Infections and Infestations. These type of disorders described are known to be relatively common among all infants less than one year of age. Events were considered common if they occurred in more than one patient.

Table 25. Common Adverse Events, Study 96 Double-blind Treatment Phase

Preferred Term	Double-blind randomized treatment [n (%)]	Placebo	Total
	Esomeprazole (n=39)	Placebo (n=41)	Total (n=80)
Patients with any adverse event*	23 (59.0)	27 (65.9)	50 (62.5)
Upper respiratory tract infection	16 (41.0)	10 (25.6)	26 (32.5)
Pyrexia	5 (12.8)	3 (7.3)	8 (10.0)
Cough	3 (7.7)	4 (9.8)	7 (8.8)
Diarrhea	4 (10.3)	2 (4.9)	6 (7.5)
Ear infection	4 (10.3)	2 (4.9)	6 (7.5)
Bronchitis	3 (7.7)	2 (4.9)	5 (6.3)
Constipation	1 (2.6)	4 (9.8)	5 (6.3)
Teething	3 (7.7)	2 (4.9)	5 (6.3)
Vomiting	2 (5.1)	2 (4.9)	4 (5.0)
Flatulence	2 (5.1)	1 (2.4)	3 (3.8)
Rash	2 (5.1)	1 (2.4)	3 (3.8)
Pharyngolaryngeal pain	2 (5.1)	0	2 (2.5)

* Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than 1 preferred term are counted once in each of those preferred terms.

During Study NEC-1, 9 patients (20.9%) ages 1-1, inclusive, months experienced AEs. These nine patients experienced a total of 11 AEs. The incidence of AEs was similar between dosage groups. See Table 26 below.

Table 26. Study NEC-1, Adverse Events by dosage group

System Organ Class Preferred Term	Esomeprazole 0.25mg/kg ≤1Year (n=22)	Esomeprazole 1.0 mg/kg ≤1Year (n=21)
	<i>Total no. of subjects with AE:</i>	4
Infections and infestations	1	1
Nasopharyngitis	0	1
Urinary tract infection	1	0
Blood and lymphatic system disorders	0	0
Neutropenia	0	0
Psychiatric disorders	1	2
Irritability	1	2
Respiratory, thoracic and mediastinal disorders	0	1
Nasal congestion	0	1
Gastrointestinal disorders	1	1
Constipation	0	0
Regurgitation of food	0	1
Vomiting	1	1
Skin and subcutaneous tissue disorders	1	1
Eczema	1	0
Rash	0	1

During Study NEC-2, a total of 17 AEs were reported by a total of 10 (38.5%) patients. The most commonly reported AES were in the gastrointestinal disorders system order class. All AEs, except two, were reported as mild in intensity.

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinical significant abnormalities, and changes over time were reviewed for clinical chemistry, hematology, and urinalysis parameters. There were no clinically important findings were seen.

7.4.3 Vital Signs

Vital sign trends, individually clinical significant abnormalities, and changes over time were reviewed. No clinically important findings were seen.

7.4.4 Electrocardiograms (ECGs)

No ECG data were collected as part of any of the studies submitted in the Application.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application

7.4.6 Immunogenicity

Not applicable. The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

7.5 Other Safety Explorations

No other safety explorations were performed. No new non-clinical safety studies were conducted in support of this application.

7.5.1 Dose Dependency for Adverse Events

Study NEC-1 tested two doses, 0.25 mg/kg and 1.0 mg/kg, of esomeprazole. No significant difference in types or rates of adverse events was seen between the two dose groups. Only twenty-two 0.25 mg/kg/day patients and twenty-one 1.0 mg/kg/day patients experienced adverse events. These numbers may not have been large enough to detect a difference even if one did exist.

7.5.2 Time Dependency for Adverse Events

No clear association between timing of study drug administration and onset of adverse events was noted in any of the submitted studies. However, further study is necessary to determine if prolonged use of esomeprazole is associated with SAEs. This trend may be suggested by the difference in SAE rates noted between the 7/8 day PK/PD studies and the 6-week clinical study (0% vs. 6% respectively). Studies involving larger numbers of patients are needed.

7.5.3 Drug-Demographic Interactions

Subpopulation analyses of the primary endpoint were done for sex and race did not reveal any efficacy differences.

7.5.4 Drug-Disease Interactions

No specific studies were submitted with this submission. Long-term PPI therapy has been associated with an increased risk of hip fracture.

7.5.5 Drug-Drug Interactions

Esomeprazole drug-drug interactions are included in the currently approved label. Concomitant use of clopidogrel and PPIs has been associated with an increased risk of adverse outcomes following acute coronary syndrome.

MO Comment:

Warnings regarding the association of PPIs with hip fractures and adverse outcomes when used with clopidogrel are not currently labeled. As more information becomes available and the strength of the associations is elucidated, it will be important to include appropriate information in the label.

7.6 Additional Safety Evaluations

No additional safety evaluations were performed by the Applicant.

7.6.1 Human Carcinogenicity

The Applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

A 26-week oral gavage carcinogenicity study with omeprazole in p53+/- transgenic mice (study #AA24YR.7G82.03.BTL) was submitted to NDA 19,810 in an amendment to supplement SE8-074 on June 11, 2001. This study was requested as part of the Pediatric Written Request. The study found omeprazole to be at high exposure levels did not induce any carcinogenic response in either p53+/- or C57BL/6 wild-type mice.

7.6.2 Human Reproduction and Pregnancy Data

The target population under investigation for this Application is infants less than one year of age. Therefore, of the patients included in the studies in support of this application, none was pregnant or lactating.

Reproductive studies involving esomeprazole administered to rats and rabbits have not shown increased risk of congenital anomalies or adverse pregnancy outcomes. Esomeprazole is currently labeled as a Pregnancy Category B drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

No association between use of esomeprazole and changes in growth were noted in Study 96. Weight, height, BMI, and head circumference parameters were measured. The longest study in the safety database (Study 96) was six weeks long. No negative trend was seen. However, study duration likely to short to reveal an association between esomeprazole use and growth trends if one does exist. Further study is

needed to more fully assess effects of growth of long-term use on growth and development.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose have been reported during any of the clinical trials submitted in support of the Application. No drug abuse potential or withdrawal phenomenon have previously been associated with esomeprazole in previously submitted pediatric and adult studies.

7.7 Additional Submissions

11 March 09	Interim Period Safety Update Report for esomeprazole covering all ages and formulation for the time period 11 March 11 2008 to 8 February 2009
16 April 09	4- Month Safety Update Report covering 9 February 09 to 30 March 09

MO Comment: Overall, Nexium[®] was safe and well-tolerated over the reporting period. See Section 8 below for further details of Nexium's post-market experience.

8 Postmarket Experience

Two changes have been made to the Core Data Sheet (document used to inform PSURs) since the approval of NDA 22-101 (the more recent US Nexium[®] approval):

1. Information that concomitant administration of esomeprazole and drugs such as atazanavir and nelfinavir is not recommended has been added. These CDS changes are reflected in the current FDA approved label.
2. Administration site reactions associated with the use of the intravenous formulations of esomeprazole has been added as a common adverse drug reaction. Current intravenous esomeprazole labeling includes this information.

During the reporting period of the most recent periodic safety update report (PSUR), which grossly approximates the time since the last esomeprazole approval and concomitant clinical review, there have been several post-marketing reporting activities.

(b) (4)

During the latest PSUR period, 21 close surveillance events were reported. None of these events was known to have occurred in pediatric patients (some reports did not include patient ages). During the reporting period, 13 pediatric adverse events were reported.

Table 27. PSUR Adverse events reported in patients ≤17 years old

Case ID	Age	Case Serious	Preferred Term
2008UW24544	0 months	Yes	Cleft palate, Cleft lip
2008CG01262	8 days	No	Hypercalcaemia
2008CG01313	8 days	No	Hypercalcaemia
2008CG00877	2 months	Yes	Intracranial pressure increased
2008CG00645	23 weeks	No	Eczema
2008UW06817	1 year	No	Drug exposure via breast milk, Drug intolerance
2008SE01370	6 years	No	Diplopia, Paraesthesia
2008UW05633	6 years	No	Swelling face, Rash, Abdominal pain, Throat irritation, Constipation
2008AC01854	9 years	Yes	Pancreatitis
2008UW26362	10 years	Yes	Visual field defect, Epistaxis
2008UW09336	15 years	No	Skin striae
2008AP09434	16 years	No	Blood creatine phosphokinase increased
2009CG00273	17 years	Yes	Nephritis interstitial

The Applicant recently completed a literature search covering the last 10 years and found an association between PPI treatment and the development of *Clostridium difficile* infection in hospitalized patients. (b) (4)

MO Comment: The Division of Adverse Event Analysis prepared a review of this subject based on AERS reports and medical literature in July 2006. Due to the scarcity of evidence supporting a causal link together, the Agency's Division of Gastroenterology Products recommended against the inclusion of a risk statement in the labeling at that time. Given that nearly three years have passed, I recommend that we request an update to the original search and determine if current evidence warrants labeling changes.

A recent clinical trial database and literature search performed by AstraZeneca at the request of authorities from the United Kingdom found that in AUC values for cilostazol and an active metabolite were increased when omeprazole was given concomitantly. (b) (4)

The

Applicant reports that the number of reports of esomeprazole/omeprazole and cilostazol given concomitantly is small.

MO Comment:

We should request that the Applicant provide the Agency with information regarding a possible cilostazol interaction for our review.

9 Appendices

9.1 Literature Review/References

In response to the Pediatric Written Request, the Applicant completed a literature search to help determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric enterochromaffin-like (ECL) cells. The literature search was submitted on 6 December 2008. From the search, the Applicant concluded that pediatric patients are not at increased risk of proliferative changes in gastric ECL cells.

9.2 Labeling Recommendations

It should be clearly stated that Nexium[®] has not been found to be effective in the target population and its use is not recommended. Information regarding the design of the clinical study and PK/PD data to properly inform provider use of this medication should also be included. See final product labeling for complete details.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned regarding this efficacy supplement.

9.4 Table of Written Request Studies

<p>Pivotal study D9614C00096 12 April 2007 to 4 June 2008</p> <p><u>Age Group</u> 1-11 months</p>	<p>Phase III, multicenter, randomized, doubleblind, placebo-controlled, parallel-group, treatment-withdrawal study comprising 4 consecutive periods:</p> <ol style="list-style-type: none"> 1) Up to 10-day screening period (Visit 1 to Visit 2; no study treatment) 2) 2-week open-label treatment phase (Visit 2 to Visit 3; once-daily open-label treatment: esomeprazole 2.5, 5.0, and 10 mg per patient, open-label dose according to body weight at Visit 2) 3) 4-week double-blind treatment-withdrawal phase (Visit 3 to Visit 5, or discontinuation; treatments: randomization to either continue original open-label dose of esomeprazole [2.5, 5.0, or 10 mg] or matched placebo) 4) 2-week safety follow-up period (no study treatment) 	<p>Primary: to evaluate the efficacy of once-daily esomeprazole for reducing the esophageal and supraesophageal signs and symptoms of infantile GERD</p> <p>Secondary: to evaluate the safety and tolerability of once-daily esomeprazole in infants aged 1 to 11 months, inclusive, with GERD</p>
<p>SH-NEC-0001 6 June 2002 to 23 March 2005</p> <p><u>Age Group</u> 1-11 months</p>	<p>Clinical pharmacology (PK/PD), single-center, randomized, single-blind, two-arm, parallel, repeated-dose study with 2 consecutive periods:</p> <ol style="list-style-type: none"> 1) Screening period (Pre-entry Visit to Study Day -2; no study treatment) 2) 1-week single-blind treatment phase (Study Days 1 to 7/8; treatments: esomeprazole 0.25 mg/kg and 1 mg/kg) 	<p>Primary: to assess the PK of esomeprazole and its efficacy in controlling intragastric pH in infants</p> <p>Secondary: to 1) assess the efficacy of esomeprazole in controlling esophageal acid exposure; 2) assess the safety and tolerability of esomeprazole in infants; and 3) assess the ability of esomeprazole to reduce GERD symptoms in infants</p>
<p>SH-NEC-0002 2 June 2004 to 8 March 2006</p> <p><u>Age Group</u> Corrected age less than 44 weeks</p>	<p>Clinical pharmacology (PK/PD), open-label, single-center study with 3 consecutive periods:</p> <ol style="list-style-type: none"> 1) Screening period (Pre-entry Visit to Study Day -7 [at most]; no study treatment) 2) 1-week treatment phase (Study Days 1 to 7/8; treatment: esomeprazole 0.5 mg/kg)^a 3) 2-week safety follow-up period (no study treatment) 	<p>Primary: to assess the PK of esomeprazole and its effect on intragastric pH in preterm infants and neonates</p> <p>Secondary: to 1) assess the effect of esomeprazole on esophageal acid exposure secondary to GER using 24-hour pH monitoring and intraluminal impedance measurements; 2) assess the safety and tolerability of esomeprazole in preterm infants and neonates; and 3) assess the ability of esomeprazole to reduce symptoms suggestive of GERD in preterm infants and neonates</p>
<p>D9614C00007 14 Aug 2006 to 08 May 2008</p>	<p>PK exposure/response randomized, open-label study</p>	<p>Primary: to determine the area under the plasma concentration-time curve (AUC) of esomeprazole after single oral</p>

<u>Age Group</u> 1-11 years		doses of 5 mg, 10 mg, or 20 mg esomeprazole
D9614C00099 22 Mar 2004 to 31 July 2004 <u>Age Group</u> 1-11 years	PK randomized, open-label study	Primary: to determine the area under the curve (AUC) of esomeprazole after multiple oral doses of 5 mg, 10 mg, and 20 mg esomeprazole magnesium
D9614C00097 13 Oct 2004 to 09 Nov 2005 <u>Age Group</u> 1-11 years	A Phase III, Randomized, Double-blind Parallel-group Study to Evaluate the Safety and Clinical Outcome of Once Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease	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, inclusive.
D9614C00094 8 Sept 2003 to 13 Oct 2003 <u>Age Group</u> 12-17 years	A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single and Multiple Doses of Esomeprazole Magnesium 20 mg and 40 mg	Primary: to determine AUC after single and repeated (multiple) oral doses of 20 mg and 40 mg esomeprazole magnesium in 12- to 17-year-olds inclusive with GERD or symptoms of GERD.
D9614C00098 20 Feb 2004 to 04 May 2005 <u>Age Group</u> 12-17 years	A Phase III, Randomized, Double-blind, Parallel-group Study to Evaluate the Safety of Once Daily Esomeprazole for the Treatment of Clinically Diagnosed Gastroesophageal Reflux Disease (GERD). Study duration 8 weeks.	Primary: to evaluate the safety and tolerability of once daily treatment with esomeprazole in pediatric and adolescent patients 12 to 17 years of age, inclusive, with clinically diagnosed GERD.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Aisha E Peterson
6/15/2009 05:59:30 PM
MEDICAL OFFICER

John Hyde
6/16/2009 01:35:20 PM
MEDICAL OFFICER