CLINICAL REVIEW

Application Type	505(b)(1) Supplemental NDA
Application Number(s)	021689/S-017
Priority or Standard	Standard
Submit Date(s)	03/31/2010
Received Date(s)	03/31/2010
PDUFA Goal Date	04/29/2011
Division / Office	Division of Gastroenterology and Inborn Errors Products/Office of New Drugs/ ODEIII
Reviewer Name(s)	Erica L. Wynn MD, MPH through Robert Fiorentino MD, MPH
Review Completion Date	04/05/2011
Established Name	Esomeprazole Sodium for Injection
Trade Name	NEXIUM® I.V.
Therapeutic Class	Proton Pump Inhibitor
Applicant	AstraZeneca LP
Formulation(s)	Powder for Injection Solution
Dosing Regimen	Once Daily
Proposed Indication(s)	The short-term treatment of Gastroesophageal Reflux Disease (GERD) in pediatric patients 1 to 17 years, inclusive and adult patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with NEXIUM Delayed-Release Capsules is not possible or appropriate
Intended Population(s)	Pediatric Patients ages 1 to 17 years, inclusive and Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has provided limited safety data in the current application. However, given the breadth of previously reviewed data from well-controlled clinical trials, it is unlikely that the risks associated with short term use of NEXIUM® I.V. are greater than that in the current labeling. It is recommended that NEXIUM® I.V. be approved provided that a modification is made to the indication. The sponsor has proposed the following indication: (b) (4)

The sponsor proposed to expand their current indication to include pediatric patients. The pediatric population studied consisted of hospitalized patients, which is the most reasonable setting where this drug will be used. The goal of any medical therapy is to use the smallest effective dosage for the shortest duration needed to treat the condition. However, as written the proposed indication (b) (4) Attempts to prevent the overutilization of pharmacotherapy are necessary to ensure that the benefits outweigh the risks. This is especially true given recent discussions regarding the overuse of proton pump inhibitors in children less than 1 year of age and the common practice of using proton pump inhibitors for stress ulcer prophylaxis in the hospital setting.[1,2] Sufficient data demonstrating the effectiveness and safety of prophylactic drugs is lacking.

The pediatric consultant suggested in her review that the indication (b) (4) This reviewer concurs with her suggestion. One can reasonably assume that the patient population most likely to benefit from this drug would be those hospitalized patients with actual mucosal damage, who are either unable to take anything per os or have marked limitations on oral consumption (e.g. NPO except for fluids). “Gastric acid production in infancy resembles that in the adult by age 6 months of life.”[3] Although the exact prevalence of erosive esophagitis in children is unknown, some data suggest that erosive esophagitis does exist in children less than 1 year of age and the occurrence progressively increases with age.[4] The reviewer suggests modification of the indication as follows: “short-term treatment of GERD with erosive esophagitis in pediatric patients 1 month to 17 years inclusive and adults as an alternative to oral therapy when oral NEXIUM® is not possible or appropriate.”

1.2 Risk Benefit Assessment

Oral esomeprazole is currently approved for use in pediatric patients 1 to 17 years, inclusive. The data submitted in the current application do not suggest that intravenous esomeprazole use will result in any new or unexpected adverse reactions not already observed with oral use in pediatric patients. However, the goal of medical pharmacotherapy is to use the lowest effective dose for the shortest duration necessary to treat the condition in the appropriate patient. Given this information, it is quite possible that the benefits of using a drug, even one with a fairly benign short-term safety profile, will not outweigh the risks if not administered in the appropriate setting to the appropriate patient. In order for this to occur, the provider must first establish that there is a need for treatment, based on their diagnosis. As stated in Section 1.1, there have been reports of use of intravenous acid reducers for stress ulcer prophylaxis in hospitalized intensive care unit patients. This is done despite a lack of adequate data to support use. In this setting where efficacy has not been established, the risks of drug therapy do not outweigh the benefits.

In the opinion of this reviewer, there is a place for intravenous esomeprazole therapy. There is some evidence that the prevalence of GERD and its complications are increasing. However, it is highly unlikely that the patient who does not have documented mucosal damage will benefit substantially from short term therapy with the intravenous preparation when oral therapy is not appropriate. The patient with a history of symptomatic GERD (e.g. heartburn, cough, chest pain) who is controlled on oral therapy may not experience any clinically significant worsening of symptoms with temporary cessation of therapy during brief hospitalizations. In order for the benefit: risk ratio to remain favorable, it is the opinion of this reviewer that the patient population be narrowed to include those patients with documented acid-mediated erosive esophagitis.

1.3 Recommendations for Postmarked Risk Evaluation and Mitigation Strategies

This section is not applicable.

1.4 Recommendations for Postmarketing Requirements and Commitments

This section is not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

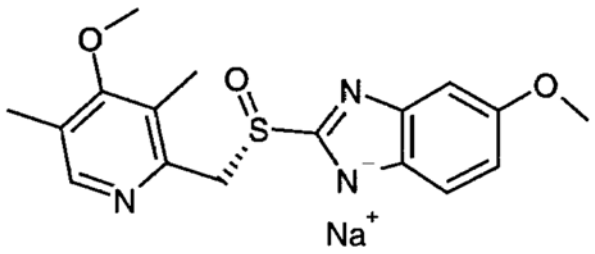
NEXIUM® I.V. (esomeprazole sodium) for Injection was initially approved by the FDA in 2005 for use in adults for the short-term treatment (up to 10 days) of GERD patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with NEXIUM® Delayed-Release Capsules is not possible or appropriate. According to the current labeling, when oral therapy is possible or appropriate, intravenous therapy with NEXIUM® I.V. should be discontinued and the therapy should be continued orally.

The active ingredient of NEXIUM® I.V. is esomeprazole sodium. Esomeprazole is the S-enantiomer of omeprazole, a substituted benzimidazole that suppresses gastric acid secretion by specific inhibition of the H^+/K^+ ATPase in the gastric parietal cell. According to the current label, esomeprazole is protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide.

Chemical formula: $C_{17}H_{18}N_3O_3SNa$

Molecular weight: 367.4 g/mol

Structural formula:



2.2 Tables of Currently Available Treatments for Proposed Indications

Transient lower esophageal sphincter relaxations are a normal physiologic response to gastric distention which allows the passage of stomach contents backwards into the esophagus. This passage of gastric contents into the esophagus, with or without regurgitation and vomiting, is referred to as GER (gastroesophageal reflux).[5] GER is a normal physiologic process occurring in healthy infants, children, and adults causing few or no symptoms for the patient.[5] One study estimated that GER occurs in up to 67% of otherwise healthy infants and resolves by age 1 year of age.[6] When the reflux of gastric contents becomes troublesome to the patient or causes complications, the patient is considered to have gastroesophageal reflux disease (GERD). GERD is a common chronic disorder. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) considers GERD to be a more serious form of gastroesophageal reflux (GER).[7] It has been suggested that the prevalence of GERD is highest in North America and Europe. The manifestations of GERD can be limited to symptoms, such as heartburn and nonerosive reflux disease (NERD), or can be more complicated, such as the case with erosive esophagitis, esophageal strictures, or Barrett's esophagus. One study has estimated that symptoms of GERD occur in 2% to 7% of children.[8] The true prevalence of GERD complications in children is unknown.

Erosive esophagitis and nonerosive reflux disease (NERD) are two manifestations of reflux disease. Erosive esophagitis is defined as the presence of evident esophageal mucosal injury at endoscopy.[8] NERD has been defined as a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy and without recent acid suppressive therapy. Acid reflux may give rise to similar symptoms in both NERD and erosive esophagitis. In both cases, patients often present with heartburn (a burning sensation behind the breastbone occasionally extending to the neck, throat, and face), chest pain, and regurgitation of sour material into the mouth. (Of note, NERD is distinct from functional heartburn, where abnormal esophageal acid exposure is absent.[9] In these patients, a different underlying mechanism may account for patient's symptoms)

There were three proton pump inhibitors available intravenously: NEXIUM® I.V., PROTONIX® I.V., and PREVACID® I.V.. According to the current labeling, the pharmacokinetics of neither PROTONIX I.V. nor PREVACID I.V. have been investigated in patients less than 18 years of age. In January of 2010, PREVACID I.V. was withdrawn from the market for reasons other than safety. PROTONIX I.V. is approved for the short-term treatment (7 to 10 days) of patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis. PROTONIX I.V. is also indicated for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions.

Other available treatments for acid-related gastrointestinal disorders include H2-receptor antagonists. ZANTAC® is available in an injectable form and is approved for use in children (1 month to 16 years). According to the current labeling, ZANTAC® is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication. Although, PEPCID® is approved for pediatric patients up to age 16 years, an injectable form of the drug was discontinued from the market. Likewise, the injectable form of TAGAMET® was also removed from the market for reasons other than safety.

2.3 Availability of Proposed Active Ingredient in the United States

Esomeprazole is the S-enantiomer of omeprazole. It belongs to the class of antisecretory compounds characterized pharmacologically as proton pump inhibitors. Currently the drug is available in the U.S. as a prescription medicine in oral and intravenous forms for a number of indications including: the treatment of symptomatic gastroesophageal reflux disease (GERD); short-term treatment in the healing and symptomatic resolution of erosive esophagitis; to maintain symptom resolution and healing of erosive esophagitis; the risk reduction of NSAID-associated gastric ulcer; *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Esomeprazole is marketed by AstraZeneca as NEXIUM®. Esomeprazole has also been combined with NAPROSYN®, an NSAID, in VIMOVO® which is also marketed by AstraZeneca.

2.4 Important Safety Issues With Consideration to Related Drugs

As with all medications, proton pump inhibitors should be used at the lowest dose for the shortest duration necessary to treat the condition. Although current labeling for the six proton pump inhibitors (PPIs) approved for use in the US acknowledge common adverse reactions (e.g. headache, abdominal pain, nausea, vomiting, flatulence and diarrhea), the class of drugs is generally very well tolerated. Current labeling of esomeprazole also states that the PPI may increase INR and prothrombin time when administered concomitantly with warfarin. Additionally esomeprazole may interfere with the absorption of drugs for which gastric pH is an important determinant of their bioavailability and those drugs metabolized by the cytochrome P450 pathways. Current labeling of esomeprazole recommends that a dose of 20mg should not be exceeded for patients with severe liver impairment.

There are a number of potential issues concerning the use of prolonged PPI therapy in children.[3] However, most of the available information regarding prolonged usage comes from adults. Some studies have suggested that PPI therapy, particularly when given long-term and/or in high doses, is associated with several potential adverse effects, including enteric infections (e.g. *Clostridium difficile*) and community acquired pneumonia due to bacterial overgrowth.[10] Other potential areas of concern regarding

long-term proton pump inhibitor use have included carcinoid formation; development of gastric adenocarcinoma, and malabsorption of fats, minerals, and vitamins, especially vitamin B_{12}.[10,11] There have also been concerns about rebound acid secretion following PPI discontinuation leading to dependency on the drug.[10] Recently the labeling of omeprazole had been updated to reflect the diminished anti-platelet activity of PLAVIX® when administered concomitantly with omeprazole.[12]

Reflex-mediated elevations in serum gastrin levels occurs secondary to acid suppressive therapy. The increased gastrin levels cause both enterochromaffin-like cell hyperplasia and increased chromogranin A levels.[13] Because gastrin is a trophic hormone, there have been concerns about whether high doses can affect the onset and development of conditions such as colon cancer in people who are genetically predisposed.[1]

The FDA has issued class labeling for all proton pump inhibitors to include language regarding a possible increased risk of hypomagnesemia and increased risk of fractures of the hip, wrist, and spine in patients taking proton pump inhibitors for prolonged periods of time. The greatest risk of fractures was reported in those taking high doses of proton pump inhibitors or those treated for more than 12 months.[14] Likewise low serum magnesium levels were seen most often in patients taking the medication for longer than one year.[15]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

March 31, 2005 – NDA 21-689 for NEXIUM® I.V. (esomeprazole sodium) for Injection initially approved for the short-term treatment (up to 10 days) of GERD in patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with NEXIUM Delayed-Release Capsules is not possible or appropriate. Pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) for ages 0 to 17 years, inclusive deferred until December 31, 2008.

December 19, 2006 – AstraZeneca submitted a Pediatric Development Plan in which the company proposed to conduct a single randomized, open-label, pharmacokinetic study in pediatric patients 0 to 17 years of age, inclusive.

April 26, 2007 – Sponsor submitted a new protocol: “A Phase 1, Randomized, Open-Label, Multi-National Study to Evaluate the Pharmacokinetics of Repeated Once-Daily Intravenous Doses of Esomeprazole in Pediatric Patients 0 to 17 Years Old, Inclusive.” This study (D9615C00021) under IND 64,865 is a pharmacokinetics study designed to meet the post-marketing study commitment required at approval. The primary objective is to evaluate the pharmacokinetics (PK) of repeated doses of esomeprazole given as a once daily (QD) injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive by assessment of the total area under the plasma concentration versus time curve within a dosing interval (AUC_{τ}) on Day 4 of the study based on population PK modeling.

May 10, 2007 – FDA accepted sponsor's pediatric development plan provided that FDA recommended revisions and comments were included. The revisions and comments proposed by the Agency are as follows:

- "For patients less than one year of age, the written request states that 'to be included in this study, infants will be considered to be candidates for acid suppressive therapy because of a presumptive diagnosis of GERD. This same criterion is reasonable for patients less than one year for the current proposed study."
- "For older children, the following comments are applicable:
  The post-marketing commitment was for the treatment of GERD in pediatric patients. You are proposing to expand the study population to 'pediatric patients who could benefit from acid suppression therapy'. This expansion would represent a departure from the identified patient population in the post-marketing commitment and the population studies with oral esomeprazole. In addition, this population is different from the adult population in which esomeprazole I.V. is currently indicated (i.e. GERD with a history of erosive esophagitis). There is a relatively high prevalence of GERD in the pediatric population (estimated at 3% to 7%) and the complications of prolonged GERD appear to be occurring with increasing frequency in children and adolescents. Please provide supporting evidence if you do not agree that a study of I.V. esomeprazole is feasible, if limited to patients with GERD."
- The aim of the study is to enable the substitution of an I.V. formulation of esomeprazole for the oral form. The efficacy of I.V. and PO NEXIUM® are well known. Therefore the first exclusion criteria (concomitant use) are acceptable in its current form. It is not necessary to disallow prior use of a PPI, nor is it necessary to have a washout period prior to receiving study medication.
- Add digoxin and iron salts to the 3rd exclusion criteria
- Add pregnancy as an additional exclusion criteria
- Hepatitis B/C and HIV screening need to be added to the screening laboratory measurements if they have not been completed previously, since these conditions are listed as exclusion criteria
- The inclusion criteria need to be modified with respect to whether "hospitalized patients with a presumptive diagnosis of GERD" is acceptable.
- The safety endpoints and assessment times are reasonable except that urine pregnancy tests should be repeated one month after randomization into the study in post-menarchal female patients. The timing of the follow-up contact should be specified.
- Determination of final dosing should be based on available data in pediatric patients. [The agency was unable to provide comment as the review of oral dosing in pediatric patients (1-11years) was currently under review (NDA 22-101)].

July 24, 2007 – Submission of updated study protocol, Edition 2.0, which included prior administrative changes and Amendment 1. The purpose of Amendment 1 was to add a more specific study population and to incorporate FDA's recommendations as outlined in prior FDA comments on the study design. Special emphasis was placed on the fact that the primary population to be studied would be patients with GERD and not just patients who could benefit from acid suppression therapy. The amendment also increased the number of participating study centers from 8 to 11.

February 26, 2008 – Clinical Study Protocol Amendment 2 submitted. "History of seizure disorder" removed from Exclusion criterion #3. Additional prohibited medications that affect the pharmacokinetic parameters of esomeprazole were added to the Exclusion criterion #7.

November 13, 2008 – Sponsor requests an extension to submit final study report due to difficulties with patient enrollment.

December 19, 2008 – Agency grants extension request for fulfillment of post-marketing commitment.

January 8, 2009 – Amendment 3 submitted to change protocol to provide for open enrollment of any pediatric patient in need of acid suppressive therapy.

March 31, 2010 – Sponsor submitted a supplemental NDA to provide pharmacokinetic, efficacy, and safety information on the use of NEXIUM® I.V. as an alternative to oral formulation for the treatment of gastroesophageal reflux disease (GERD) in pediatric patients, ages 0 – 17 inclusive.

January 06, 2011 – PDUFA clock extended due to receipt of data from solicited information request dated December 22, 2010

2.6 Other Relevant Background Information

November 5, 2010 – Pediatric Advisory Committee held to discuss the safety of the use of proton pump inhibitors in children less than 1 year of age. It was agreed that the pathophysiology of symptomatic GERD is not the same in patients less than 1 year of age as it is in adults. However, there is a small subset of patients less than 1 year of age who have erosive esophagitis secondary to acid-mediated GERD. In this subpopulation, it is reasonable to extrapolate adult efficacy data related to use of PPIs for treatment of endoscopically diagnosed erosive esophagitis secondary to acid-mediated GERD.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was acceptable for review. It was organized and navigable. The sponsor submitted one trial (D9614C00004) as a reference. However, the study did not contribute useful data towards justifying the proposed labeling changes. Initially this created some minor confusion. However, clarity was achieved via a solicited information request.

There were a total of 3 solicited information requests during this review cycle. The information request dated December 13, 2010 regarding dosing recommendations for pediatric patients less than 1 year of age resulted in a major amendment and extension of the review clock.

3.2 Compliance with Good Clinical Practices

A DSI inspection was requested by the Division of Gastroenterology and Inborn Error Products and Office of Clinical Pharmacology. The Division of Scientific Investigations (DSI) conducted inspections of clinical and analytical portions of study D9615C00021. The Women's and Children's Hospital Center for Pediatric and Adolescent Gastroenterology in North Adelaide, South Australia was chosen for the clinical site inspection. The analytical site inspection was conducted at AstraZeneca R&D Mölndal (Gothenburg), Sweden.

A form 483 was issued following inspection at AstraZeneca. After receiving the company's response, the DSI consult determined that, "The drug concentrations and recalculated pharmacokinetic data for study D9615C00021 are acceptable for DGP and OCP review."

3.3 Financial Disclosures

Financial disclosure forms were reviewed. The possible impact of financial bias is very limited. The applicant submitted a form 3453 certifying that they had not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The applicant also certified that each investigator who was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21CFR 54.2(b) did not disclose any such interests. Furthermore the applicant certified that no investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new Chemistry, Manufacturing, and Controls information included in this NDA.

4.2 Clinical Microbiology

This section is not applicable for this NDA.

4.3 Preclinical Pharmacology/Toxicology

There were no new nonclinical study reports submitted with the current NDA. The applicant reports that previous nonclinical studies conducted with omeprazole showed that the drug was well tolerated in animals at dose levels that were “well above” those used in clinical practice. Because esomeprazole is the s-enantiomer of omeprazole, the applicant limited their nonclinical program used to support clinical use. The bridging plan for esomeprazole and omeprazole has been previously presented and reviewed.

According to the applicant, the primary safety concern for short-term intravenous administration in pediatric patients is the magnitude of the $C_{ss, max}$ value, as very high plasma concentrations of both omeprazole and esomeprazole have been shown to have effects on the central nervous system in adult and neonatal/juvenile animals. The exposure margins for the C_{max} for all pediatric age groups compared to animals are considered sufficient. Please see the preclinical review for additional details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Esomeprazole is a substituted benzimidazole that irreversibly inhibits the H^+/K^+-ATPase pump in the gastric parietal cell reducing acid production.

4.4.2 Pharmacodynamic

Please see the clinical pharmacology review for more details.

There were no assessments of pharmacodynamic outcomes in trial D9615C00021. The lack of PD data is suboptimal, especially given the large amount of off-label use of proton pump inhibitors in pediatric patients.

According to the current labeling for I.V. NEXIUM®, the antisecrectory effect of the drug on intragastric pH was determined in two previous studies of the 20mg and 40mg doses. Additionally four multicenter, open-label, two period crossover studies comparing intravenous esomeprazole (20 and 40mg) with oral esomeprazole delayed-release capsules at corresponding doses, showed that after 10 days of administration, the I.V. dosage forms were similar to the oral dosage forms in suppression of basal acid output and maximal acid output.

The label states that there are no data on the effects of intravenous NEXIUM® on serum gastrin, or enterochromaffin-like cells. Oral NEXIUM has been shown to increase fasting gastrin levels in a dose-dependent manner. Data from nonclinical studies of oral omeprazole has shown a dose-related increase in ECL cell hyperplasia and carcinoid tumors. However, in long-term clinical trials, although the incidence of ECL hyperplasia increased with time and dose, no carcinoid tumors were detected.

Finally, the current labeling states that decreased gastric acid increases gastric counts of bacteria normally present in the gut which may result in an increased risk of infection.

4.4.3 Pharmacokinetics

Please refer to the clinical pharmacology review for additional details.
Depending on the dose administered, the plasma half-life of I.V. NEXIUM® is between 1.1 and 1.4 hours. The half-life is prolonged with increasing doses the drug. According to the current labeling, esomeprazole is 97% bound to plasma proteins and extensively metabolized in the liver by the cytochrome P450 enzymes (mainly CYP2C19). Metabolites are primarily excreted in the urine.

According to the applicant of the current submission, the pharmacokinetics of I.V. NEXIUM®, were found to be related to body weight and age. AUC_{τ} for esomeprazole ranged between 2.9 and 42 µmol*h/L in the studied population and the $C_{ss,max}$ ranged between 2.73 µmol/L and 29.4 µmol/L. These results were reported to be consistent with previous results obtained for esomeprazole in children and adults. Again, please refer to the clinical pharmacology review for additional details.

5 Sources of Clinical Data

On March 31, 2005, under the original approval for NEXIUM®, the sponsor committed to conducting deferred pediatric clinical trials for the treatment of GERD in pediatric patients 0 – 17 years of age. The current submission presents new data from one pediatric trial, D9615C000021, and the pharmacokinetic (PK) modeling to bridge the intravenous data to existing oral pediatric data. (Please see the review of Dr. Justin Earp, clinical pharmacology reviewer, for additional details.)

Per the clinical pharmacology reviewer, the sponsor matched exposures to the oral pediatric data from previously conducted trials SH-NEC-0002 (<1 month post term where term is 38 weeks gestational weeks, SH-NEC-001 (1 to 24 months), D9614C00099 (1 to 11 years), and D961C00094 (12 to 17 years). Trials SH-NEC-002 and SH-NEC-001 were reviewed under NDA 21-957. Trials D9614C00099 and D961C00094 were reviewed under NDA 22-101 and NDA 21-153. (Of note, there were no significant safety issues with either application.)

To support their dosing recommendations, the sponsor bridged the pharmacokinetic data from esomeprazole administered intravenously with pharmacokinetic data from esomeprazole administered orally to pediatric patients. To account for differences in the rate of absorption and bioavailability of NEXIUM® administered orally and intravenously in pediatric patients, the clinical pharmacology reviewer compared the C_{max} and AUC of I.V. esomeprazole administration in pediatric patients to C_{max} and AUC from adults following I.V. administration. Adult C_{max} and AUC values were obtained from Studies NEP0003 and NEP0008 in the adult NEXIUM submission dated September 10, 2003.

Safety data is presented from the one new trial submitted with this NDA.

5.1 Tables of Studies/Clinical Trials

Safety data is presented from the one new trial submitted with this NDA, trial D9615C000021. All other trials listed in the table below have been reviewed under previous NDAs. There were no unexpected safety signals detected in these trials that were inconsistent with the labeling for esomeprazole. However for the sake of completeness, they are listed here because they were part of the pharmacokinetic modeling.

Table 1. Table of Clinical Trials

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
*D9615C000021	Phase 1 Pharmacokinetic	To evaluate the PK of repeated doses of esomeprazole given as a once daily (QD) injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of the total area under the plasma concentration versus time curve within a dosing interval (AUC_τ) on Day 4 of the study based on population PK modeling	Randomized Open-label Multinational	Intravenous esomeprazole injection over 3 minutes 0.5mg/kg: 0 – 1 month 1 mg/kg: 1 – 11 months 10mg: 1 – 5 years and 6 – 11 years 20mg: 6 – 11 years 12 -- 17 years 40mg 12 – 17 years (Pts were randomized to dosing regimens based on age)	59 enrolled/ 57 treated 2: not randomized 6: 0–1 month 9: 1-11 months 8: 1- 5 years 17: 6-11 years 17: 12-17 years	Hospitalized pediatric patients, 0 to 17 years, inclusive with GERD	4 days
SH-NEC-002	Phase 1 Pharmacokinetic	To assess the PK of esomeprazole and its effect on intragastric pH in preterm infants and neonates (<1 month post-term where term is 38 weeks gestational weeks)	Single-center, open label, repeated-dose	Esomeprazole 0.5 mg/kg	26 enrolled	Neonates less than 44 weeks corrected age	7 days
SH-NEC-001	Phase 1 Pharmacokinetic and Pharmacodynamic (pH-monitoring study)	To assess the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants (1 -24 months)	Single-Blind, Randomized Parallel-Group, Single-Center	Esomeprazole pellets 0.25mg/kg 1.0mg/kg	50 enrolled	Pediatric patients 1 – 24 months	7 – 8 days

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
D9614C00099	Phase 1, Pharmacokinetic	To determine the area under the curve (AUC) of esomeprazole after multiple doses in 1 – 11 year olds, inclusive with GERD or symptoms of GERD	Randomized Open-Label Single Center Conducted in the US	Esomeprazole (b) (4) for oral suspension 5mg 10mg 20mg	31 enrolled 18: 1-5 yrs 13: 6-11 yrs	Pediatric patients ages 1 to 11 years	5 days
D9614C00094	Phase 1 Pharmacokinetic	To assess the pharmacokinetics of esomeprazole	Randomized Open-label	Esomeprazole 20mg 40mg	28 enrolled	Pediatric patients aged 12 to 17 years	
** Population PK Modeling Study consisting of SH-NEC-0001 SH-NEC-0002 D9614C00094 D9614C00099 DC9615C0021	Population PK Modeling Trial	To develop a population pharmacokinetic model for IV and oral esomeprazole in children aged 0 to 17 inclusive with respect to typical mean parameters and their variability and perform simulations from the final model in order to make dose recommendations for esomeprazole in children	Joint Population Pharmacokinetic analysis on pediatric data from 4 oral PK studies (SH-NEC-0002, SH-NEC-0001. DC9614C00094, DC9614C00099) and from 1 PK IV study (DC9615C0021)	See individual studies above	See individual studies above	See individual studies above	See individual studies above

5.2 Review Strategy

One new pharmacokinetic (PK) trial, D9615C000021 was submitted in the current application. The applicant designed their pediatric clinical development program such that data from the single I.V. trial and the pharmacokinetic modeling could be used to bridge the current I.V. data to existing oral pediatric PK data and safety data. However, it was deemed more appropriate to bridge the pediatric I.V. data to adult I.V. data. (Please see the clinical pharmacology review for more details.)

For the purposes of completing the safety analysis, only the newly submitted PK trial will be discussed. There is a wealth of previously reviewed safety and pharmacokinetic information for the use of NEXIUM® I.V. in adults, as well as for oral NEXIUM® treatment in pediatric patients. This safety information was not reanalyzed for this review. The reader may refer to NDA 21-957, NDA 22-101, and NDA 21-153 for analyses of adverse events related to the use of oral NEXIUM® in pediatric patients.

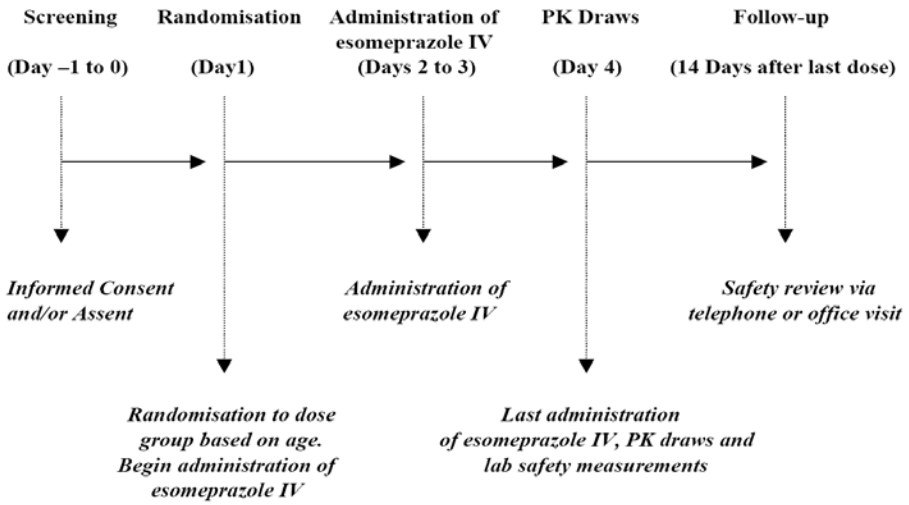
There were no new efficacy data submitted with this NDA. Extrapolation of efficacy based on adult data is appropriate for pediatric patients 1 to 17 years of age. (Please see the reviews of Drs. Justin Earp and Kristina Estes for additional details.) During the Gastrointestinal Advisory Committee, which was held on November 5, 2010, committee members determined that for the age group less than 1 year of age, extrapolation of efficacy concerning the use of proton pump inhibitors based on adult data is reasonable in the small subset of patients in this age range who have erosive esophagitis secondary to acid-mediated GERD. The Division agreed with the recommendations of the committee. Pharmacokinetic data will be used to determine dosing. (Please see the clinical pharmacology review for details.)

There were no new CMC or Clinical Microbiology data submitted with this application, therefore those sections were omitted in this review. Only a brief reference is made to the nonclinical section of the review because no nonclinical study reports were submitted.

5.3 Discussion of Individual Studies/Clinical Trials

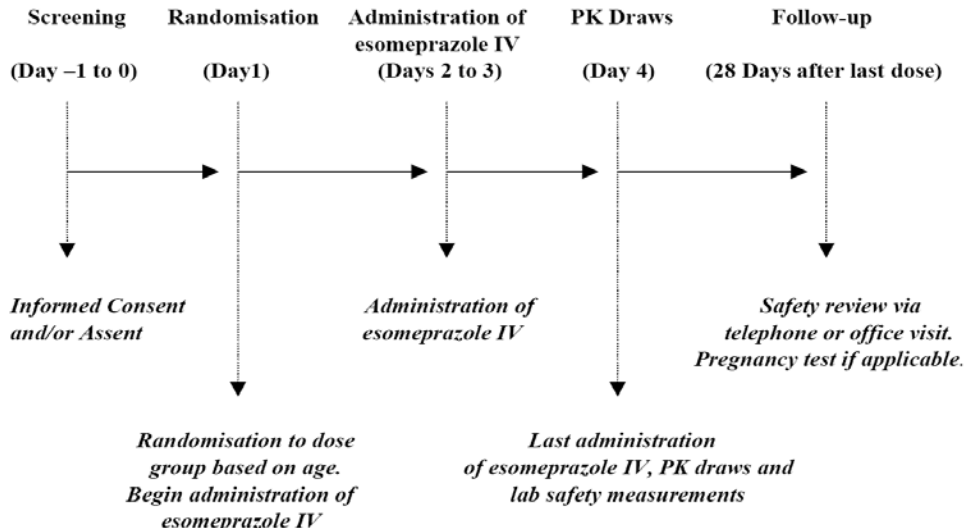
The following is a schematic of the overall study design for Trial D9615C00021. Details are also summarized in the subsequent table.

Figure 1 Original Trial D9615C00021 Schematic



Reproduced from the sponsors submission of under IND 64,865 dated February 20, 2007

Figure 2 Final Schematic for Trial D9615C00021



Reproduced from the sponsor's submission under IND 64,865 dated December 18, 2008

Figure 3 Study Plan (Assessments, Procedures, Timeline) for D9615C00021

Assessment/Procedure	Screening (Pre-entry visit before Randomisation) Days –1 to 0	Randomisation/ Dosing Day 1	Dosing Days 2-3	Dosing /PK Day 4	Follow-Up Contact 28 Days after final dose
Informed consent/Assent	X				
Demographics	X				
Review inclusion/exclusion	X				
Medical/surgical history	X				
Physical exam	X			X	
Vital signs	X			X [a]	
ECG [b]	X			X [a]	
Concomitant medications	X	X	X	X	X
Clinical chemistry, haematology, urinalysis [b]	X			X	
Urine Pregnancy Test [c]	X				X
Randomisation		X			
Administration investigational product [d]		X	X	X	
PK Blood samples [e]				X	
Non-serious Adverse Events		X	X	X	X
Serious Adverse Events	X	X	X	X	X

[a] ECG, blood pressure, heart rate, respiratory rate, and body temperature are completed prior to administration of investigational product on Day 4.
[b] Studies obtained up to 7 days prior to randomisation for standard of care are allowed if the investigator has not observed a change in the patient's clinical status.
[c] Urine pregnancy tests are required for all post-menarchal females.
[d] The investigational product will be administered by the investigational site personnel between 8AM-10AM and at the same time each day.
[e] Blood samples (0.6 – 1 mL each) for measurement of esomeprazole and its main metabolites will be collected prior to dosing and at selected time points up to 9 hours after the final dose on Study Day 4.

Reproduced from the sponsor's submission under IND 64,865 dated December 18, 2008

Table 2 Reviewer's Summary of Trial Protocol D9615C00021

Study # and Period	**D9615C00021 (October 13, 2007 – October 20, 2009)**
Design	Randomized, Open-label, Multi-National
Primary Objectives	To evaluate the PK of repeated, once-daily, 3-minute injections of esomeprazole in pediatric patients 0 to 17 years old, inclusive by assessment of AUC_{τ} on Day 4, based on population PK Modeling
Secondary Objectives	To evaluate the PK of repeated doses of esomeprazole given as a once daily injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of the maximum plasma concentration ($C_{ss,max}$), total plasma clearance (CL), and steady-state volume of distribution (V_{ss}) on Day 4 of the study based on population PK modeling. To evaluate the PK of the main metabolites of esomeprazole (sulphone metabolite and 5-hydroxy metabolite) after repeated doses of esomeprazole given as a once daily injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of $C_{ss,max}$, AUC_{τ}, clearance scaled by fraction metabolized (V_{ss}/fm) on Day 4 of the study based on population PK modeling. To evaluate the safety of esomeprazole given as once daily injection over 3 minutes for 4 days in pediatric patients 0 to 17 years old, inclusive, by assessment of adverse events (AEs), laboratory values, blood pressure, heart rate, respiratory rate, body temperature, and electrocardiogram (ECG).
Treatments	Intravenous Esomeprazole Sodium daily for 4 days administered in the following doses to each respective age group: 0 to 1 month — 0.5 mg/kg 1 to 11 months — 1.0 mg/kg 1 to 5 years — 10mg 6 to 11 years — 10 and 20mg 12 to 17 years — 20 and 40mg
Sample Patient Population	Any hospitalized patient, 0 to 17 years of age, who may benefit from acid suppression therapy. Hospitalized patient defined as a patient who was anticipated to be hospitalized for at least 4 days.
Number Planned	A maximum of 12 patients in each age bracket and at each dose were randomized to ensure that at least 6 patients were evaluable. [10 study sites total: Australia (1 center), Hungary (1 center), Sweden (1 center) and the United States (7 centers)]

<table>
<tr><th>Study # and Period</th><th>D9615C00021 (October 13, 2007 – October 20, 2009)</th></tr>
<tr><td>Key Inclusion/Exclusion Criteria</td><td>
<table>
<tr><th>Inclusion Criteria</th><th>Exclusion Criteria</th></tr>
<tr><td>Female and/or male hospitalized patient 0 to 17 years, inclusive</td><td>Unstable diabetes mellitus</td></tr>
<tr><td>Patients who are considered, in the judgment of the investigator to be a candidate for acid suppression therapy, including, but not limited to patients with a presumptive diagnosis of GERD, a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proved GERD</td><td>Participation in a clinical study during the 28 days prior to the screening visit, until the trial used investigational devices or products that are not systemically absorbed, in which case enrollment is determined on a case-by-case basis and discussed with the Sponsor prior to study enrollment.</td></tr>
<tr><td>Weight of at least 1.5 kilograms</td><td>Concomitant use of other PPIs during the treatment with the investigational product. PPIs are allowed up to but not including the day of randomization</td></tr>
<tr><td>For patients 2 to 17 years, BMI must be between 5th and 95th percentile for age at inclusion
For patients 0 and up to 2 years old, weight and height should be plotted on a standard weight for stature curve and must be between the 5th and 95th percentile at inclusion</td><td>Concomitant use of digoxin or iron salts. These are allowed up to but not including the day of randomization</td></tr>
<tr><td></td><td>Use of any drug known to affect the PK parameter of esomeprazole within 14 days prior to administration of investigational product on Day 1. A single dose of an excluded medication is allowed up to 7 days prior to administration of study drug. These drugs include enzyme cP450 inducers and inhibitors</td></tr>
<tr><td></td><td>Any acute or chronic illness which, in the opinion of the investigator and/or sponsor, could compromise the patients safety or successful participation in the study including: history of severe liver disease, severe renal disease, generalized bleeding disorder, significant cardiac abnormalities,</td></tr>
<tr><td></td><td>Clinically significant abnormal laboratory values, PE, or vital signs that may put the patient at risk when participating in the study, may influence study results, or may affect a patients ability to participate</td></tr>
<tr><td colspan="2">* Restrictions: Enrollees were required to not use any drug known to affect the PK parameters of esomeprazole during the dosing period, Day 1 though Day 4</td></tr>
</table>
</td></tr>
<tr><td>Primary Variables</td><td>AUCτ for esomeprazole on Day 4 of the study</td></tr>
<tr><td>Secondary Variables</td><td>$C_{ss,max}$, $T_{1/2}$, CL, and V_{ss} for esomeprazole on Day 4 of the study
AUCτ , $C_{ss,\ max,}$ $T_{1/2,}$ CL/fm and V_{ss}/fm and V_{ss}/fm on Day 4 of the study for the esomeprazole sulphone metabolite and esomeprazole 5-hydroxy metabolite.</td></tr>
</table>

Study # and Period	D9615C00021 (October 13, 2007 – October 20, 2009)
Key Safety and Tolerability Parameters	Adverse events, laboratory values (alkaline phosphatase, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Albumin, Urinanalysis, hematocrit, hemoglobin, platelet count, RBC, WBC and WBC differential), blood pressure, heart rate, respiratory rate, body temperature, and ECG
Protocol Amendment 1	Protocol amended to include a more specific study population in compliance with FDA comments on the Study Design Concept. Only pediatric patients 0 to 17 years, inclusive with GERD (Gastroesophageal Reflux Disease) could be enrolled. All relevant sections updated so that the study would focus on patients with GERD and not just those may potentially benefit from acid suppression therapy. The number of study centers increased from 8 to 11 centers in Australia, Sweden, and the U.S. Study amended so that all post-menarchal females must complete an in-office visit at follow-up that included a pregnancy test. The follow-up visit was changed from day 14 to day 28. New exclusion criteria were added and revisions made per FDA comments and feedback from investigational centers. Digoxin and Iron salts were added to the list of prohibited medications. Language added to emphasize the importance of avoiding contaminating samples.
Protocol Amendment 2 (after start of patient recruitment)	Additional revisions to the exclusion criteria: “History of seizure disorders” removed. Additional medications that may affect the pharmacokinetics of esomeprazole were added to the list of prohibited medications.
Protocol Amendment 3	Study population again amended due the large number of patients who failed the pre-screening process because of a lack of GERD diagnosis. Study population was broadened to include pediatric patients who may benefit from I.V. acid suppression therapy, including those patients with a diagnosis of GERD. List of possible reasons a child might require I.V. esomeprazole administration added to the protocol and investigators were permitted to give preoperative and postoperative I.V. esomeprazole when it was judged that treatment was indicated by the investigator. Patients were permitted to take a single dose of an excluded medication up to 7days prior to administration of study drug on Day 1. Exclusive use of arterial OR venous sampling permitted.

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6 Review of Efficacy

Efficacy Summary

There were no new efficacy data submitted with the current application. According to the applicant, there are no clinically relevant differences in pharmacodynamic parameters of the I.V. and oral forms of esomeprazole in adults, therefore efficacy can be extrapolated. This is the first time that the I.V. formulation has been given to pediatric patients and according to the applicant, the exposures are expected to be similar to what is seen in adults. While the availability of pharmacodynamic data for use of the I.V. esomeprazole in children would have been preferred, the current approach by the applicant seems reasonable. (Please see the clinical pharmacology review for additional details.)

6.1 Indication

The applicant seeks to expand upon the adult indication for use of NEXIUM® I.V. to include pediatric patients, ages (b) (4) – 17 years, inclusive. The proposed indication is (b) (4)

Although the indication is for "GERD patients with a history of erosive esophagitis", it is important to note that in the original label provided by the sponsor, there were two separate dosing recommendations for pediatrics patients. One of the dosing recommendations was for pediatric patients 1 to 17 years, inclusive for treatment of erosive reflux esophagitis. The other dosing recommendation was for pediatric patients 1 to 17 years, inclusive with symptomatic GERD.

6.1.1 Methods

See sections 5.1 and 5.3 above as well as the clinical pharmacology review for additional information. In addition to expanding the indication for NEXIUM® I.V. to pediatric patients 1 to 17 years, inclusive, the applicant also proposed appropriate doses for this age group. The clinical development program used existing oral pediatric PK, safety, and efficacy data to bridge to the proposed population which was studied in a single intravenous PK trial (trial D9615C00021). Trial D9615C0021 was a multi-national randomized, open-label parallel-group trial of intravenous esomeprazole administered once daily for 4 days in hospitalized patients 0 to 17 years old. Doses were selected based on previous adult and pediatric trials using oral esomeprazole. Consideration was also given to ICH E11 Guidance "Clinical Investigation of Medicinal Products in the Pediatric Population" during the design of the trial. The primary endpoint

was AUCτ for esomeprazole on Day 4 of the study. Secondary endpoints were maximum plasma concentration ($C_{ss, max}$), total plasma concentration (CL), and steady state volume of distribution (V_{ss}) for esomeprazole on Day 4 of the study. Given the large amount of data available for oral esomeprazole, the sponsor's approach seems reasonable. Corresponding pharmacodynamic data would have been preferable but is not necessary given our current level of knowledge.

6.1.2 Demographics

Baseline demographic data are presented for all patients in the safety population in the table below. The number of individuals in groups was, too small to allow adequate comparison with regard to demographic data. Overall, most of the patients enrolled were white and male. In previous trials with oral esomeprazole, females were shown to have slightly higher AUC and C_{max} values. However, current labeling does not recommend dose adjustments for gender differences. Although a small percentage of Caucasians lack CYP2C19, there is no reason to believe that this would affect the pharmacokinetic results of this trial markedly. Mean body mass index (BMI) data are also presented for patients over the age of 2 years at baseline. However, while patients who are overweight or obese may experience more GERD-symptoms, this is less useful in and of itself, as there are several problems inherent to the calculation of the BMI. Furthermore plotting the BMI on percentile curves allows the clinician to put the numbers in perspective. Notwithstanding, it is unlikely that BMI will affect the pharmacokinetics in this intravenously administered drug that is 97% plasma bound.

There were 5 patients who had a past medical history of renal disease (E1008003, E1008006, E1013005, E1015002, and E1016001). Renal diagnoses for these patients included acute renal failure, urinary retention, and nephrolithiasis. Of these five patients only 3 had active disease. According to the current label, the pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers.

The current label states that in patients with mild and moderate hepatic insufficiency, the AUCs of esomeprazole were within the normal range that could be expected with normal liver function. Patients with severe hepatic disease had AUCs that were 2 to 3 times higher than in patient with normal liver function. There were no patients in the study population that had a past medical history of hepatic insufficiency and therefore this is unlikely to affect the outcomes of the PK trial.

A small number of patients in each of the treatment groups were taking benzodiazepine derivatives. However, there were no other concomitant medications that would affect the outcome of the trials.

Table 3 Baseline Demographics and Characteristics Trial D9615C00021

	Esomeprazole Treatment Group						
	Eso 0.5mg/kg (0 to 1 mo) N = 6	Eso 1mg/kg (1 - 11 mo) N = 9	Eso 10mg (1 - 5 yr) N = 8	Eso 10mg (6 - 11 yr) N = 8	Eso 20mg (6 - 11 yr) N = 9	Eso 20mg (12 -17 yr) N = 8	Eso 40mg (12 - 17 yr) N = 9
Category							
Mean Age (SD) Days Months Years	 9.0 (13.28) - -	 - 4.2 (2.49) -	 - - 2.4 (1.51)	 - - 7.9 (1.73)	 - - 8.8 (1.79)	 - - 15.5 (1.69)	 - - 15.7 (1.32)
Mean Corrected Age (weeks) (Gestational Age +Age after Birth in weeks)	37.8 (3.31)	57.6 (10.44)					
Sex Male (%) Female (%)	 4 (66.7%) 2 (33.3%)	 7 (77.8%) 2 (22.2%)	 5 (62.5%) 3 (37.5%)	 5 (62.5%) 3 (37.5%)	 6 (66.7%) 3 (33.3%)	 5 (62.5%) 3 (37.5%)	 3 (33.3%) 6(66.7%)
Race Black (%) White (%) Asian (%) Other (%)	 1 (16.7%) 4 (66.7%) 1(16.7%) 0 (0%)	 0 7 (77.8%) 0 (0%) 2 (22.2%)	 2 (25.0%) 5 (62.5%) 0 (0%) 1 (12.5%)	 0 (0) 8 (100 %) 0 (0%) 0 (0%)	 1 (11.1%) 6 (66.7%) 1 (11.1%) 1 (11.1%)	 1 (12.5%) 6 (75%) 1(12.5%) 0 (0%)	 0 (0%) 8 (88.9%) 0 (0%) 1(11.1%)
Mean Length (SD)	50.8 (3.76)	61.1 (4.40)	-	-	-	-	-
Mean Height in centimeters (SD)	-	-	92 (16.94)	133.6 (10.88)	134.4 (12.89)	165.8 (11.66)	162.9(9.63)
Mean Weight in kg (SD) Min, Max	3.0 (0.64) 2,4	6 (1.08) 5,8	14.5 (5.14) 9, 23	33.1 (9.75) 25, 50	33.9 (14.66) 19,69	63.8 (15.85) 38,90	55.5 (10.95) 45,82
Mean Body Mass Index in kg/m^2 (SD)	-	-	16.8 (0.84)	18.1 (3.60)	18.4 (6.56)	22.9 (3.64)	20.7 (2.12)
Mean Head Circumference in cm (SD)	33.5 (2.34)	40.4 (2.39)	-	-	-	-	

Reviewers Table

6.1.3 Subject Disposition

A total of 62 patients were enrolled in 10 study centers. Seven centers in the United States enrolled 20 patients. Each of the study centers in Australia, Sweden, and Hungary enrolled 15 patients, 7 patients, and 10 patients respectively.

The following table shows the disposition of patients enrolled in the study.

Table 4 Accountability and Disposition of Trial Enrollees in D9615C00021

	ESOMEPRAZOLE TREATMENT GROUPS									
	Eso 0.5mg/kg (0 to 1 mo)‡	Eso 1mg/kg (1 - 11 mo)£	Eso 10mg (1 - 5 yr)	Eso 10mg (6 - 11 yr)	Eso 20mg (6 - 11 yr)	Eso 20mg (12 -17 yr)	Eso 40mg (12 - 17 yr)	Not Randomized	Randomized and not dosed	Total
Enrolled/Screened/ and Randomized to Dosage Group(N)	6	9	8	8	9	8	9	2	3	62
Safety Population	6	9	8	8	9	8	9	0	0	57
Completed the Study	6	8	7	8	7	6	8	0	0	50
Evaluable PK data	6	7	7	8	8	6	8	0	0	50
Prematurely Discontinued Study	0	1	1	0	2	2	1	2	3	12
Adverse Events	0	0	1	0	1	0	0	0	0	2
Withdrew consent	0	0	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0	0	0
Severe Noncompliance	0	0	0	0	0	0	0	0	0	0
Other	0	1	0	0	1	2	1	2	0	7
With Protocol Reviewers Table. Safety Population includes all those patients who received at least 1 dose of the study drug.										

‡0 to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age is the sum of the gestational age and the age after birth in complete week.

£ A patient in the 1 to 11 months age group had ≥44 complete weeks (31days to <12months)

It is important to note that not all patients in the trial had a diagnosis of GERD. Because of difficulties with recruiting GERD patients, the study protocol was amended to include any hospitalized patient considered for acid therapy, including but not limited to, patients with a presumptive diagnosis of GERD. Patients were considered "hospitalized" if the anticipated hospital stay was at least 4 days. Eight participants were considered "Non-GERD" patients. Of these 8, 2 were in the 1 to 11 month (1mg/kg) group; 3 were in the 6 to 11 year (10mg) group; 1 in the 6 to 11 year (20mg) group; and 2 were in the 12 to 17 year (20mg) group. It is unlikely that these patients would significantly affect the pharmacokinetic or the safety outcomes of this trial as the GERD diagnosis alone is unlikely to affect the absorption, distribution, metabolism, or excretion of a drug given intravenously. It is more likely that another co-morbidity (e.g. renal disease or hepatic insufficiency) of the hospitalized child would affect the pharmacokinetic outcome.

Of the 62 patients enrolled and screened, three patients failed to meet inclusion/exclusion criteria and were not randomized to a treatment group. Two patients were randomized but did not receive a dose of the study mediation. One of these patients (E1014001) was on a prohibited medication. The other (E10010003) did not have IV access and was discharged prior to dosing with the study medication.

One patient (E1001002) in the 1 to 5 year (10mg) group and one patient (E1013004) in the 6 to 11 year (20mg) group experienced an adverse event that lead to discontinuation. (For additional details please refer to the Section 7.3.3)

6.1.4 Analysis of Primary Endpoint(s)

There was no new efficacy data submitted with the application. The primary endpoint in the pharmacokinetic study was assessed as the total area under the plasma concentration versus time curve within a dosing interval ($AUC\tau$) on day 4 of the study, based on population PK modeling. Please see the clinical pharmacology review for more details.

6.1.5 Analysis of Secondary Endpoints(s)

Reference is made to the clinical pharmacology review for details. Secondary endpoints were the observed maximum plasma clearance at steady state ($C_{ss,max}$), total plasma clearance (CL), and steady state volume of distribution ($V_{ss)}$ for esomeprazole on Day 4 of the study. Additionally measures included the area under the plasma concentration versus time curve during a dosage interval at steady state ($AUC\tau$); $C_{ss,max,}$; clearance scaled by the fraction metabolized (CL/fm); and steady state volume of distribution scaled by fraction metabolizes (V_{ss}/fm) on study Day 4 for the esomeprazole sulphone metabolite and the esomeprazole 5-hydroxy metabolite.

6.1.6 Other Endpoints

Safety and tolerability endpoints were assessed during this trial. Please see Section 7 for details.

6.1.7 Subpopulations

Please see the clinical pharmacology review.
There were no efficacy data submitted with this trial. Body weight, age, body surface area, dose group, serum albumin, presence or absence of GERD, and arterial sampling of blood (as opposed to venous sampling) were evaluated as potential covariates in the pharmacokinetic analyses

Because of the small number of patients on potentially interacting concomitant medications, no conclusion could be drawn regarding drug-drug interactions. The same is true for those patients with renal insufficiency and hepatic impairment. The small number of trial participants with these conditions precludes establishing any definitive conclusions.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see the clinical pharmacology review. There were no pharmacodynamic data submitted with the current trial. According to the applicant, doses for NEXIUM® I.V. in the pediatric population were selected based on previous adult and pediatric trials using the oral preparations and the finding that the effect on intragastric acidity of the 20mg and 40 mg intravenous forms is comparable to that of the corresponding oral doses in adults. The sponsor submitted literature to show that when pediatric dosing achieves exposures that are similar to the exposures achieved in adults given repeated doses of esomeprazole 20mg once daily, the time with intragastric pH >4.0 correlated with that seen in adults.[16,17,18]

According to the clinical pharmacology reviewer, the sponsor's proposed doses provided higher AUC and C_{max} values in pediatric patients. Because of this, dosing recommendations are provided based on weight and age and are as follows:

- Age 1 year to 17 years
  - 10mg once daily for patients with body weight < 55kg
  - 20mg once daily for patients with body weight ≥ 55kg
- Age 1 month to 11 months
  - 0.5 mg/kg once daily

Dosing recommendations include an intravenous infusion duration over 10 minutes to 30 minutes. Please see the clinical pharmacology review for additional details on the dosing recommendations. In general age and weight based dosing recommendations are appropriate for pediatric populations, especially those under 1 year. The body size of children changes as a function of age. Clearance of a drug may also change as the child matures. Children have smaller volumes of distribution and clearance than adult

patients, which directly impacts the safety of the drug. Our primary concerns for this drug would concern its metabolism and excretion. The inclusion of pharmacodynamic data in this trial would have been preferred. However, given our previous knowledge of the drug's effects and the fact that gastric acid secretion in children ages 6 month and older mimics that seen in adults, it is unlikely that the age and weight based dosing will significantly affect the pharmacodynamics of intravenous esomeprazole.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No efficacy data were presented in this application. There are no data that would allow one to definitively conclude that the therapeutic effects would diminish over time. There have been some reports of rebound acid hypersecretion after 8 weeks of treatment with proton-pump inhibitor therapy leading to dependence on the drug.[19] However, this drug is designed to be used short-term, therefore this section is not relevant for the current application. There are no strict definitions of "short-term".

6.1.10 Additional Efficacy Issues/Analyses

This section is not applicable.

7 Review of Safety

Safety Summary

There was one new trial submitted with this application. A total of 57 study participants were exposed to at least one dose of the study drug as doses ranging from 0.5mg/kg to 40mg. Because the population pK model consisted of trials that had been previously reviewed, the safety assessment was largely based on the new data presented in trial D9615C00021. In this trial, information about adverse events was collected after the first dose of the study drug on Day 1 until completion of the 28-day follow-up contact after the last dose of the study drug on Day 4.

The safety and tolerability of NEXIUM® I.V. in pediatric patients, was consistent with that of current labeling, NEXIUM® I.V. use in adults, and oral NEXIUM® use in both pediatric and adults patients. Overall, there were no unexpected safety signals identified. There were 122 adverse events in total. There were no deaths during the 4 day trial period. A total of 31 (54.4%) of the 57 patients who were randomized and dosed with NEXIUM® I.V., experienced an adverse event. The majority of the adverse events reported were of mild to moderate intensity and from the Gastrointestinal system organ class with constipation being the most commonly reported preferred term. There were 8 serious adverse events (SAEs) recorded for 6 patients. The rate of SAEs was similar across the treatment groups. One patient in the 1 to 5 year old group and one patient in the 6 to 11 year old group experienced at least 1 adverse event that lead to discontinuation. Overall there were a total of 3 adverse events leading to discontinuation

of the investigational drug. However, none of these were assessed as being treatment-related. Three patients experienced a treatment related adverse event. However all three of these were able to continue in the trial.

Four patients (E2001013, E2001012, E1015003, and E1008004) had pharmacokinetic data suggesting high exposure to esomeprazole. However, no safety signals were identified for any of these patients. There were no new safety concerns related to laboratory analyses, ECG findings or vital signs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

To support the safety of NEXIUM® I.V. the sponsor submitted new data from trial D9615C0021. All other trials that provided clinical data for oral esomeprazole use in pediatric patients were previously reviewed under other NDAs. Additionally the applicant also provided information from their global safety database (SAPPHIRE) for adverse events reported overseas in association with intravenous NEXIUM® use in pediatric patients. The applicant's methodology for conducting the safety evaluation seems reasonable and appropriate.

7.1.2 Categorization of Adverse Events

The applicant used MedDRA (Version 12.0) in their summary of adverse events. The appropriateness of the applicant's coding was assessed by comparing a sampling of the "Preferred Terms", "Lower Level Terms" and "System Organ Class" columns in the Adverse Events dataset with "AE Text" column. The "AE Text" terms were recorded transcribed from case report forms as recorded by the investigator. Overall, the coding appeared accurate with minimal splitting or lumping.

The applicant defined an adverse event as the development of an undesirable medical condition or deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to that product. Adverse events were classified by severity (a measure of intensity- mild, moderate, or severe) and by whether the AE was considered to be serious or not.

A serious adverse event (SAE) was defined as an adverse event occurring during any study phase and at any dose of the investigational product that fulfilled one of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require a medical intervention to prevent one of the outcomes listed above.

This definition of a serious adverse event is consistent with that in regulations.

Causality of the SAE was assessed by the investigator. Other significant adverse events were identified by the Study Delivery Team physician after consulting with the Global Safety Physician. Adverse events were recorded on electronic case report forms after the first dose of study drug was administered on Day until completion of the 28-day follow-up contact after the last dose of study drug. Only abnormal laboratory values lead to discontinuation, were considered SAEs, or considered to be of clinical importance were recorded as adverse events.

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

This section is not applicable as there was only one new trial submitted.
Safety analyses consisted of descriptive statistics.

7.2 Adequacy of Safety Assessments

Assessment of tolerability and safety was a secondary objective of this study. Safety variables included adverse events, clinical laboratory evaluations, vital signs, electrocardiograms, and physical examination findings. Laboratory assessments included alkaline phosphatase, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Albumin, hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count (differential), and urinalysis. It appears as if safety assessments performed were adequate and all reasonably applicable tests were conducted to assess safety.

The safety population was defined as all patients who received at least once dose the investigational product. Of the 62 patients enrolled in the study, 57 were considered to be part of the safety population. Three patients were not randomized and two patients were randomized but did not receive a dose of the study drug.

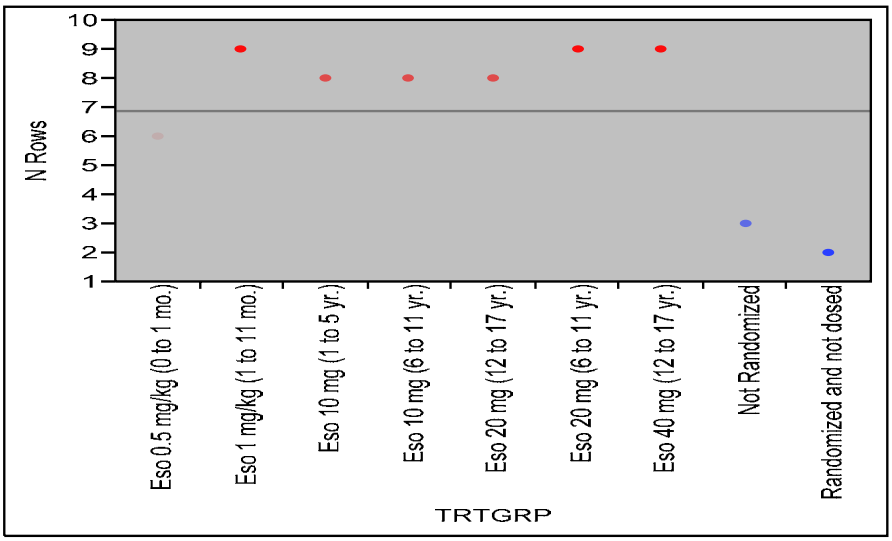
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

According to the sponsor, doses for NEXIUM® I.V. in the different pediatric age groups were selected based on results from previous pediatric studies using oral esomeprazole and the results from trials in adults showing that the effect on intragastric acidity of 20mg and 40mg esomeprazole IV is comparable to that of corresponding oral doses.

The proposed indication is for short-term use of NEXIUM® I.V. Consequently exposure guidelines as outlined in ICH E-1 are not applicable.

The figure below illustrates the number of individual study participants exposed to each of the treatment doses over the 4 day treatment period. The number of enrollees in each of the treatment groups was fairly comparable with the exception of the youngest age group (0 to 1 month). This is not overly concerning because those patients are not likely to have GERD with endoscopic findings suggestive of erosive esophagitis.

Figure 4 Distribution of Patients Enrolled at each Treatment Dose Trial D9615C0021



7.2.2 Explorations for Dose Response

Please see the clinical pharmacology review for details. Using the data from previous trials conducted with intravenous esomeprazole in adults and oral esomeprazole in children and adults, doses were selected and assigned to each age group such that exposures would mimic those seen with the 20mg adult intravenous exposure. There were no pharmacodynamic assessments in the new trial. No dose response safety analyses were performed.

The following table provides a summary of total esomeprazole doses administered by dose group.

Table 5 Summary of Esomeprazole doses administered by dose group

	ESOMEPRAZOLE TREATMENT GROUPS						
	Eso 0.5mg/kg (0 to 1 mo) N = 6	Eso 1mg/kg (1 - 11 mo) N = 9	Eso 10mg (1 - 5 yr) N = 8	Eso 10mg (6 - 11 yr) N = 8	Eso 20mg (6 - 11 yr) N = 9	Eso 20mg (12 -17 yr) N = 8	Eso 40mg (12 - 17 yr) N = 9
Mean dose mg/kg/day (Range)	0.5 (0.49-0.51)	0.95 (0.52-1.04)	-	-	-	-	-
Mean dose mg/day (Range)	-	-	10.05 (10.0 – 10.4)	10.05 (10.0 – 10.4)	20 (20)	20 (20)	40 (40)
Mean total cumulative dose mg (Range)	6.07 (4.8 – 8.0)	22.67 (13.2 – 32.0)	37.60 (20.8 – 40.0)	40.20 (40.0 – 41.6)	73.33 (20.0 – 80.0)	77.50 (60.0 – 80.0)	155.56 (120.0 – 160.0)

There did not appear to be a relationship between the occurrence of adverse events and dose of drug administered across the age groups. In other words, the number of adverse events did not increase or decrease with age or dose. Five of the nine patients in the 1 to 11 month (1mg/kg) group experienced the most adverse events (31 totals) in the trial and only 1 was thought to be secondary to study drug. The most frequently reported adverse events were abdominal distension, constipation, central venous line occlusion and hyponatremia, all common complications of hospitalized intensive care unit patients.

The following table summarizes the number of patients experiencing an adverse event and the number of adverse events in each of the treatment groups.

Table 6 Overall Summary of Adverse Events by Treatment Group

	ESOMEPRAZOLE TREATMENT GROUPS						
	Eso 0.5mg/kg (0 to 1 mo)	Eso 1mg/kg (1 - 11 mo)	Eso 10mg (1 - 5 yr)	Eso 10mg (6 - 11 yr)	Eso 20mg (6 - 11 yr)	Eso 20mg (12 -17 yr)	Eso 40mg (12 - 17 yr)
Total Number of Patients in each group	N = 6	N= 9	N = 8	N = 8	N = 9	N = 8	N = 9
Number of Patients Experiencing an Adverse Event	n = 2	n = 5	n = 7	n = 5	n = 2	n = 5	n = 5
Number of Adverse Events in Treatment Arm	10	31	25	9	23	8	16

7.2.3 Special Animal and/or In Vitro Testing

There were no new nonclinical data submitted in support of this application. Reference is made to section 4.3 for additional information regarding animal data.

7.2.4 Routine Clinical Testing

Section 7.2 describes routine clinical tests conducted as a part of the safety analysis. Section 5.3 also contains a schematic illustrating the timing of the assessments. Urine samples for analysis and blood samples for determination of hematology and clinical chemistry variables were taken at the screening visit and on Day 4. Labs were drawn at the screening visit if they were not previously taken up to 7 days prior to randomization as part of the child's standard of care. Lab draws on Day 4 were conducted only if they were not already taken on the same day as part of the normal standard of care for the child. Given the short duration of this trial, the methodology and frequency of laboratory assessments seems appropriate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Reference is made to the clinical pharmacology review for information on the metabolic, clearance, and interaction of NEXIUM® I.V. According to the current labeling, NEXIUM® is extensively metabolized by the cytochrome P450 enzyme system. Prior studies have shown that for the youngest patients (those <2 years), clearance increases with age.

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

Adverse events associated with the use of oral and intravenous NEXIUM® in adults have been studied and reported extensively. Reference is made to section 2.4 above. Most of adverse events identified in the literature and listed in the "Warnings and Precautions" section of the labeling are associated with long term use. The sponsor made no specific attempts to include monitoring of these adverse events in their clinical trial. This seems appropriate and reasonable. Proton pump inhibitors have been shown to interfere with the absorption of drugs where gastric pH is a determinant of bioavailability. In there protocol, the sponsor included a list of prohibited concomitant medications.

7.3 Major Safety Results

The safety evaluation of NEXIUM® I.V. in pediatric patients is based largely upon the data submitted study D9615C00021. Safety experience from previous trials with intravenous and oral forms of NEXIUM® in adults and children is supportive. For the purposes of this review, that data was not reanalyzed.

7.3.1 Deaths

There were no deaths during the conduct of trial D9615C00021. One patient (E1014004), a 14 year old with an extensive past medical history including Burkitt's Lymphoma and Ataxia Telangiectasia died approximately 7 weeks after the end of treatment with study drug. It is reasonable to assume that this was not related to study drug.

Of note, there were no fatalities documented in any of the previous trials conducted with oral esomeprazole.

7.3.2 Nonfatal Serious Adverse Events

A total of 6 patients in this open label trial experienced 8 serious adverse events (SAEs). None of the SAEs were considered to be treatment related. The table below summarizes the SAEs in this trial. When the reviewer's assessment of the AE relatedness is different from that of the investigator, it is presented in parentheses in the "Relatedness" column.

Table 7 Summary and Narrative of Serious Adverse Events for Trial D9615C00021

Subject/ Patient Number	Center	Treatment	Preferred Term for SAE	Narrative	Relatedness
E1001001/503	1001	Eso 0.5mg/kg (0 to 1 mo)	Bronchial Hyper reactivity	1 month old female with a Past medical history significant for prematurity (37wk gestation), apnea, bradycardia. The patient also had respiratory distress, respiratory failure, suspected bronchiolitis and pneumonia in addition to a metabolic alkalosis, anemia leukocytosis, and reflux. The patient enrolled in the study on 12/7/2007(received study drug on 12/8 – 12/11) (b) (6) days after the patient received last dose, she developed respiratory distress, tachycardia, and fever. Patient was hospitalized for Influenza A and received the appropriate treatment. The patient had not been discharged from the hospital at the time of study completion	Unrelated
E1001002/301	1001	Eso 10mg (1 to 5yr)	Acute Respiratory Distress	1 year old female child with a past medical history of congenital vertical talus, osteomyelitis and right septic arthritis, left cephalohematoma, patent ductus arteriosus, and possible seizures. The patient also had spastic encephalopathy, respiratory distress secondary to recurrent pneumonia, bronchiolitis, GERD, hyperchloremia, hyperglycemia, and hypoalbuminemia Patient entered the study on 02/10/2008 and received her last dose of study medication on 02/11/2008. After loss of access secondary to IV infiltration the patient was discontinued from the study. There is no mention of when the patient was discharged from the hospital (b) (6) days late the patient developed respiratory distress and was again hospitalized, treated with steroids, anticholinergics, beta agonists and released after 2 days of admission.	Unrelated (Very unlikely related to study drug given timing of event. However, can not rule out completely as PPIs have been associated with increased risk of pneumonia)
E1001005/212	1001	Eso 10mg (6 to 11 yr)	Ulcerative Colitis	7 year old male child with a past medical history of lymphadenitis, sinusitis, anemia, hematochezia, gastritis, and ulcerative colitis. Randomized and dosed with study drug on 03/20/2009. Last dose administered on 03/23/2008. Two days later patient developed bloody stools and increased frequency. On (b) (6), patient was hospitalized for UC flare and treated with steroids, antibiotics, and immunomodulators. Pt discharged on (b) (6).	Unrelated

E1013004/211	1013	Eso 20mg (6 to 11 yr)	Acute Respiratory Failure	10 year old male with chronic abdominal pain, chronic constipation, fecal impaction, and presumptive GERD. Enrolled on 02/23/2009. Randomized and dosed on 02/24/2009. Pt diagnosed with pneumonia on (b) (6) day and later developed acute respiratory failure. Pt was intubated and treated with appropriate antibiotics prior to being transferred to the PICU of another hospital. Upon transfer patient was discontinued from the study.	Unrelated
E1016001/111	1016	Eso 40mg (12 to 17 yr)	Gastroenteritis Abdominal Abscess Psoas Abscess	This 15year old patient experienced three SAES. Past medical history was significant for tonsillitis, adenoiditis, chronic serous otitis media, Crohns, anemia, and GERD. On 01/07/2009 patient randomized and received study drug. Last dose administered on 01/10/2009. (b) (6) days later (b) (6) patient experienced abdominal pain and dehydration secondary to nausea and vomiting and was hospitalized two days later with a diagnosis of gastroenteritis. After receiving appropriate therapy, the patient was discharged on (b) (6) and with complete resolution of her symptoms on 01/25/2009. On (b) (6), patient developed increasing abdominal pain and was later hospitalized for an abdominal abscess and illiopsoas abscess. Patient was still hospitalized at the time of study completion	Unrelated
E3001003/502	3001	Eso 0.5mg/kg (0 to 1 mo)	Candidal sepsis	2 day old male. Past medical history significant for prematurity (33 weeks), duodenal atresia, partial bowel resection, and suspected GERD. Patient enrolled into study on day of life #3 and randomized to drug on day of life #4. Last dose of study drug administered on day of life #7. (b) (6) days after last dose patient developed petechiae, tachycardia, increased oxygen requirements. Diagnosis of fungal septicemia confirmed by cultures from the patient's central venous line. Septicemia had not resolved by the time of study completion	Unrelated

7.3.3 Dropouts and/or Discontinuations

Of the 62 patients enrolled, two patients were discontinued from the trial.

Patient E1001002 was a 1 year old female with an extensive past medical history including osteomyelitis, septic arthritis, arthrogryposis, spastic encephalopathy, respiratory distress, recurrent pneumonia, GERD, hyperchloremia, hyperglycemia and hypoalbuminemia. On the 2nd day of study therapy the patient's intravenous line infiltrated and the patient was discontinued from the trial. (b) (6) days after the patient was discontinued, she was hospitalized again for acute respiratory distress and treated with steroids, Albuterol, Atrovent, metoclopramide and ranitidine. The patient was discharged 2 days after admission.

Patient E1013004 was a 10 year old male child with a medical history of chronic abdominal pain, chronic constipation, fecal impaction, and presumptive GERD who received one dose of the study drug prior to discontinuation for acute respiratory failure thought to be secondary to pneumonia complications diagnosed earlier in the day.

7.3.4 Significant Adverse Events

There were no other significant adverse events. Most adverse events were mild or moderate in intensity. A total of 5 adverse events of severe intensity were recorded for 3 patients. However, these were also reported as SAEs above. (See narratives for patient E1016001, E1013004, and E101002 in section 7.3.2.)

7.3.5 Submission Specific Primary Safety Concerns

There are no submission specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events were from the "Gastrointestinal disorders" SOC and constipation was the most commonly reported term. The following tables, reproduced from the sponsor's submission provides the number of patient in the trial with adverse events by SOC and most commonly reported adverse events. This information was verified by the reviewer.

Table 8 Number of patients with adverse events by system organ class

	Esomeprazole treatment group							
	0 to 1 month[b] (0.5 mg/kg) N=6	1 to 11 months[c] (1 mg/kg) N=9	1 to 5 years (10 mg) N=8	6 to 11 years (10 mg) N=8	6 to 11 years (20 mg) N=9	12 to 17 years (20 mg) N=8	12 to 17 years (40 mg) N=9	Total N=57
System organ class	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any AE	2 (33.3)	5 (55.6)	7 (87.5)	5 (62.5)	2 (22.2)	5 (62.5)	5 (55.6)	31 (54.4)
Gastrointestinal disorders	0	3 (33.3)	6 (75.0)	5 (62.5)	2 (22.2)	3 (37.5)	1 (11.1)	20 (35.1)
Respiratory, thoracic, and mediastinal disorders	1 (16.7)	5 (55.6)	3 (37.5)	0	1 (11.1)	2 (25.0)	0	12 (21.1)
General disorders and administration site conditions	1 (16.7)	2 (22.2)	3 (37.5)	1 (12.5)	1 (11.1)	2 (25.0)	1 (11.1)	11 (19.3)
Skin and subcutaneous tissue disorders	0	3 (33.3)	1 (12.5)	1 (12.5)	0	3 (37.5)	2 (22.2)	10 (17.5)
Infections and infestations	2 (33.3)	3 (33.3)	0	0	2 (22.2)	0	1 (11.1)	8 (14.0)
Investigations	0	2 (22.2)	0	1 (12.5)	0	0	1 (11.1)	4 (7.0)
Metabolism and nutrition disorders	1 (16.7)	2 (22.2)	1 (12.5)	0	0	0	0	4 (7.0)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	3 (37.5)	1 (11.1)	4 (7.0)
Cardiac disorders	1 (16.7)	0	1 (12.5)	0	0	1 (12.5)	0	3 (5.3)
Injury, poisoning, and procedural complications	0	1 (11.1)	1 (12.5)	0	0	1 (12.5)	0	3 (5.3)
Nervous system disorders	0	0	0	0	1 (11.1)	0	2 (22.2)	3 (5.3)
Blood and lymphatic system disorders	1 (16.7)	0	0	0	0	1 (12.5)	0	2 (3.5)
Psychiatric disorders	0	0	1 (12.5)	0	0	1 (12.5)	0	2 (3.5)
Vascular disorders	1 (16.7)	0	0	0	0	1 (12.5)	0	2 (3.5)
Congenital, familial, and genetic disorders	0	1 (11.1)	0	0	0	0	0	1 (1.8)
Eye disorders	0	1 (11.1)	0	0	0	0	0	1 (1.8)
Reproductive system and breast disorders	0	0	1 (12.5)	0	0	0	0	1 (1.8)

Reproduced from Table 21 of the Clinical Study Report for Trial D9615C00021

Table 9 Most Commonly Reported Adverse Events By Treatment Group

	Esomeprazole treatment group							
	0 to 1 month[c] (0.5 mg/kg) N=6	1 to 11 months[d] (1 mg/kg) N=9	1 to 5 years (10 mg) N=8	6 to 11 years (10 mg) N=8	6 to 11 years (20 mg) N=9	12 to 17 years (20 mg) N=8	12 to 17 years (40 mg) N=9	Total N=57
MedDRA preferred term	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any AE	2 (33.3)	5 (55.6)	7 (87.5)	5 (62.5)	2 (22.2)	5 (62.5)	5 (55.6)	31 (54.4)
Constipation	0	2 (22.2)	2 (25.0)	1 (12.5)	0	0	1 (11.1)	6 (10.5)
Pyrexia	0	1 (11.1)	1 (12.5)	0	1 (11.1)	2 (25.0)	0	5 (8.8)
Arthralgia	0	0	0	0	0	2 (25.0)	1 (11.1)	3 (5.3)
Erythema	0	3 (33.3)	0	0	0	0	0	3 (5.3)
Pruritus	0	0	0	0	0	2 (25.0)	1 (1.11)	3 (5.3)
Rash	0	1 (11.1)	1 (12.5)	0	0	0	1 (11.1)	3 (5.3)
Tachycardia	1 (16.7)	0	1 (12.5)	0	0	1 (12.5)	0	3 (5.3)
Abdominal distension	0	2 (22.2)	0	0	0	0	0	2 (3.5)
Abdominal pain	0	0	2 (25.0)	0	0	0	0	2 (3.5)
Agitation	0	0	1 (12.5)	0	0	1 (12.5)	0	2 (3.5)
Anemia	1 (16.7)	0	0	0	0	1 (12.5)	0	2 (3.5)
Catheter related complication	0	1 (1.11)	1 (12.5)	0	0	0	0	2 (3.5)
Diarrhea	0	0	1 (12.5)	1 (12.5)	0	0	0	2 (3.5)
Gastroesophageal reflux disease	0	1 (11.1)	0	0	0	1 (12.5)	0	2 (3.5)
Hypokalemia	1 (16.7)	0	1 (12.5)	0	0	0	0	2 (3.5)
Hyponatremia	0	2 (22.2)	0	0	0	0	0	2 (3.5)

Reproduced from Table 21 of the Clinical Study Report for Trial D9615C00021

7.4.2 Laboratory Findings

Clinical laboratory trends and abnormal values were reviewed. There were no clinically important changes notes.

7.4.3 Vital Signs

Vital sign trends, individual abnormalities, and changes over the 4 days were reviewed. There were no vital sign changes of clinical significance.

7.4.4 Electrocardiograms (ECGs)

There were no clinically significant ECG recordings during the trial.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were submitted in support of this application.

7.4.6 Immunogenicity

This section is not applicable

7.5 Other Safety Explorations

This section is not applicable.

7.5.1 Dose Dependency for Adverse Events

As stated previously, the adverse events observed did not appear to be dose dependent. Reference is made to Section 7.2.2.

7.5.2 Time Dependency for Adverse Events

The applicant did not submit any data on the time dependency of adverse events. Given the short duration of the trial, it is very unlikely that any reasonable conclusions could have been drawn.

7.5.3 Drug-Demographic Interactions

There were no formal evaluations done to demonstrate the effect of intrinsic characteristics of the patient on the safety outcomes. This seems appropriate since the study numbers were small, not allowing the reviewer to establish any definitive

conclusions. As stated previously none of the patient subgroups experienced any noteworthy increase in the number of adverse events.

7.5.4 Drug-Disease Interactions

There were no new data related to drug-disease interactions that would affect the current labeling.

7.5.5 Drug-Drug Interactions

Current labeling for NEXIUM® reports drug interactions for antiretrovirals; drugs for which gastric pH can affect bioavailability; drugs metabolized by the cytochrome p-450 pathway; and clarithromycin. Concomitant use of clopidogrel and omeprazole has been associated with an increased risk of adverse outcomes following acute coronary syndrome. Current labeling states to avoid concomitant use of clopidogrel and omeprazole.

Most of the patients in the study used concomitant medications. However none were thought to interfere with the pharmacokinetics of the study drug or alter safety outcomes. There were no findings in the submitted trial that would change the current labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No additional carcinogenicity data were submitted. Per current labeling for NEXIUM® the carcinogenic potential was assessed using studies from omeprazole. While, there was an increased incidence of treatment related enterochromaffin-like cell hyperplasia in preclinical trials, the data was inconclusive.

7.6.2 Human Reproduction and Pregnancy Data

According to the label, this drug is a Pregnancy Category B.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment of growth effects was provided. The drug is intended for short-term use and unlikely to affect overall growth parameters long term.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose were reported during the clinical trial. There is limited experience with NEXIUM® overdosage (excess of 240mg/day). Symptoms are transient and manifestations may vary. The drug abuse potential is small. As stated previously, proton-pump inhibitor therapy in healthy volunteers may induce acid-related symptoms after withdrawal, a phenomenon referred to as rebound acid hypersecretion.

7.7 Additional Submissions / Safety Issues

8 Postmarketing Experience

NEXIUM® I.V. was approved for use in adults in 2005 in the United States. According to the applicant, from the time the drug first became commercially available in 2004 until 2009, more than (b) (4) intravenous doses have been delivered to wholesalers worldwide. The drug has been approved for marketing in more than 90 countries. Actual usage of the drug in children is unknown. The applicant conducted a search of their global safety database (SAPPHIRE) for adverse events associated with use of intravenous esomeprazole in pediatric patients through December 31, 2009. There were 7 cases reports with 15 events involving patients 0 to 17 years, inclusive. There were 5 non-serious case reports. Two cases met criteria for serious adverse events. One patient, a 4 month old, experienced what appeared to be a hypersensitivity reaction. She was given intravenous omeprazole and developed respiratory distress and facial swelling 30 minutes after drug administration. Later when given intravenous esomeprazole, the patient again had respiratory decomposition. The other patient who experienced an SAE was a 16 year old male with type 4 acute myeloblastic leukemia. This patient was on esomeprazole and several other medications when he developed cytotoxic edema, left hemiplegia, facial palsy, dysarthria, and an “epileptic fit.” The patient remained on esomeprazole and recovered from the event. It is unlikely that this was study drug related.

Changes have also been made to the core data sheet and labeling of NEXIUM® since this application was submitted. Information regarding digoxin and chromogranin A has been added to the label.

9 Appendices

9.1 Literature Review/References

The applicant provided information on natural history, manifestations, and prevalence of GERD in pediatric patients. The sponsor provided literature to support their dosing recommendations. The submitted information seemed adequate and appropriate for review.

9.2 Labeling Recommendations

Final label recommendations are subject to negotiations with the sponsor. The main labeling changes are related to the dosing recommendations as outlined in section 6.1.8. This reviewer also recommends that the instructions for the dosage and administration section be modified to be consistent with the indication. There were no new safety signals for pediatric patients in this application. The labeling should reflect this appropriately in the clinical trials section. See final labeling product for complete details.

9.3 Advisory Committee Meeting

On November 5, 2010, the Gastrointestinal Drug Advisory Committee met to determine if the pathophysiology of GERD is the same in patients 1 month to less than one year and adults. Additionally the committee was asked if acid suppressing agents are approved for symptomatic GERD in adults, should studies in pediatric patients ages 1 month to less than 1 year be required. The committee agreed that there is a small subset of patients in the 1 month to less than one year age range who have erosive esophagitis secondary to acid-mediated GERD. Therefore extrapolation of efficacy based on adult data is appropriate for this population in the age group.

10 References

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/s/

ERICA L WYNN
04/07/2011

ROBERT FIORENTINO
04/08/2011
I concur.