OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**21-689; SDN 94 & SDN 114**
	Submission Date: 3/31/2010
Brand Name	**Nexium IV**
Generic Name	**Esomeprazole Sodium**
PM Reviewer (Primary)	**Justin C. Earp, Ph.D.**
PM Team Leader	**Christine Garnett, Pharm.D.**
Clin Pharm Reviewer	**Kristina Estes, Pharm.D.**
Clin Pharm Team Leader	**Sue-Chih Lee, Ph.D.**
OCP Divisions	**DPM and DCP-3**
ORM Division	**OND/DGP**
Sponsor	**AstraZeneca**
Submission Type; Code	**Efficacy Supplement, SE1, SES, S017**
Formulation; Strength(s)	**Freeze-Dried Powder for Reconstitution & Injection. Vials are available as (b) (4) 20, or 40 mg dose strengths to be reconstituted in 5 mL of 0.9% Sodium Chloride Injection, USP.**
Indication	**Patients 1 month –17 years old: Treatment of Gastroesophageal Reflux Disease (GERD).**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology finds the application acceptable provided that the Agency and Sponsor can agree to the recommended dosing regimen for Nexium IV in pediatric patients 1 month to 17 years of age, and the label language. This application fulfills the PREA requirement identified in the approval letter dated March 31, 2005. Based on our review and independent analysis of the PK data in pediatrics and adults, we are recommending the following doses:

- Pediatric patients ages 1–17 years, inclusive: 10 mg QD for patients with body weight < 55 kg and 20 mg QD for patients with body weight ≥55 kg by intravenous infusion over 10–30 minutes.
- Pediatric patients ages 1–11 months, inclusive: 0.5 mg/kg QD given by intravenous infusion over 10–30 minutes.

Specific labeling recommendations are presented in Section 3.

1.2 Post Marketing Commitments

There are no post marketing commitments for this submission.

1.3 Post Marketing Requirements

There are no post marketing requirements for this submission.

1.4 Summary of Important Clinical Pharmacology Findings

Nexium is currently approved for use as an oral formulation in adults and pediatrics 1–17 years of age and as an IV formulation for use in adults only. The approved doses in adults are 20 mg and 40 mg QD. For pediatrics, the approved oral doses are 10 mg or 20 mg for 1–11 year old patients and 20 mg or 40 mg for 12–17 year old patients. A recent gastrointestinal division advisory committee meeting (GIDAC) on Nov. 5, 2010 concluded that it is reasonable to extrapolate adult PPI efficacy data to pediatric patients 1 month to < 1 year of age for the treatment of endoscopically-diagnosed erosive esophagitis secondary to acid related GERD provided that there are supporting PK and PD data. Therefore, the sponsor provided dosing recommendations for infants (b) (4)

The sponsor's proposed dosing for Nexium IV is as follows:

(b) (4)

In this submission, esomeprazole PK data were provided by 48 pediatric patients ranging in age from 3 days to 17 years. An inspection by the Division of Scientific Investigations found the methodology used in this study to be acceptable. Based on the population PK analyses, esomeprazole clearance and volume of distribution increased with body weight. No other covariates were found to correlate with esomeprazole clearance or volume of distribution.

The proposed doses gives [redacted] (b) (4) in pediatrics compared to 1) exposures observed at the minimally effective 20 mg IV dose in adults and 2) exposures observed in pediatrics after oral administration. Geometric mean C_{max} and AUC values are 10.5-fold and 2.44-fold higher that those observed in adults at the 20 mg dose. There are 11 minutes post-infusion before esomeprazole concentrations are comparable to those expected after the 20 mg 3-minute injection in adults. While exposures are higher within the first 11-minutes post-infusion, we are not aware of any acute safety issues. Esomeprazole exposures are also higher when compared to pediatric patients who received oral Nexium at the same dose. Pediatric patients 1–11 months and 12–17 years have 17- and 2.6-fold higher concentrations at 5-minutes post infusion and 6.5- and 1.34-fold higher AUC values when compared to oral administration in pediatrics for the same dose. The increased exposures after IV compared to oral Nexium are attributed to increasing bioavailability with age.

Using the population PK model, we selected doses to match pediatric exposures (AUC and C_{max}) to those observed in adults at the 20 mg IV dose (geometric mean AUC = 5.09 μmol•hr/L). Our results indicate that pediatrics 1–11 months old should receive 0.5 mg/kg QD. The geometric mean AUC for pediatrics 1–11 months old is 5.57 μmol•hr/L. For pediatric patients 1–17 years, the dose is 10 mg QD for patients whose body weight is < 55 kg and 20 mg QD for patients whose body weight is ≥ 55 kg. Geometric mean AUC values for the 10 and 20 mg dose groups are 6.80 and 9.69 μmol•hr/L, respectively. For all pediatric patients, increasing the infusion duration to 10–30 minutes reduces the C_{max} values to match those observed in adults. Geometric mean C_{max} values following a 30-minute infusion duration for the 0.5 mg/kg, 10, and 20 mg recommended pediatric doses are expected to be 5.21, 5.13, and 6.20 μmol•hr/L compared to 6.78 μmol•hr/L for the 20 mg dose given as a 3-minute injection in adults. Furthermore, esomeprazole AUC values are expected to be 16.7-, 2.87-, and 1.92-fold higher than those after oral administration in pediatrics for the FDA recommended 0.5 mg/kg, 10 mg, and 20 mg esomeprazole dose groups in pediatrics. This is due to increasing bioavailability of esomeprazole with increasing age. The joint oral/IV population PK model determined bioavailability to be 15% at 1 year of age increasing to 77% at 17 years of age.

Gastric pH was used as a biomarker for esomeprazole activity following administration of oral Nexium to pediatrics 1–11 months and IV Nexium to adults. Gastric pH endpoints evaluated were percentage time of pH >4 over 24 h and median pH over 24 h. A scatter plot of the exposure-response relationship for gastric pH (change from baseline) was similar between pediatrics and adults, with a plateau effect at AUC values >2–4 μmol•hr/L. Therefore, the exposures produced with the FDA recommended dosing regimens in pediatrics (median AUC (90% CI) of 6.8 (3.4, 17) μmol•hr/L for all dose groups) are expected result in a near maximal effect on gastric pH.

2 QUESTION BASED REVIEW

2.1 Key Review Questions

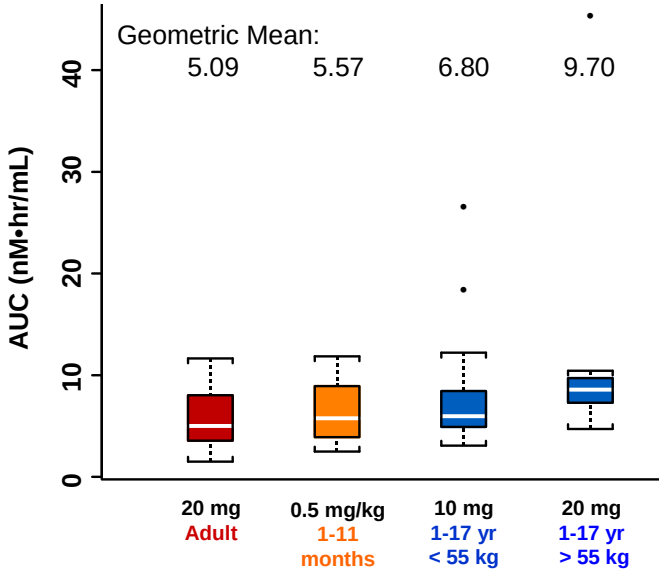
2.1.1 What dose in pediatric patients gives comparable exposures to those observed for adults at the lowest effective dose of 20 mg?

The FDA recommended pediatric dosing regimens are as follows:

- Pediatric patients ages 1–17 years, inclusive: 10 mg QD for patients with body weight < 55 kg and 20 mg QD for patients with body weight ≥55 kg by intravenous infusion over 10–30 minutes.
- Pediatric patients ages 1–11 months, inclusive: 0.5 mg/kg QD given by intravenous infusion over 10–30 minutes.

Because there is no therapeutic advantage of dosing 40 mg over 20 mg Nexium for the healing rate of erosive esophagitis and sustained resolution of heartburn in adult clinical trials (see the oral Nexium label)[1], the review team decided it is reasonable in pediatrics to give the minimally effective dose by matching exposures to the 20 mg dose in adults for both erosive esophagitis and symptomatic treatment of GERD. Figure 13 shows that AUC values from the FDA proposed doses are similar to the AUC values from 20-mg in adults. The revised regimen uses body weight cutoffs instead of age for pediatrics 1–17 years because the population PK model showed body weight (not age) is correlated with esomeprazole clearance.

Figure 1. The final FDA proposed dosing regimen produces similar AUC values compared to those in adults (red).

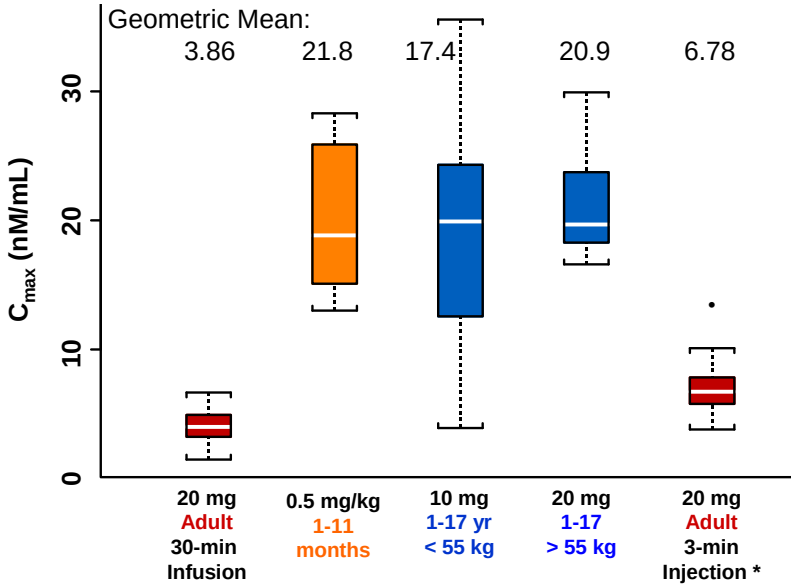


While the AUC values from the FDA regimen matched the AUC values from the 20 mg adult dose, the geometric mean C_{max} values for the FDA recommended 0.5 mg/kg, 10 mg, and 20 mg

[1] The approved IV label indicates a similar degree of response to Nexium in adults, "the intravenous dosage forms of Nexium 20 mg and 40 mg were similar to the corresponding oral dosage forms in their ability to suppress basal acid output and maximal acid output."

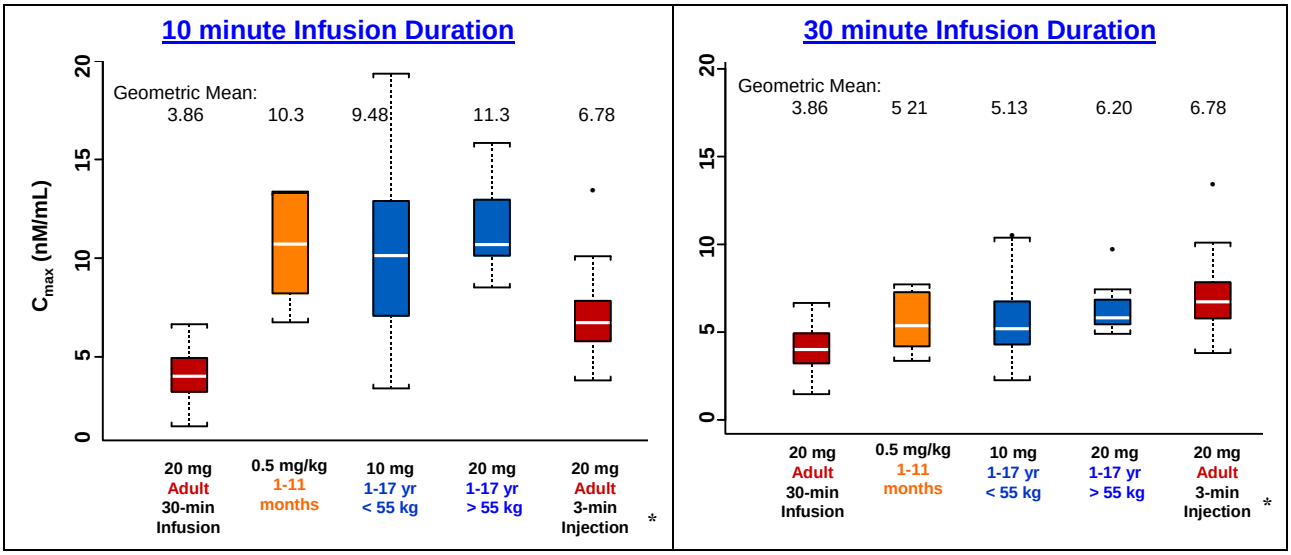
pediatric dose groups are 3.22-, 2.57-, and 3.08-fold higher than the geometric mean C_{max} value for the adult 20 mg dose given as a 3-minute injection (Figure 2).

Figure 2. Esomeprazole C_{max} values following 3-min injections in pediatrics are higher than those after 20 mg in adults.



* C_{max} values for the 3-minute injection are dose-normalized to 20 mg using the observed C_{max} values for the 40 mg dose given as a 3-minute injection in adults (Study SH-NEP-0003).

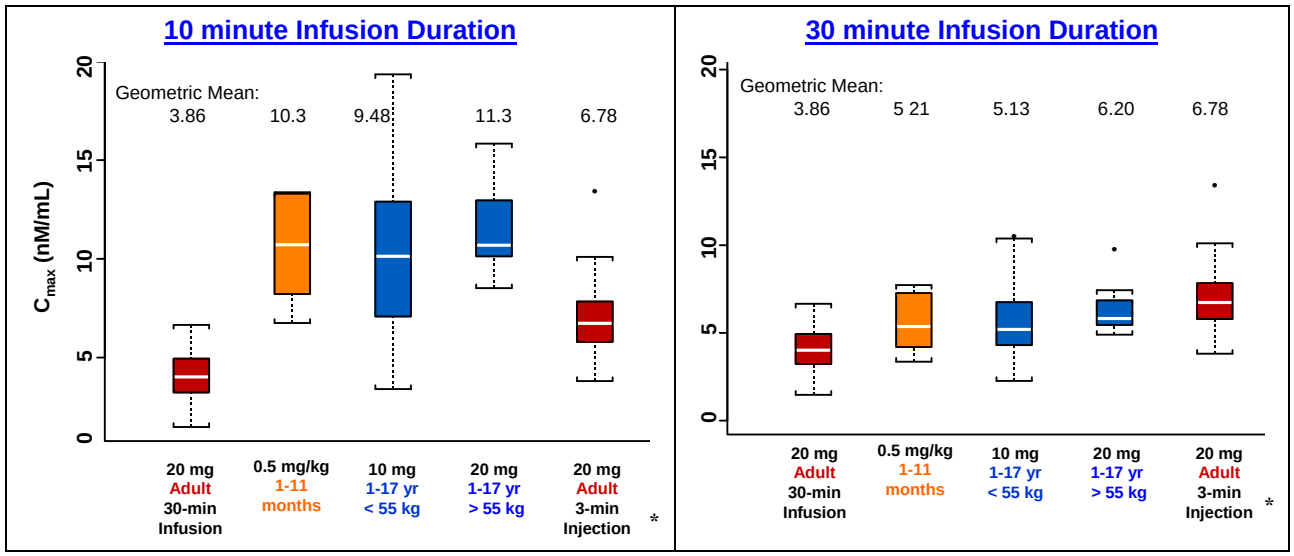
Increasing the infusion duration to 10 minutes matches the steady-state C_{max} values to that for the 40-mg, 3-minute injection in adults (Figure 3Figure 3. Increasing the IV Nexium infusion duration in pediatrics to 30- minutes matches steady-state C_{max} values to the 20 mg dose in adults. An 10-minute infusion duration in pediatrics produces steady-state C_{max} values that are less than those observed after the 40 mg dose in adults (13.5 nM/mL).



, left panel). Increasing the infusion time to 30 minutes matches the C_{max} values with that for the 20-mg, 3- or 30-minute infusion in adults (Figure 3, right panel). The 10-min infusion duration may be necessary if infusion durations of 30 minutes are impractical in pediatrics. Although

exposures in pediatrics are expected to be higher than the 20 mg dose in adults for infusions less than 30 minutes, these exposures are acute, and are projected to decline to concentrations comparable to the 20 mg adult dose within 2.4 minutes post-dose for a 10-minute infusion. We are not aware of what safety is targeted by this.

Figure 3. Increasing the IV Nexium infusion duration in pediatrics to 30- minutes matches steady-state C_{max} values to the 20 mg dose in adults. An 10-minute infusion duration in pediatrics produces steady-state C_{max} values that are less than those observed after the 40 mg dose in adults (13.5 nM/mL).



* C_{max} values for the 3-minute injection are dose-normalized to 20 mg using the observed C_{max} values for the 40 mg dose given as a 3-minute injection in adults (Study SH-NEP-0003).

2.2 General Attributes of the Drug

2.2.1 What is the pertinent regulatory history?

Oral esomeprazole was first approved in the US in 2001 in adults, for the treatment of GERD. A Nexium pediatric clinical program was designed to investigate the potential of esomeprazole to safely treat GERD in children from birth through age 17 years, inclusive. Label extensions for esomeprazole use in patients 12 years of age or older were approved in the US on 28 April 2006. Label extensions for esomeprazole use in patients 1 to 11 years of age and a new oral dosage form (sachet) of Nexium for children who require a 10 mg dose of esomeprazole were approved in the US on 27 February 2008.

The IV formulation of Nexium was approved in adults for injection and infusion in the US in 2005. The approved indication is for short-term (up to 10 days) treatment 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, The approval letter deferred pediatric study of esomeprazole IV required under the Pediatric Research Equity Act (PREA) and included a post-marketing commitment to conduct a pediatric study for the treatment of GERD in pediatric patients 0-17 years of age.

The sponsor submitted their pediatric development plan, which consisted of a single PK study in patients 0-17 years of age, in December 2006. The Agency provided feedback regarding the

pediatric development program in May 2007 and the full protocol for Study D9615C00021 was submitted in July 2007.

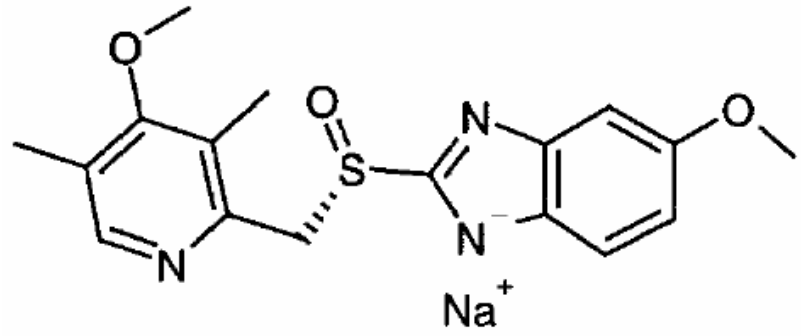
The current submission includes pharmacokinetic and safety data in pediatrics <17 years in order to bridge exposures to the approved oral formulation in the same age range and support the use of Nexium IV in pediatrics 1–17 years with GERD.

Currently oral Nexium is not approved for the treatment of GERD in patients less than one year of age. Results of a recent gastrointestinal division advisory committee meeting (GIDAC) on Nov. 5, 2010 indicate that it is reasonable to extrapolate adult efficacy data concerning the use of proton pump inhibitors in pediatric patients 1 month to < 1 year of age for the treatment of endoscopically-diagnosed erosive esophagitis secondary to acid related GERD provided that there are supporting PK and PD data. Consequently, the agency requested the sponsor propose dosing in patients from 1–11 months. (b) (4)

[redacted]

2.2.2 What are the highlights of chemistry and physio-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The active ingredient in Nexium IV (esomeprazole sodium) for Injection is (S)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1 H-benzimidazole sodium a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is C17H18N3O3SNa with molecular weight of 367.4 g/mol (sodium salt) and 345.4 g/mol (parent compound). Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%). The structural formula is:



Nexium IV for Injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 5 mL vial, intended for intravenous administration after reconstitution with 0.9% Sodium Chloride Injection, USP. Nexium IV for Injection contains esomeprazole sodium 21.3 mg or 42.5 mg equivalent to esomeprazole 20 mg or 40 mg, edetate disodium 1.5 mg and sodium hydroxide q.s. for pH adjustment.2 The pH of reconstituted solution of Nexium IV for Injection depends on the reconstitution volume and is in the pH range of 9 to 11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent.3 The rate of degradation increases with decreasing pH.

2.2.3 What are the proposed mechanism(s) of action and therapeutic indications?

Esomeprazole irreversibly inhibits the gastric proton pump, which reduces gastric acid production resulting in an increase in gastric pH.

Nexium is currently indicated for the treatment of GERD in adults with both IV and oral formulations and in pediatrics with oral Nexium. With this submission AstraZeneca is seeking the indication of GERD for Nexium IV.

2.2.4 What are the sponsor's proposed dosage(s) and route(s) of administration?

The proposed route of administration is intravenous (b) (4) 10-30 minute infusion. Table 1 shows the proposed dose amounts for Nexium IV.

Table 1. Sponsor's Proposed Dose Adjustments

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor supported the proposed pediatric indication by matching esomeprazole PK exposures with the approved oral formulation for the same age range. The sponsor studied esomeprazole PK & safety in patients <17 years old (Study D9615C00021) and used a population PK analysis to compare exposures in pediatrics after IV and oral dosing. There is one pivotal study.

Study D9615C00021: This was a randomized, open-label, multi-national, repeated dose study. Subjects were given a 4-day regimen of esomeprazole iv once daily. The study consisted of the following 7 treatment groups: 0 up to 1 month (0.5 mg/kg), 1 to 11 months (1.0 mg/kg), 1 to 5 years (10 mg), 6 to 11 years (10 mg), 6 to 11 years (20 mg), 12 to 17 years (20 mg) and 12 to 17 years (40 mg). The doses were given as a 3-minute injection. Blood samples for PK assessments were taken pre-dose and up to 8.5 hours post dose on day 4 (6 samples in 0 to 11 year olds and 8 samples in 12 to 17 year olds).

2.3.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Not applicable to this submission. Efficacy or PD data were not collected. For details on the PD and clinical endpoints used for approval in adults please refer to the labeling and general Clinical Pharmacology reviews in DARRTS by Dr. Suliman Al-Fayoumi, Ph.D. Primary reviews are dated 6/18/2004 and 9/18/2000. The original Nexium clinical pharmacology review can also be found in the approval package for NDA 021153 dated 2/20/2001. For details on the PD and clinical endpoints used for approval in pediatrics with the oral formulation see the clinical pharmacology review by Dr. Kristina Estes dated 6/16/2009

2.3.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, see Section 2.6.

2.3.4 Exposure-Response

2.3.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Not applicable to this submission. Data for effectiveness were neither collected nor submitted as part of this supplement.

2.3.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

No new types of adverse events were reported for Study D9615C00021 and the events that did occur were not considered serious adverse events. The most common events were constipation and pyrexia. Further the data were too few in number to establish a correlation between exposure and safety. As such, no exposure-safety relationships were established.

2.3.4.3 Does this drug prolong the QT or QTc interval?

Not applicable to this submission. Thorough QT prolongation studies have not been performed for Nexium.

2.3.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose is consistent with producing AUC values in pediatrics following IV administration compared to following oral dosing in pediatrics. However, C_{max} values are expected to be higher for pediatric patients receiving 3-minute injections compared to oral dosing and IV dosing in adults (See Section 4.4). Further the dose cutoffs are determined by age. Clearance is correlated with body weight rather than age and as such dosing recommendations are made for using body weight cutoffs between dose groups. Also, recommendations are made to increase the infusion

duration to 10-30 minutes to prevent high C_{max} values. (See Sections 1.1 and 2.1 for Dosing Recommendations and Justifications)

2.3.5 What are the PK Characteristics of the drug and its major metabolite?

The pharmacokinetics of esomeprazole have been previously established in adults. Please refer to the clinical pharmacology review by Dr. Suliman Al-Fayoumi, Ph.D dated 9/18/2000 for a complete description of esomeprazole PK characteristics in adults. In brief, in adults the PK of esomeprazole IV in patients are similar to healthy volunteers. Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady state in adult healthy volunteers is approximately 16 L. Esomeprazole is extensively metabolized in the liver by CYP3A4 and CYP2C19. The metabolites of esomeprazole do not exhibit antisecretory activity. Less than 1% of the esomeprazole dose is excreted unchanged in the urine.

2.3.5.1 What are the single dose and multiple dose PK parameters in pediatric patients?

Steady-state esomeprazole PK parameters and exposure estimates for each age group are shown in Table 2. Single dose PK were not evaluated in this age range for Nexium IV. However, studies in adults have indicated there is no accumulation with once daily dosing, owing to the short half-life of the drug (~1.4 hours). Esomeprazole pharmacokinetics in pediatrics after IV dosing are linear in the dose-range of 10–40 mg.

Table 2. Esomeprazole PK variables and exposure estimates across age groups. Data are presented as geometric means (range) of estimates from the final population PK model.

Analyte	Age group	0-1 month[a]	1-11 months[b,c]	1-5 years	6-11 years[d]		12-17 years	
	Dose group	0.5 mg/kg (n=6)	1.0 mg/kg (n=6)	10 mg (n=7)	10 mg (n=8)	20 mg (n=8)	20 mg (n=6)	40 mg (n=8)
Patient characteristics	Median age[e] (range)	4 days (2-36)	5.3 months (1.3-7.5)	2.8 years (1.3-5.2)	8.3 years (6.3-11.4)	8.6 years (6.4-11.7)	16.0 years (13.2-17.6)	16.2 years (13.2-17.4)
	Mean dose (mg/kg)	0.50 (0.49-0.51)	1.00 (0.97-1.00)	0.73 (0.43-1.18)	0.32 (0.20- 0.42)	0.67 (0.29-1.08)	0.36 (0.26-0.53)	0.77 (0.67-0.89)
	Median BW[f] (kg)	2.8 (2.4-4.1)	6.1 (5.1-8.0)	16.8 (8.5-23.0)	30.0 (24.8-49.7)	32.8 (18.5-69.0)	58.0 38.0-76.0)	52.4 (45.0-60.0)
Pharmacokinetic variables[g]	$C_{ss,max}$ (µmol/L)	3.71 (2.73-5.77)	8.68 (4.51-14)	9.37 (4.40-17.2)	5.60 (3.13-13.2)	8.83 (3.36-29.4)	7.10 (4.76-9.02)	10.5 (7.82-14.2)[h]
	AUC_τ (µmol*h/L)	7.5 (4.5-20.5)	10.5 (4.5-22.2)	7.9 (2.9-16.6)	6.9 (3.5-10.9)	14.4 (7.2-42.3)	8.1 (4.7-15.9)	17.6 (13.1-19.8)
	CL (L/h)	0.5 (0.1-1.0)	1.7 (0.9-3.1)	3.4 (1.6-9.5)	3.8 (2.7-5.1)	3.6 (1.1-8.0)	7.0 (3.4-12.3)	6.4 (5.5-8.7)
	CL (L/h/kg)	0.17 (0.04-0.32)	0.26 (0.12-0.58)	0.24 (0.09-0.66)	0.12 (0.08-0.17)	0.11 (0.02-0.25)	0.12 (0.09-0.21)	0.12 (0.10-0.16)
	V_{ss}[i] (L)	1.1 (0.8-2.2)	1.6 (1.5-1.7)	3.3 (2.4-4.6)	6.7 (4.0-14.0)	6.8 (4.9-10.7)	9.5 (7.8-11.3)	10.9 (8.0-15.9)
	V_{ss}[i] (L/kg)	0.38 (0.28-0.53)	0.25 (0.21-0.29)	0.23 (0.17-0.29)	0.21 (0.15-0.29)	0.20 (0.13-0.32)	0.17 (0.14-0.21)	0.21 (0.16-0.29)

[a] A patient in the age group 0 up 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 weeks. Corrected age is defined as the sum of gestational age and postnatal age.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks.

[c] Estimates for the outlier, ID39 (E1008004), are excluded.

[d] Estimates for ID18 (E4001003) excluded in the calculations of geometric mean/ranges for all variables except $C_{ss,max}$, because only 1 post-dose sample was taken and individual bayesian estimates were therefore deemed uncertain.

[e] Postnatal age.

[f] BW body weight.

[g] $C_{ss,max}$, maximum observed plasma concentration at steady-state; AUC_τ, area under the plasma concentration versus time curve during a dosage interval at Day 4; CL, total body clearance; V_{ss} , steady-state volume of distribution.

[h] $C_{ss,max}$ value for ID 1 (E1011001) not included in the analysis, due to contamination of the first sample taken.

[i] V_{ss} sum of individual estimates of central and peripheral volumes of distribution.

(Source: Sponsor's IV Population PK Report for Study D9615C00021, Table 5)

2.3.5.2 What is the pediatric inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Esomeprazole PK after IV administration in healthy pediatric volunteers has not been studied. For pediatric patients, inter-subject variability, expressed as %CV for population PK estimates, are 57% for esomeprazole clearance by CYP2C19 and 79% for esomeprazole clearance by CYP3A4. Each pathways' clearance was determined by the pharmacokinetic model for the metabolite of the respective elimination pathway. Intersubject variability is 61% for the central volume of distribution and 36% for the peripheral volume of distribution. Body weight was used as a covariate on both esomeprazole CL and V_D (See Section 4.1.1 for further details on the pediatric population PK model). The effects of other intrinsic factors such as age, albumin, and gender were evaluated and were not found to be significant covariates for CL and Vss.

2.4 Intrinsic Factors

2.4.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK

usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

See Sections 2.1.1, 2.3.5, and 4.2.4.1 for differences in PK between adults and pediatrics age 1 month to 17 years.

No efficacy information was collected. Also safety events data were too limited in sample size to conduct exposure-response analysis for safety.

2.4.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.4.2.1 Pediatric patients.

Please refer to Section 2.1

2.4.2.2 What is the status of pediatric studies and/or any pediatric plan for study?

The pediatric development program is complete with this submission.

Please refer to Section 2.2.1 for further details on the history of approvals in different pediatric age groups.

2.4.2.3 Elderly, Gender, Race, Renal impairment, Hepatic impairment

Not applicable to this submission. Please refer to the labeling and general clinical pharmacology reviews in DARRTS by Dr. Suliman Al-Fayoumi, Ph.D. Primary reviews are dated 6/18/2004 and 9/18/2000. The original Nexium clinical pharmacology review can also be found in the approval package for NDA 021153 dated 2/20/2001.

2.4.2.4 What pregnancy and lactation use information is there in the application?

Not applicable to this submission. Please refer to the labeling and general clinical pharmacology reviews in DARRTS by Dr. Suliman Al-Fayoumi, Ph.D. Primary reviews are dated 6/18/2004 and 9/18/2000. The original Nexium clinical pharmacology review can also be found in the approval package for NDA 021153 dated 2/20/2001.

2.5 Extrinsic Factors, General Biopharmaceutics

Please refer to the labeling and general clinical pharmacology reviews in DARRTS by Dr. Suliman Al-Fayoumi, Ph.D. Primary reviews are dated 6/18/2004 and 9/18/2000. The original Nexium clinical pharmacology review can also be found in the approval package for NDA 021153 dated 2/20/2001.

2.6 Analytical Topics

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The plasma concentrations of esomeprazole, the sulphone metabolite, and the 5-hydroxy metabolite were determined by LC/MS/MS by AstraZeneca R&D in Mölndal, Sweden. An inspection by the Division of Scientific Investigations (DSI) found the methodology used in this study to be acceptable (see the DSI review in DARRTS by Dr. Michael Skelly, dated 11/15/2010).

2.6.2 Which metabolites have been selected for analysis and why?

The esomeprazole 5-hydroxy and sulphone metabolites were also analyzed. These are the two primary metabolites formed via CYP 2C19 and 3A.

2.6.3 For all moieties measured, is free, bound or total measured?

Total concentrations were reported.

2.6.4 What bioanalytical methods are used to assess concentrations?

Esomeprazole, the sulphone metabolite, and the 5-hydroxy metabolite were quantified by LC/MS/MS.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

For all three analytes, the range of the standard curve was 20 to 20,000 nmol/L. This range is consistent with the esomeprazole concentrations observed in study D9615C00021 in which the mean C_{max} ranged from approximately 3710 – 10,500 nmol/L across the various age groups.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

For all three analytes, the range of quantification in both studies was 20 to 20,000 nmol/L.

2.6.4.3 What is the accuracy and precision at these limits?

For the esomeprazole calibration standards, the accuracy was -1.6% to +3.2% and the precision was 2.8% to 7.6%. For the sulphone metabolite calibration standards, the accuracy was -2.3% to +2.9% and the precision was 3.0% to 7.2%. For the 5-hydroxy metabolite calibration standards, the accuracy was -3.7% to +3.8% and the precision was 3.5% to 7.7%. The R^2 value for each run exceeded 0.9954.

For the esomeprazole QC samples, the accuracy was -8.3% to +1.4% and the precision was 3.0% to 5.3 %. For the sulphone metabolite QC samples, the accuracy was -4.0% to +1.5% and the precision was 3.8% to 8.0%. For the 5-hydroxy metabolite QC samples, the accuracy was -7.9% to +2.1% and the precision was 2.4% to 9.1%.

2.6.4.4 What is the sample stability under the conditions used in the study?

The esomeprazole plasma samples were stored at -20°C, at which they are stable for one year.

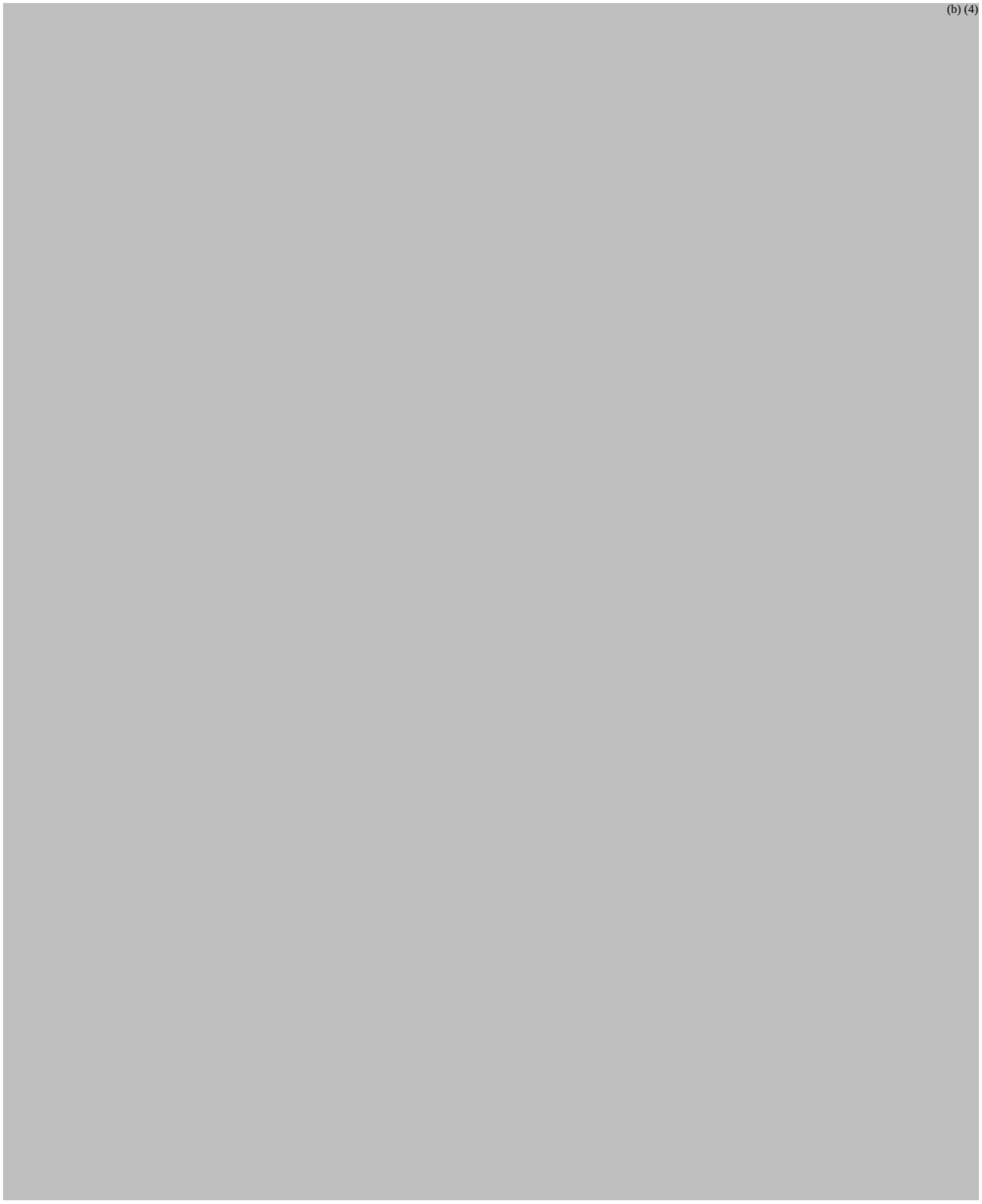
2.6.4.5 What is the QC sample plan?

Two QC samples at three concentration levels were analyzed in each run. For all three analytes, QC sample concentrations were 60, 600, and 16,000 nmol/L.

3 DETAILED LABELING RECOMMENDATIONS

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



3.1.2 Patient Product Labeling

There were no Clinical Pharmacology revisions to the Patient Product Labeling

4 PHARMACOMETRIC REVIEW

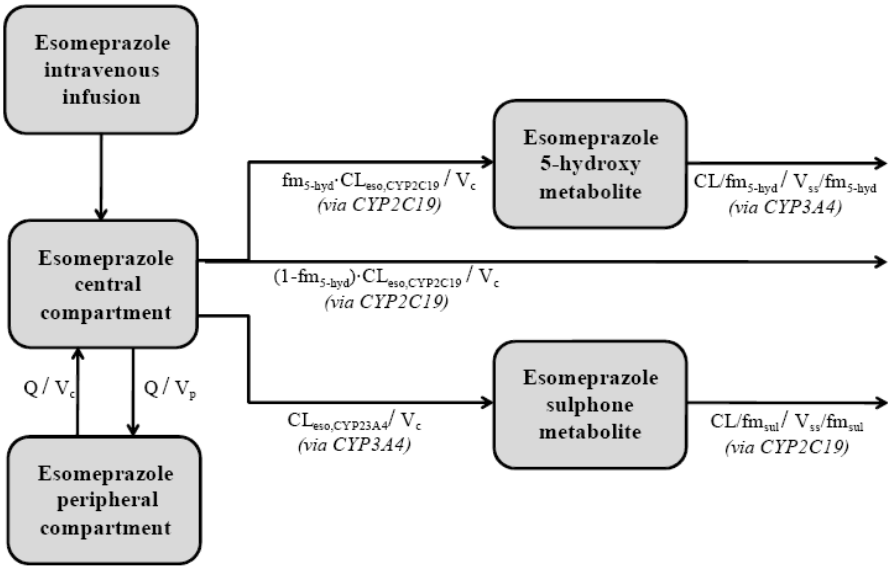
4.1 Results of Sponsor's Analysis

The sponsor analyzed both 1) IV esomeprazole PK data alone and 2) IV and PO esomeprazole PK data jointly for the IV dose selection in pediatrics and pediatric PK label statements. Both modeling efforts are briefly presented here. The population PK analysis for IV dosing is relevant to the labeling statements made in the Nexium IV label section 12.3. The model results were used to summarize the PK of esomeprazole for Nexium IV use. The results of the joint IV and PO analysis are the basis for the sponsor's dose selection for IV administration in pediatric patients 1–17 years old. The sponsor used the joint PK analysis to show the PK between formulations is comparable in pediatric patients at the same dose levels. However, we disagree with the sponsor's dosing proposals (see reviewer's comments in section 4.1.5).

4.1.1 IV Population PK Modeling Results

The sponsor's aim of the IV population PK analysis was to develop a population model, using the data collected in Study D9615C00021, which describes the steady-state pharmacokinetics of intravenously administered esomeprazole and its 5-hydroxy and sulphone metabolites using data from 0 to 17 year olds. Figure 4 and Table 3 show the structural model and final parameters estimates.

Figure 4. Schematic of structural modeling describing the steady-state PK of esomeprazole and its 5-hydroxy and sulphone metabolites after IV administration



(Source: Sponsor's IV Population PK Report, page 18)

Table 3. Estimated population PK parameters in the final models

		Basic model		Final model		Nonparametric bootstrap (N=200)			
	Parameter [a]	Estimate [b]	IIV [c] %	Estimate	IIV%	Median	%RSE [d]	IIV%	%RSE [d]
Typical population values	$CLeso_{,CYP3A4}$ (L/h/70kg$^{3/4}$)	3.09	76	2.55	79	2.05	58.9	76	44.0
	$CLeso_{,CYP2C19}$ (L/h/70kg$^{3/4}$)	4.53	59	5.1	57	5.03	24.6	67	27.7
	CL/fm5-hyd (L/h/70kg$^{3/4}$)	36.9	53	32.9	45	27.80	25.2	73	27.8
	CL/fmsul (L/h/70kg$^{3/4}$)	3.14	59	3.53	59	3.44	49.9	50	36.0
	Vc (L/70kg)	2.65	60	2.65	61	2.64	19.0	60	44.5
	Q (L/h/70kg$^{3/4}$)	27.2	52	27.3	52	26.70	12.9	52	52.5
	Vp (L/70kg)	12.8	36	12.8	36	12.45	5.6	38	27.1
	$Vss/fm_{,5\text{-}hyd}$ (L/70kg)	30.4	53	25.2	56 [e]	21.80	46.9	62 [e]	26.6
	$Vss/fm_{,sul}$ (L/70kg)	20	61	22.5	56 [e]	22.40	25.5	62 [e]	26.6
	Maturation half-life $CL/fm_{5\text{-}hyd}$ (w)	NA	NA	41.6	NE	41.30	3.7	NE	NA
	Slope of maturation function	NA	NA	18.9	NE	16.95	37.6	NE	NA
Residual variability	Eso_{prop}	0.19	12	0.19	13	0.20	18.1	15	81.0
	Eso_{add} (µmol/L)	0.01	12	0.01	13	0.01	33.3	15	81.0
	Sul_{prop}	0.11	NE	0.11	NE	0.12	12.9	NE	NA
	Sul_{add} (µmol/L)	0.03	NE	0.03	NE	0.03	26.2	NE	NA
	$5\text{-}hyd_{prop}$	0.08	NE	0.08	NE	0.07	28.6	NE	NA
	$5\text{-}hyd_{add}$ (µmol/L)	0.01	NE	0.01	NE	0.02	22.0	NE	NA

[a] $CLeso_{,CYP3A4}$, esomeprazole clearance via CYP3A4, $CLeso_{,CYP2C19}$, esomeprazole clearance via CYP2C19, CL/fm5-hyd, clearance of esomprazole 5-hydroxy metabolite confounded for the fraction metabolized, CL/fmsul, clearance of esomprazole sulphone metabolite confounded for the fraction metabolized, Vc, esomeprazole central volume of distribution, Q , esomeprazole intercompartmental clearance, Vp, esomeprazole peripheral volume of distribution $Vss/fm_{5\text{-}hyd}$, esomprazole 5-hydroxy metabolite volume of distribution, $Vss/fm_{,sul}$, esomprazole sulphone metabolite volume of distribution, . Eso_{prop}, esomeprazole proportional residual variability, Eso_{add}, esomeprazole additive residual variability, Sul_{prop}, esomeprazole sulphone metabolite proportional residual variability, Sul_{add}, esomeprazole sulphone metabolite additive residual variability, $5\text{-}hyd_{prop}$, esomeprazole 5-hydroxy metabolite proportional residual variability, $5\text{-}hyd_{add}$, esomeprazole 5-hydroxy metabolite additive residual variability, $CL/fm_{5\text{-}hyd}$, maturation half-life of esomeprazole 5-hydroxy metabolite clearance

[b] The values for the parameter estimates presented in the table represent estimates for the typical individual in the studied population.

[c] IIV, inter-individual variability, given in %; NE, not estimated.

[d] %RSE, relative standard error = (standard estimate of estimate/median estimate) * 100

[e] A single IIV term was estimated for $Vss/fm_{5\text{-}hyd}$ and $Vss/fm_{,sul}$

(Source : Sponsor's IV population PK Report, page 47)

The sponsor's covariate model affects only the individual clearance estimates. Clearance was modeled as follows:

$$\text{Clearance} = (BW/70)^{3/4} \cdot MF \cdot \theta_{CL}$$

where:

θ_{CL} = Population estimate of clearance term (L/h).

BW = Body weight (kg).

$MF = \text{maturation function} = 1/(1+(age/t_{½,maturation})^{-Hill}$

The maturation function was described as a change in clearance using a sigmoidal asymptotic function.

This approach to modeling clearance was tested on the clearance estimates for esomeprazole and each of the metabolites. Body weight was included as a covariate for the clearance values of each analyte. However, the model was significantly improved by including the maturation function for only the sulphone metabolite.

The sponsor made qualitative comparisons between the pediatric IV and the adult Cmax and AUC values in the label, but did not report the actual exposure values for each age and dose group. The sponsor's final population PK values for each age and dose group, based on the IV population PK model, are presented in Table 4.

Table 4. Esomeprazole PK variable and exposure estimates at Day 4 by age and dose group. Vales are presented as geometric means of individual Bayesian estimates from the final population PK model.

Analyte	Age group	0-1 month[a]	1-11 months[b,c]	1-5 years	6-11 years[d]		12-17 years	
	Dose group	0.5 mg/kg (n=6)	1.0 mg/kg (n=6)	10 mg (n=7)	10 mg (n=8)	20 mg (n=8)	20 mg (n=6)	40 mg (n=8)
Patient characteristics	Median age[e] (range)	4 days (2-36)	5.3 months (1.3-7.5)	2.8 years (1.3-5.2)	8.3 years (6.3-11.4)	8.6 years (6.4-11.7)	16.0 years (13.2-17.6)	16.2 years (13.2-17.4)
	Mean dose (mg/kg)	0.50 (0.49-0.51)	1.00 (0.97-1.00)	0.73 (0.43-1.18)	0.32 (0.20- 0.42)	0.67 (0.29-1.08)	0.36 (0.26-0.53)	0.77 (0.67-0.89)
	Median BW[f] (kg)	2.8 (2.4-4.1)	6.1 (5.1-8.0)	16.8 (8.5-23.0)	30.0 (24.8-49.7)	32.8 (18.5-69.0)	58.0 38.0-76.0)	52.4 (45.0-60.0)
Pharmacokinetic variables[g]	$C_{ss,max}$ (µmol/L)	3.71 (2.73-5.77)	8.68 (4.51-14)	9.37 (4.40-17.2)	5.60 (3.13-13.2)	8.83 (3.36-29.4)	7.10 (4.76-9.02)	10.5 (7.82-14.2)[h]
	AUC_τ (µmol*h/L)	7.5 (4.5-20.5)	10.5 (4.5-22.2)	7.9 (2.9-16.6)	6.9 (3.5-10.9)	14.4 (7.2-42.3)	8.1 (4.7-15.9)	17.6 (13.1-19.8)
	CL (L/h)	0.5 (0.1-1.0)	1.7 (0.9-3.1)	3.4 (1.6-9.5)	3.8 (2.7-5.1)	3.6 (1.1-8.0)	7.0 (3.4-12.3)	6.4 (5.5-8.7)
	CL (L/h/kg)	0.17 (0.04-0.32)	0.26 (0.12-0.58)	0.24 (0.09-0.66)	0.12 (0.08-0.17)	0.11 (0.02-0.25)	0.12 (0.09-0.21)	0.12 (0.10-0.16)
	V_{ss}[i] (L)	1.1 (0.8-2.2)	1.6 (1.5-1.7)	3.3 (2.4-4.6)	6.7 (4.0-14.0)	6.8 (4.9-10.7)	9.5 (7.8-11.3)	10.9 (8.0-15.9)
	V_{ss}[i] (L/kg)	0.38 (0.28-0.53)	0.25 (0.21-0.29)	0.23 (0.17-0.29)	0.21 (0.15-0.29)	0.20 (0.13-0.32)	0.17 (0.14-0.21)	0.21 (0.16-0.29)

[a] A patient in the age group 0 up 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 weeks. Corrected age is defined as the sum of gestational age and postnatal age.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks.

[c] Estimates for the outlier, ID39 (E1008004), are excluded.

[d] Estimates for ID18 (E4001003) excluded in the calculations of geometric mean/ranges for all variables except $C_{ss,max}$, because only 1 post-dose sample was taken and individual bayesian estimates were therefore deemed uncertain.

[e] Postnatal age.

[f] BW body weight.

[g] $C_{ss,max}$, maximum observed plasma concentration at steady-state; AUC_τ, area under the plasma concentration versus time curve during a dosage interval at Day 4; CL, total body clearance; V_{ss} , steady-state volume of distribution.

[h] $C_{ss,max}$ value for ID 1 (E1011001) not included in the analysis, due to contamination of the first sample taken.

[i] V_{ss} sum of individual estimates of central and peripheral volumes of distribution.

(Source : Sponsor's IV population PK Report, page 53)

4.1.2 Joint IV and Oral Population PK Modeling Results

The sponsor's aim of the joint IV and PO analysis was to develop a population model describing the steady-state pharmacokinetics of oral and IV esomeprazole across the age range of (b) to 17 years. The model was developed based on data from the pediatric IV data collected in Study D9615C00021 and oral data derived from studies SH-NEC-0002 (<1 month post term where term is 38 gestational weeks), SH-NEC-0001 (1 to 24 months), D9614C00099 (1 to 11 years), and D9614C00094 (12 to 17 years).

Estimates of the model parameters describing the disposition of esomeprazole were fixed to the final values in the previous analysis on IV data. Raw data from Study D9615C00021 was ignored. The model was further developed to describe also the absorption properties and oral bioavailability of esomeprazole. Data from 117 patients (591 samples) from the oral studies were included in the analysis.

- The final population pharmacokinetic model is a two-compartment disposition model, with the clearances and volumes allometrically scaled, and with a series of transit

compartments to capture the delay in esomeprazole absorption. Esomeprazole oral bioavailability, rate of absorption and residual variability were in the present analysis found to be related to age.

- The model predicted bioavailability was estimated to decline from 86% at birth at a rate of 1.4% per day, reaching a minimum of approximately 15% at the age of 7.5 months and thereafter maturing according to a sigmoidal function to reach a hypothetical maximum value of 99.6% at infinity age. However, for a patient at the upper limit of the studied age range (17.9 years) the bioavailability is predicted to 77%.
- The rate of absorption increased with age and C_{max} appears to occur earlier in the oldest age group (approximately 1.5 hour after dose) than in the youngest age group (approximately 2 hours after dose).

The model describes the data from the pediatric population included in the analysis. The results of the analysis indicate that the PK of PO esomeprazole is weight and age-dependent.

Table 5 shows the resulting geometric means for PK parameter estimates from the model by age group. C_{max} was not determined from the model. Instead, the maximum observed value after a steady-state dose was used.

Table 5. Final Joint Population PK Parameter Estimates

	Parameter [a,b]	Estimate	Bootstrap median (%RSE) [d]	IIV% [c]	%RSE[d]
Typical population values	$CL_{eso,CYP3A4}$ (L/h/70kg$^{3/4}$)	2.55	Fixed	79	Fixed
	$CL_{eso,CYP2C19}$ (L/h/70kg$^{3/4}$)	5.1	Fixed	57	Fixed
	CL/fm_{5-hyd} (L/h/70kg$^{3/4}$)	32.9	Fixed	45	Fixed
	CL/fm_{sul} (L/h/70kg$^{3/4}$)	3.53	Fixed	59	Fixed
	V_c (L/70kg)	2.65	Fixed	61	Fixed
	Q (L/h/70kg$^{3/4}$)	27.3	Fixed	52	Fixed
	V_p (L/70kg)	12.8	Fixed	36	Fixed
	Vss/fm_{5-hyd} (L/70kg)	25.2	Fixed	56 [e]	Fixed
	Vss/fm_{sul} (L/70kg)	22.5	Fixed	56 [e]	Fixed
	$MAT_{CL/fm\ 5-hyd}$ (w)	41.6	Fixed	NE	NA
	$SL_{MAT_{CL/fm\ 5-hyd}}$	18.9	Fixed	NE	NA
	F_{max} (%) [f]	99.6	17	NE	NA
	$MAT_{F_{max}}$ (day) [f]	1920	62	NE	NA
	$\theta_{Fmax_{PNA=0}}$ (%) [f]	85.7	19	NE	NA
	θ_{kFmax} (%/day) [f]	1.4	14	NE	NA
	θ_{PNA_F} [g]	-0.458	143	87.2	65
	$MAbsT$ [h] (h)	0.151	Fixed	NE	NA
	MTT (h)	1.6	6	41	35
	n	8.43	55	104	66
	$\theta_{PNA_{MTT}}$ [g]	-0.369	51	NE	NA
	θ_{PNA_n} [g]	2.75	33	NE	NA
Residual variability	Eso_{prop}	0.252	24	NE	NA
	Eso_{add} (µmol/L)	0.035	51	NE	NA
	$\theta_{PNA_{prop}}$ [g]	-0.307	116	NE	NA
	$\theta_{PNA_{add}}$ [g]	1.5	62	NE	NA
	Sul_{prop}	0.11	Fixed	NE	NA
	Sul_{add} (µmol/L)	0.03	Fixed	NE	NA
	$5-hyd_{prop}$	0.08	Fixed	NE	NA
	$5-hyd_{add}$ (µmol/L)	0.01	Fixed	NE	NA

[a] $CL_{eso,CYP3A4}$, esomeprazole clearance via CYP3A4, $CL_{eso,CYP2C19}$, esomeprazole clearance via CYP2C19, CL/fm_{5-hyd}, clearance of esomprazole 5-hydroxy metabolite confounded for the fraction metabolite volume of distribution, Vss/fm_{sul}, esomeprazole sulphone metabolite volume of distribution, Eso_{prop}, esomeprazole proportional residual variability, Eso_{add}, esomeprazole additive residual variability, Sul_{prop}, esomeprazole sulphone metabolite proportional residual variability, Sul_{add}, esomeprazole sulphone metabolite additive residual variability, $5-hyd_{prop}$, esomeprazole 5-hydroxy metabolite proportional residual variability, $5-hyd_{add}$, esomeprazole 5-hydroxy metabolite additive residual variability, $MAT_{CL/fm\ 5-hyd}$, maturation half-life of esomeprazole 5-hydroxy metabolite clearance, $MAbsT$ = mean absorption time, MTT = mean transit time, n = number of transit compartments.

[b] The values for the parameter estimates presented in the table represent estimates for the typical individual i the studied population.

[c] IIV, inter-individual variability, given in %; NE, not estimated.

[d] %RSE, relative standard error = (standard estimate of estimate/median estimate) * 100

[e] A single IIV term was estimated for Vss/fm_{5-hyd} and Vss/fm_{sul}

[f] Oral bioavailability (F)was described as an initial decrease in maximum oral bioavailability (Fmax)from birth ($\theta_{Fmax_{PNA=0}}$) at rate (θ_{kFmax})before maturing with a maturation half-life of $MAT_{F_{max}}$ to reach F_{max} in the oldest subjects and where IIV was a function of postnatal age (PNA) (see g)

[g] $\log(PNA/6)^{\theta_{effect}}$ where PNA = postnatal age (days) normalized to the log of the mean PNA and θ = fixe effect

[h] Mean absorption time (MAT) estimated as $1/k_a$ where k_a is the first-order absorption rate constant.

(Source: Sponsor's Joint Population PK Report, p39)

4.1.3 Dose Selection for Pediatrics Patients 1–17 years

The sponsor selected their doses based on a matching the AUC values from pediatric patients who received the IV formulation with AUC values in pediatric patients who received the oral formulation. To compare esomeprazole AUC values between the oral and IV administration across age groups model predictions of individual values, were generated based on the joint IV and oral population PK model and are presented in Table 6.

Table 6. Esomeprazole PK variable comparison between IV and oral formulations. Comparisons are made from steady-state values and are done by age group.

	Age group	**0-1 month** [a]		**1-11 months** [b]		**1-5 years**		**6-11 years**				**12-17 years**			
	Dose group	**0.5 mg/kg**		**1.0 mg/kg**		**10 mg**		**10 mg**		**20 mg**		**20 mg**		**40 mg**	
Patient characteristics	Median age [c] (range)	45 days (2-112)		6.0 months (1.39-8.79)		2.7 years (1.15-5.16)		8.6 years (6.18-11.95)		8.6 years (6.10-11.95)		14.6 years (12.04-17.58)		15.7 years (12.45-17.74)	
	Mean dose (mg/kg)	0.51		0.95		0.69		0.33		0.64		0.35		0.66	
	Median BW [d] (kg)	3.1		7.3		16.8		30.0		31.3		57.1		60.7	
	Formulation	Iv	Oral	Iv	Oral	Iv	Oral	Iv	Oral	Iv	Oral	Iv	Oral	Iv	Oral
Pharmacokinetic variables [e]	$C_{ss,max}$ (µmol/L)	5.3	0.9	11.9	0.7	10.1	1.7	5.8	1.8	11.2	3.4	7.0	2.6	13.4	5.1
	AUC_{τ} (µmol*h/L)	5.5	2.6	13.0	2.0	11.2	3.8	6.5	4.0	12.6	7.8	7.9	5.9	15.3	11.4
	F (%) [f]	-	46	-	15	-	34	-	62	-	62	-	73	-	75

[a] A patient in the age group 0 to 1 month is defined as a patient with a corrected age ≥ 32 complete weeks and < 44 complete weeks where corrected age is the sum of the gestational age and the age after birth in complete weeks.
[b] A patient in the age group 1 to 11 months had ≥ 44 complete weeks
[c] postnatal age
[d] BW = body weight
[e] $C_{ss,max}$ = maximum predicted plasma concentration at steady-state (5 minutes after stop of infusion); AUC_{τ} = area under the plasma concentration versus time curve during a dosing interval at day 4
[f] Bioavalability (F=1 for iv, and estimated for oral)
Data derived from "Population pharmacokinetic analysis of oral and iv esomeprazole in paediatric patients 0 to 17 years old, inclusive" (Module 5.3.3.5).

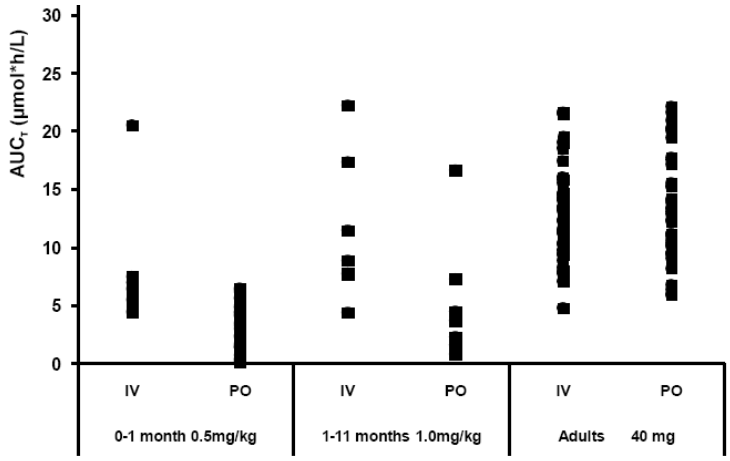
(Source: Sponsor's Summary of Clinical Pharmacology Studies, p39)

4.1.4 Dose Selection for Pediatrics 1–11 months

4.1.4.1 Esomeprazole exposure in patients < 1 year and adults

Individual AUCτ values following IV and oral administration in children and adults are presented in Figure 5. As can be seen in Figure 5, there is a large overlap of observed exposures in infants receiving Nexium IV and the infants receiving corresponding oral doses of esomeprazole, indicating that the safety data achieved in children on oral treatment is also relevant for IV administration in children. Furthermore, the exposures observed in the infants are similar or lower than those observed in adults receiving Nexium IV 40 mg.

Figure 5. Individual esomeprazole exposure (AUCτ) following repeated IV (3-min injection) and oral administration in infants 0 to 11 months old and adults.*

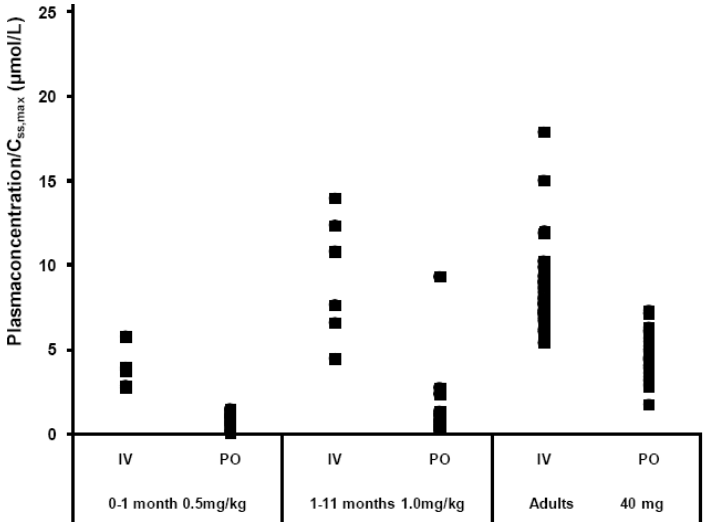


*Data derived from studies D9615C00021 (IV 0-17 years), SH-NEC-0002 (IV 0-1 month), SH-NEC-0001 (1-11 months), SH-NEP-0003 (IV adults) and SH-NEP-0002 (po adults)

(Source: Sponsor's Response to FDA's Information Request, SDN 114, Figure 1)

Regarding C_{max}, the model predicted values, in infants receiving Nexium IV is just before stop of injection, a time point when no observation was available to support the model and there are no corresponding data in adults. The sponsor compared the actual plasma concentrations measured in children 5 minutes after stop of injection with those measured in adults 7 minutes after stop of injection. These values together with C_{max} following oral administration of corresponding doses are presented in Figure 6. The peak plasma concentrations are higher when the dose is administered IV as a 3-minute injection compared to oral administration. The relationship between oral and IV administration seems to be similar in children and adults (Figure 6). Furthermore, all infants had similar or lower plasma concentrations compared to those observed in adults receiving IV esomeprazole 40 mg as 3-minute injection.

Figure 6. Individual plasma esomeprazole concentrations observed 5 minutes (infants) or 7 minutes (adults) after stop of a 3-minute injection and C_{max} following oral administration.*

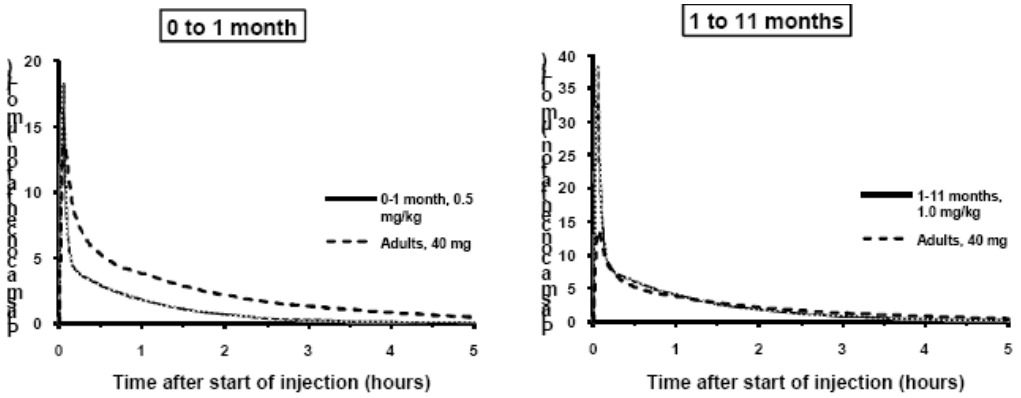


*Data derived from studies D9615C00021 (IV 0-17 years), SH-NEC-0002 (IV 0-1 month), SH-NEC-0001 (1-11 months), SH-NEP-0003 (40 mg IV injection adults) and SH-NEP-0002 (40 mg po adults)

(Source: Sponsor's Response to FDA's Information Request, SDN 114, Figure 2)

The esomeprazole plasma profiles predicted for a typical individual in each age (0 to 11 months) and dose group together with the mean plasma profile following IV esomeprazole 40 mg administered as a 3-minute injection in adults are presented in Figure 7. The predicted plasma profile following IV esomeprazole 1.0 mg/kg in 1 to 11 month olds and the mean plasma profile following IV esomeprazole 40 mg in adults are virtually super imposed. The predicted plasma profile following IV esomeprazole 0.5 mg/kg in 0 to 1 month olds is lower than the mean plasma profile in adults receiving IV esomeprazole 40 mg. The profiles only differ during the very first minutes when no observations were available from either the children or adults.

Figure 7. Esomeprazole plasma profiles following repeated IV administration as a 3-min injection for typical individual (median weight, median age and mean dose) in each age/dose group compared to mean plasma profile following repeated IV administration of esomeprazole 40 mg as a 3-min injection in adults.*



*Data derived from studies D9615C00021 (children) and SH-NEP-0003 (adults)

(Source: Sponsor's Response to FDA's Information Request, SDN 114, Figure 3)

Simulations were also conducted for IV administration of the dose as a 3-minute injection. The results of the simulations of C_{max} and plasma concentration versus time curves are presented in Table 7.

Based on these simulations, C_{max} (the concentration predicted 45 seconds after stop of injection or infusion), following IV administration of esomeprazole as a 10-minute infusion is expected to be reduced by an average 37% to 49% across all age and dose groups compared to when the dose is administered as a 3-minute injection (Table 7). Corresponding reductions for administration as a 20-minute and 30-minute infusion are 54% to 66% and 61% to 72%, respectively. The geometric mean of the corresponding predicted C_{max} following IV administration of esomeprazole as a 3-minute injection in the pediatric patients (Table 7) are higher than that reported for IV administration of 40 mg esomeprazole as 3 minute injection in adults (13.5 μmol/L) (SH-NEP-0003). However, the majority of the individual simulations for the 3-minute injection are within the range of those observed in the adults (range: 7.6 μmol/L to 26.7 μmol/L). The simulated C_{max} following IV administration of esomeprazole as a 30-minute infusion in the pediatric patients (Table 7) are similar to those observed following IV administration of 20 mg esomeprazole (geometric mean [range]: 3.68 μmol/L [1.47-6.62]) (SH-NEP-0008) and 40 mg esomeprazole (geometric mean [range]: 7.01 μmol/L [4.60-10.57]) (SH-NEP-0003) as 30-minutes infusions in adults.

The sponsor also notes:

The predicted values presented in Table 7 are for an exact time point (45 seconds after stop of administration). Even a small deviation from this time point could result in an appreciable change in plasma concentration especially for the 3-minute injection as the plasma concentration decrease quickly during the initial distribution phase (Figure 7). This should be borne in mind when comparing the predicted data with observed data such as those in studies SH-NEP-0003 and SH-NEP-0008.

Table 7. Model based predicted[a] C_{max} for esomeprazole (μmol/L; geometric mean and range) 45 seconds following stop of IV administration of esomeprazole as a 3-minute injection and 10-minute, 20-minute and 30-minute infusions. Difference (%, mean and range) versus 3-minute injection is also presented for the infusions.

Age/dose group	Injection	Infusion					
	3-minute	10-minute		20-minute		30-minute	
	$C_{ss,max}$	$C_{ss,max}$	Diff[b]	$C_{ss,max}$	Diff[b]	$C_{ss,max}$	Diff[b]
0-1 month, 0.5 mg/kg (n=6)	14.8 (10.1-26.1)	7.4 (5.2-11.7)	49 (40-57)	5.0 (3.7-7.2)	66 (55-75)	4.1 (3.1-5.7)	72 (61-81)
1-11 months, 1 mg/kg (n=6)[c]	30.4 (20.7-39.9)	16.3 (10.4-25.3)	45 (25-52)	11.1 (6.9-18.4)	62 (45-67)	9.0 (5.5-14.6)	70 (57-74)
1-5 years, 10 mg (n=7)	21.1 (14.7-28.8)	12.5 (8.7-16.7)	40 (18-51)	8.6 (5.4-12.0)	58 (35-70)	6.9 (4.0-10.0)	66 (46-77)
6-11 years, 10 mg (n=8)	15.1 (8.8-20.0)	8.8 (5.5-12.2)	41 (30-54)	6.1 (4.2-8.0)	60 (52-69)	4.9 (3.7-6.5)	67 (58-74)
6-11 years, 20 mg (n=8)	22.9 (7.6-36.0)	14.1 (6.7-24.4)	37 (12-56)	10.1 (5.8-16.0)	54 (23-71)	8.4 (5.2-12.9)	61 (31-76)
12-17 years, 20 mg (n=6)	18.0 (14.4-26.7)	10.4 (8.0-16.4)	42 (35-50)	7.1 (5.4-11.1)	61 (54-66)	5.7 (4.3-8.9)	68 (62-73)
12-17 years, 40 mg (n=8)	33.6 (22.6-62.9)	18.8 (12.9-29.9)	44 (37-52)	12.9 (9.5-18.2)	61 (56-71)	10.7 (8.2-14.1)	68 (62-78)

[a] Predictions are given for patients included in Study 21 and based on the individual Bayes estimates of the pharmacokinetic variables
[b] Difference calculated as 100*(injection-infusion)/injection
[c] The outlier E1008004 not included (suspected incorrect dose)

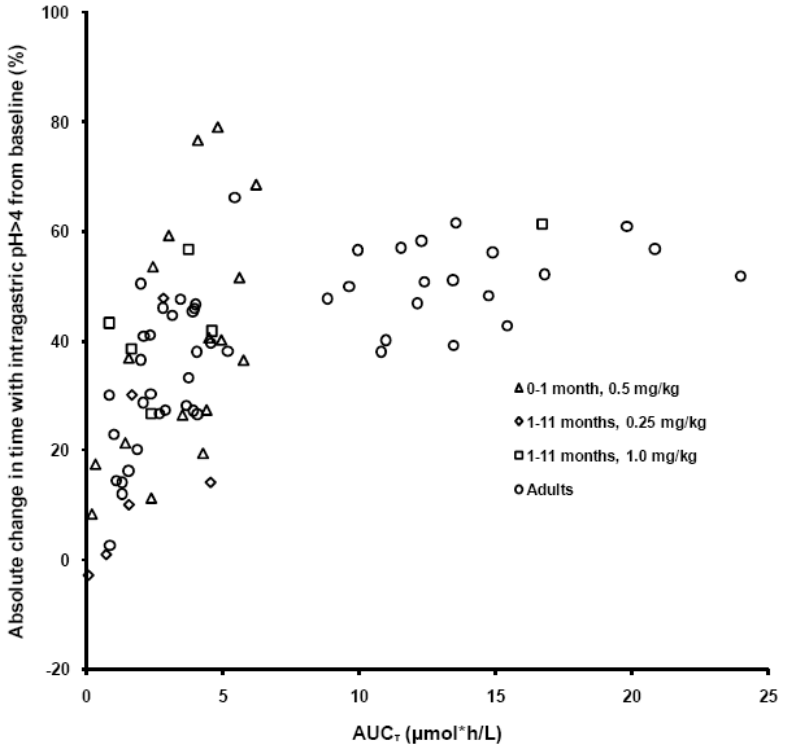
(Source: Sponsor's Response to FDA's Information Request, SDN 114, Table 1)

4.1.4.2 Sponsor's Exposure Response for pH Biomarkers

Intragastric pH data were not available after dosing with Nexium IV in pediatrics. The sponsor used data from studies SH-NEC-0001 (infants 1-11 months), SH-NEC-0002 (infants 0-1 month), and SH-QBE-0095 (adults) to compare the PK/PD relationships between pediatrics and adults and predict the effect on pH with their proposed Nexium IV dosing.

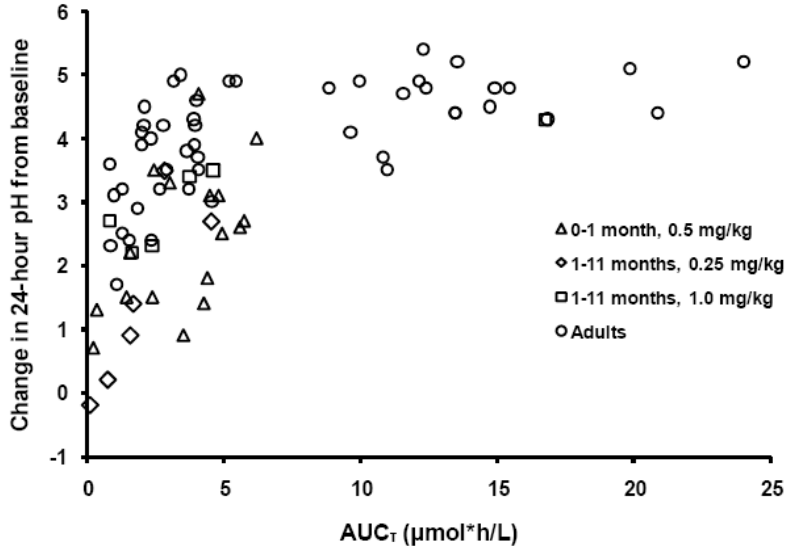
The effect on intragastric pH measured as change from baseline for percentage of time with intragastric pH>4 and 24-hour median intragastric pH versus AUCτ following oral administration of esomeprazole in infants 0–11 months and adults are presented in Figure 8 and Figure 9.

Figure 8. Effect on intragastric pH (absolute change in percentage of time with intragastric pH > 4 from baseline) versus exposure (AUCτ) in infants 0 to 11 months old and adults following repeated once daily oral dosing with esomeprazole.



(Source: Sponsor's Response to FDA's Information Request, SDN 114, Figure 5)

Figure 9. Effect on 24-hour median intragastric pH (change from baseline) versus exposure (AUC_τ) in infants 0 to 11 months old and adults following repeated once daily oral dosing with esomeprazole.



(Source: Sponsor's Response to FDA's Information Request, SDN 114, Figure 6)

The relationship between exposure and effect on intragastric pH, measured as absolute change in intragastric pH>4 from baseline, is similar in infants 0 to 11 months old and adults although the infants tend to have slightly higher and more variable effect on intragastric pH for a given exposure compared to adults (Figure 8). The relationship between esomeprazole exposure and effect on intragastric pH, measured as change in 24-hour median intragastric pH from baseline, is also similar in infants 0 to 11 months old and adults, with no apparent difference between infants and adults (Figure 9).

Based on this comparison the sponsor concludes the following:

- Although, there are no pharmacodynamic data available for pediatric patients of any age following IV esomeprazole administration, the exposure-response relationship in infants 0 to 11 months old is expected to be similar to that in adults also for IV administration of esomeprazole.
- Based on the plasma profiles presented in Figure 7 and the exposure (AUC) data presented in Figure 5,
    - The effect on intragastric pH following IV administration of esomeprazole 1.0 mg/kg in 1 to 11 month olds will be similar to that for IV esomeprazole 40 mg in adults
    - The effect on intragastric pH following IV administration of 0.5 mg/kg in 0 to 1 month olds is more likely to be approximately similar to that for IV esomeprazole 20 mg in adults.

4.1.5 Reviewer's Comments

There are aspects of the pediatric analysis that limit comparisons to the adult C_{max} and AUC results. This section will discuss these aspects of the pediatric analysis while more detailed discussion of the adult values can be found in the study reports for studies NEP0003 and NEP0008 from the original submission dated September 10, 2003 and in the clinical pharmacology review by Suliman 1. AI-Fayoumi, Ph.D on 6/18/2004.

Determination of Exposure Measures C_{max} for IV Data

The sponsor acknowledges the FDA's statement that longer infusion durations may reduce the C_{max} by simulations (Table 7). However, they still propose (b) (4) Their model-based results are consistent with the FDA's predictions for concentrations with different infusion durations.

Sponsor's Methodology for Dose Selection

- We do not agree with the sponsor's (b) (4)
    - The C_{max} and AUC values are comparable to the 40 mg dose in adults. Matching the 20 mg dose is preferred (b) (4)

- We do not agree (b) (4) [redacted]

- We agree with the sponsor's exposure-response analysis for pH markers % time pH > 4 in 24 hrs and median pH in 24 hrs represented as change from baseline that the PK/PD relationship for pH is similar between pediatrics and adults.

See the Reviewer's Analysis for matching pediatric exposures (C_{max} and AUC) to adult exposures following IV administration.

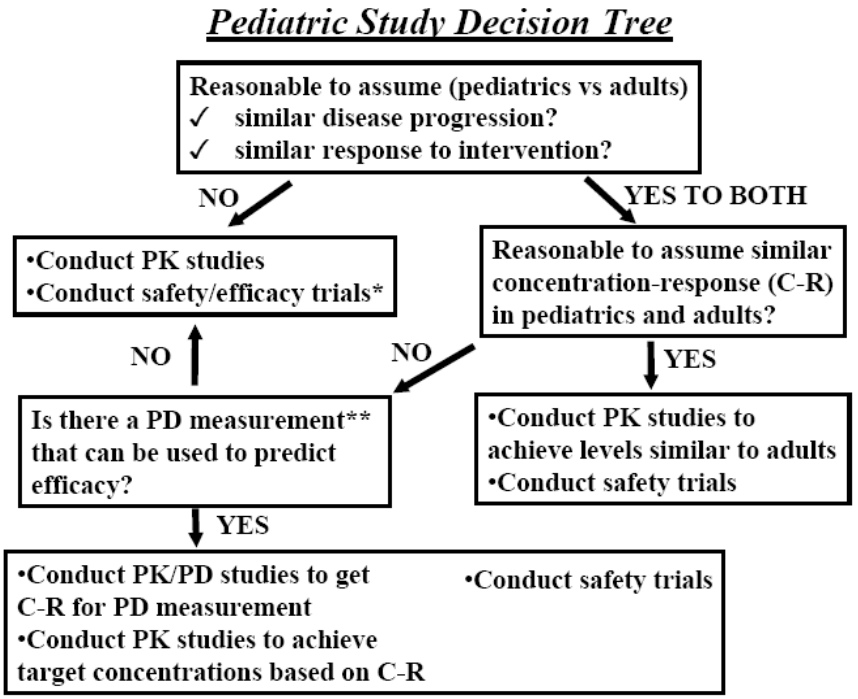
4.2 Reviewer's Analysis

4.2.1 Introduction

The sponsor is relying on efficacy data from previous clinical trials in adults for oral and IV Nexium and from clinical trials in pediatrics for oral Nexium. Since the disease progression and response to treatment is similar between pediatrics and adults, matching pediatric IV esomeprazole exposures with the adult exposures are expected to produce comparable effectiveness. This approach is consistent with the Pediatric Study Decision Tree found in the Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (Figure 10).

This pharmacometric review compares the C_{max} and AUC values resulting from the sponsor's proposed dosing regimen with the observed C_{max} and AUC values in the approved 20 and 40 mg IV doses in adult patients.

Figure 10. Schematic of Pediatric Decision Tree Used to Determine Review Strategy.



(Source: Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, page 21)

4.2.2 Objectives

Analysis objectives are:

1. Determine if proposed pediatric IV dosing regimen produces exposures similar to those in adult patients with IV administration.
2. Identify suitable dosing regimen if the proposed regimen does not match exposures in adult patients.

4.2.3 Methods

4.2.3.1 Data Sets

Data sets used are summarized in Table 8.

Table 8. Analysis Data Sets

Study Number	Name	Link to EDR
D9615C00021	pl1-6-1.xpt	\\Cdsesub1\evsprod\NDA021689\0031\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\stf-population-pk\crt\datasets
SH-NEC-0001, SH-NEC-0002, D9614C00094, D9614C00099, D9615C00021	allstd-6.xpt	\\Cdsesub1\evsprod\NDA021689\0031\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\stf-pk-joint-modelling\crt\datasets
SH-NEP-003	KINETIK.XPT	\\Fdswa150\nonectd\n21689\N_000\2003-09-10\crt\datasets\nep0003
SH-NEP-003	QU_LIMS.XPT	\\Fdswa150\nonectd\n21689\N_000\2003-09-10\crt\datasets\nep0003
SH-NEP-003	PHMON.XPT	\\Fdswa150\nonectd\n21689\N_000\2003-09-10\crt\datasets\nep0003
SH-NEP-008	KINETIK.XPT	\\Fdswa150\nonectd\n21689\N_000\2003-09-10\crt\datasets\nep0008
SH-NEP-008	QU_LIMS.XPT	\\Fdswa150\nonectd\n21689\N_000\2003-09-10\crt\datasets\nep0008
SH-NEP-008	PHMON.XPT	\\Fdswa150\nonectd\n21689\N_000\2003-09-10\crt\datasets\nep0008

4.2.3.2 Software

NONMEM VI (Icon, Ellicott City, MD) was used to review the sponsor's population PK model. S-PLUS 8.0 (TIBCO Software Inc., Palo Alto, CA) was used to generate all plots and manage datasets. The statistical software R (www.r-project.org) was used in combination with the population PK tool library in order to generate diagnostic and pertinent covariate plots.

4.2.3.3 Models

The sponsor's population PK model is acceptable and does not require further refinement (see Section 4.2.5.1 and the Appendix).

4.2.4 Results

Esomeprazole exposures at approved oral doses in pediatrics are shown to be effective in raising gastric pH. The reviewer's analysis also compares AUC values for the FDA proposed regimen to those observed with approved oral doses in pediatric patients. This is done to ensure the

esomeprazole exposures in pediatrics after IV dosing are not less than the exposures observed after approved oral doses.

4.2.4.1 Matching Pediatric IV to Adult IV exposures

For exposure matching to adults, the AUC and C_{max} values for the 20 mg dose in adults were 5.09 nM•hr/mL and 6.78 nM/mL. PK data were not available for the 20 mg 3-minute injection after dosing to steady-state. Thus, steady-state C_{max} data from study SH-NEP-0003 were dose-normalized to 20 mg.

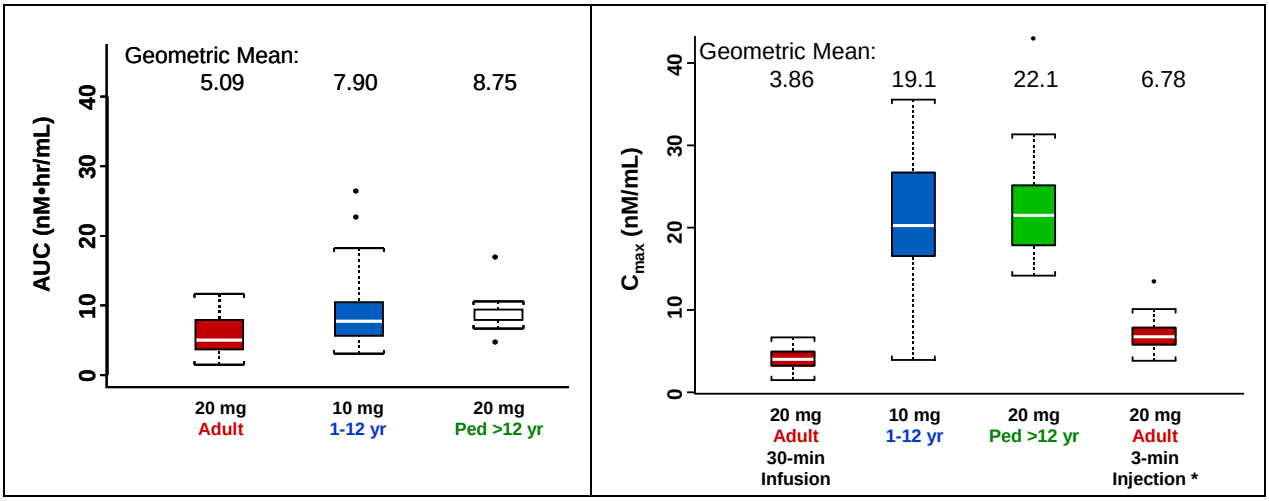
This part of the review identifies the exposures predicted by the sponsor's proposed dosing regimen, compares them to the adult IV exposures, and proposes alternate dosing scenarios to keep pediatric exposures in the adult therapeutic window.

Sponsor's Proposed Dosing for Symptomatic GERD & Erosive Esophagitis

Figure 11 and Figure 12 show the distributions of AUC values and C_{max} values for the proposed dosing scenarios compared to the observed values in adults for the approved 20 mg esomeprazole IV dose after either a 3-minute IV injection or 30-minute IV infusion. Esomeprazole AUC values are expected to be the same for either a 3-minute IV bolus or 30 minute IV infusion. Therefore, observed AUC values are shown only for study SH-NEP-0008.

Figure 11 shows that the proposed pediatric IV regimen for GERD produces AUC and C_{max} values that are higher for the proposed dosing when compared to exposures after the adult 20 mg dose. Esomeprazole AUC is 1.6–1.7-fold higher and C_{max} is 5.0–5.7-fold higher compared to the adult 20 mg dose.

Figure 11. The proposed GERD dosing produces similar AUC and higher C_{max} values (blue and green box plots) for pediatrics compared to those observed for adults (red).



* C_{max} values for the 3-minute injection are dose-normalized to 20 mg using the observed C_{max} values for the 40 mg dose given as a 3-minute injection in adults (Study SH-NEP-0003).

Figure 12 shows that the C_{max} values for the proposed erosive esophagitis dosing are higher than those observed in adults after the 20 mg dose. The proposed regimen for erosive-esophagitis produces 1.5–3.4-fold higher AUC values across the pediatric dose groups compared to the AUC values for the 20 mg dose in adults. Geometric means for C_{max} values are 3.8–6.5-fold higher

across pediatric dose groups compared to those projected in adults following 20 mg Nexium IV as a 3-minute IV injection.

Figure 12. The proposed erosive esophagitis dosing produces pediatric AUC and C_{max} values (blue and green box plots) that are higher than those observed for adults (red).

(b) (4)

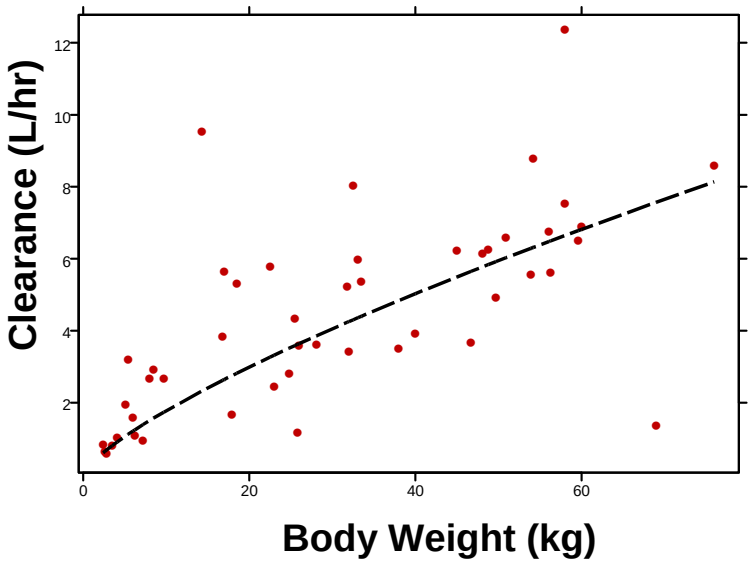
FDA's approach to exposure matching for pediatrics

Exposure comparisons from the proposed pediatric regimen were made to the adult 20 mg dose because there was no therapeutic advantage of the 40-mg dose over the 20-mg dose for either the healing rate of erosive esophagitis and sustained resolution of heartburn in adults (See the approved labels for oral Nexium and Nexium IV), the review team decided to target the exposure range (90% confidence interval of AUC and C_{max} values) for the lowest effective dose in adults for adjusting the pediatric dosing regimen.

Furthermore, we do not agree (b) (4)

Thus, the question arose as to whether fixed dosing with body weight cutoffs could be used to match AUC values between pediatrics and adults. Different body-weight cutoff values for defining the who received the 10 and 20 mg doses were tested by simulating exposures in each pediatric dose group, defined by that particular weight cutoff, and then comparing them with those from the 20 mg dose in adults. The body weight cutoff was chosen based on the regimen that produced comparable AUC values between the pediatric doses and the 20 mg dose in adults. Figure 1 shows that using a body weight cutoff of 55 kg in pediatrics 1-17 years old and weight based dosing (0.5 mg/kg) dosing in patients 1–11 months old matches the AUC values in pediatrics with the exposures from the 20-mg dose in adults. The body weight cutoff is recommended for its physiological relevance to pediatric dosing and is supported by the results of population PK analysis for both IV and oral esomeprazole data.

Figure 13. Clearance is correlated with patient body weight. Individual estimates of clearance are shown as red points. The dashed line depicts the population PK model correlation between bodyweight and clearance.

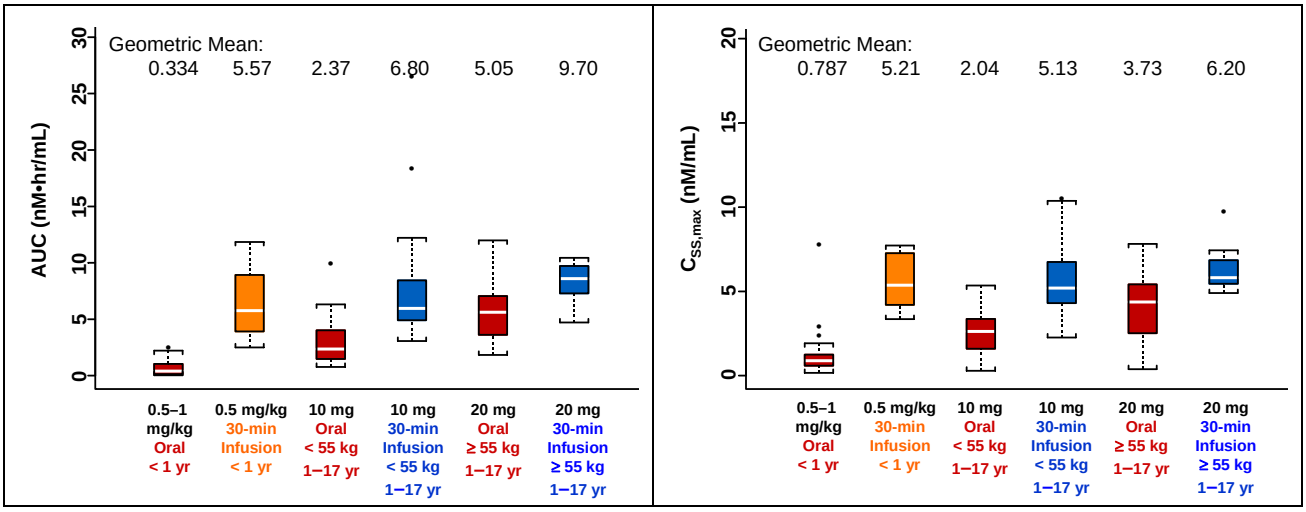


To match C_{max} values, we used the predicted concentrations at end-of-infusion. Figure 2 shows that for the revised regimen with a bodyweight cutoff, the esomeprazole C_{max} values after a 3-minute Nexium injection were higher than the C_{max} values for the adult 20-mg dose given as either a 3-minute injection or 30-minute infusion. The C_{max} in pediatric patients can be reduced by increasing the infusion duration. Figure 3 shows that increasing the infusion duration to 10–30 minutes produces C_{max} values that fall within the adult IV range for both 20 and 40 mg doses. Increasing the infusion duration to 10 minutes matches the steady-state C_{max} values to that for the 40-mg, 3-minute injection in adults. Increasing the infusion time to 30 minutes matches the C_{max} values with that for the 20-mg, 3-minute injection in adults. The 10-minute infusion duration may be necessary if infusion durations of 30 minutes are impractical in pediatrics.

4.2.4.2 Pediatric IV Compared to Pediatric Oral Esomeprazole Exposures

We also compared the predicted exposures for the FDA recommend IV dosing regimen to the observed pediatric oral data to ensure that reducing the Nexium IV dose in pediatrics did not yield exposures lower than those approved for pediatrics with oral Nexium. Figure 14 shows the exposures after the FDA recommend IV dosing are higher than after oral administration and more consistent across dose groups. This is expected since the bioavailability (~15% at 1 year of age and ~77% at 17 years of age) and the rate of absorption of oral esomeprazole are less than for Nexium IV.

Figure 14. Pediatric steady-state AUC and C_{max} values are shown for the FDA proposed IV dosing scenario (55 kg body weight cutoff & 30-minute infusion duration). Box plots show AUC and C_{max} values by dose group.

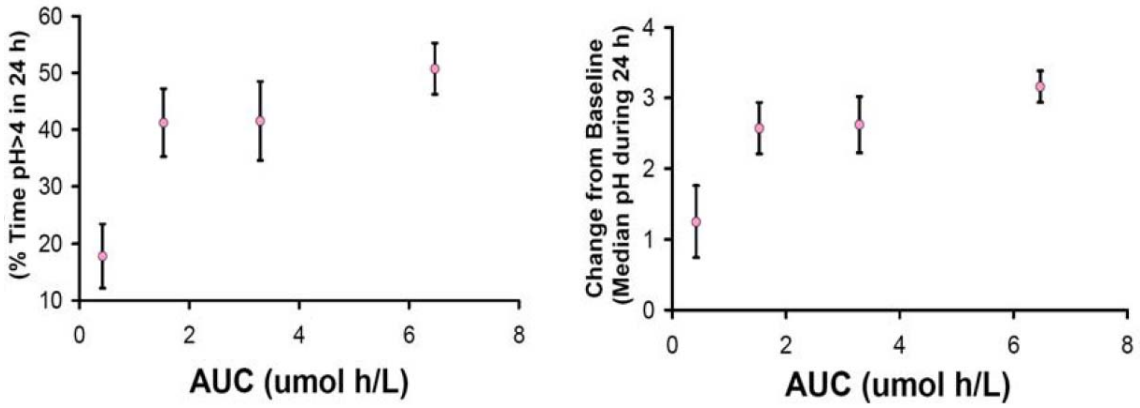


4.2.5 Esomeprazole Exposure-Response Analysis for pH Biomarkers in Pediatrics and Adults

The PK-PD relationships for pH response (% time pH > 4 in 24 hours and median pH in 24 hrs) after oral administration in 1–11 month pediatrics and after IV adminstration in adults were evaluated to determine if the exposures from the FDA recommended pediatric regimen produced a pH-response comparable to that approved for oral Nexium in pediatrics. The exposure-response relationship for oral administration in infants was established previously by Dr. Nitin Mehrotra for the review of oral Nexium for patients less than 1 year of age (NDA 21,957, S-004).

Figure 15 shows there are PK-PD relationships for % time pH > 4 in 24 hours and median pH in 24 hrs in pediatrics age birth to 11 months and that the response for each biomarker reaches a plateau above 2-4 µmol•hr/L.

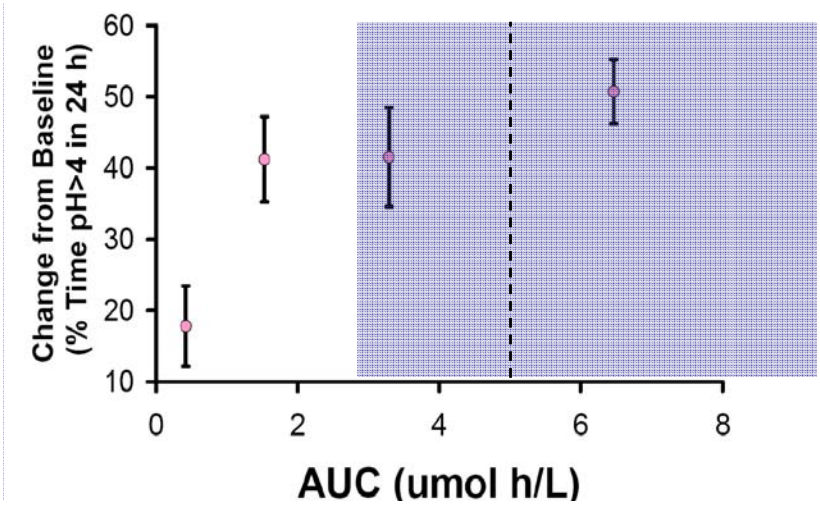
Figure 15. Change from Baseline for the % Time pH>4 and median pH during a 24 hour interval increases with increasing esomeprazole exposure in birth to 11 month pediatrics. Change from baseline in % Time (mean ± SE) is shown against the median time for each of 4 esomeprazole exposure quartiles



(Source: Clinical Pharmacology Review of NDA 21-957 by Drs. Kristina Estes and Nitin Mehrotra in DARRTS, dated 6/16/2009)

Figure 16 shows that the target exposure range (90% confidence interval for adult 20 mg data) produces a response for change from baseline % time pH > 4 in 24 hrs that is in the plateau of the PK-PD relationship. The median AUC (90% CI) from the FDA recommended dosing regimen is estimated to be 6.81 (3.38, 17.3) µmol•hr/L. More than 90% of exposures produced by the FDA regimen are expected to be result in a near maximal effect on % Time pH > 4 and median pH during a 24 hour interval.

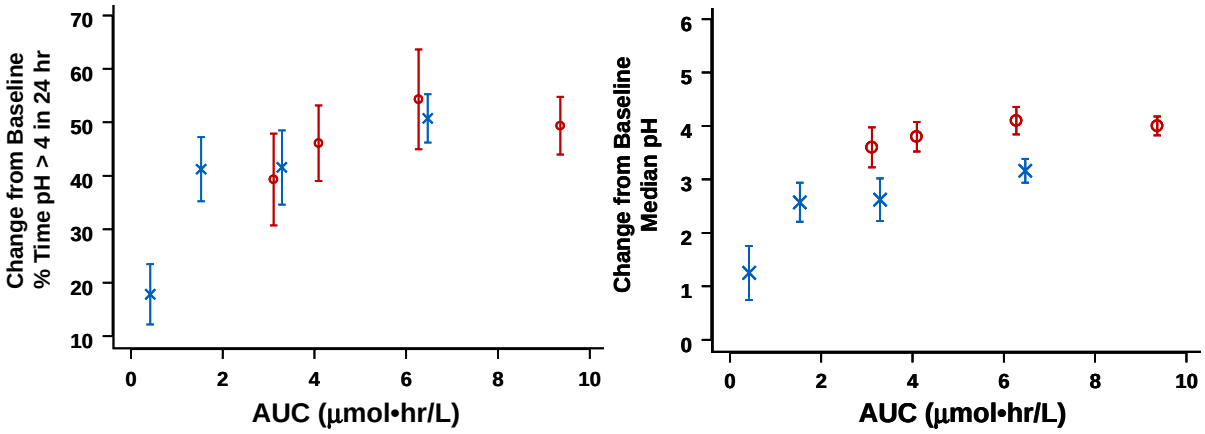
Figure 16. The adult 20 mg dose produces exposures in the plateau of pH effect for change from baseline in % time pH > 4 in 24 hrs for pediatrics 1 to 11 months old. The dashed vertical line is the geometric mean (5.09 µmol•hr/L) AUC for the adult 20 mg dose (Study SH-NEP-0008) and the shaded area represents the 90% confidence interval for the data at steady-state



(Source: Clinical Pharmacology Review of NDA 21-957 by Drs. Kristina Estes and Nitin Mehrotra in DARRTS, dated 6/16/2009)

Figure 17 indicates that the PK-PD relationships for both pH measures are similar between infants and adults. This is supportive of a comparable pH response in pediatrics 1–17 years of age where pH data are not available. This is also supportive of the GIDAC meeting's conclusion that efficacy can be extrapolated from adults to pediatric patients less than 1 year of age for the treatment of erosive esophagitis secondary to acid related GERD.

Figure 17. The PK/PD relationships for pH biomarkers represented as change from baseline are similar between infants (blue symbols) and adults (red symbols).



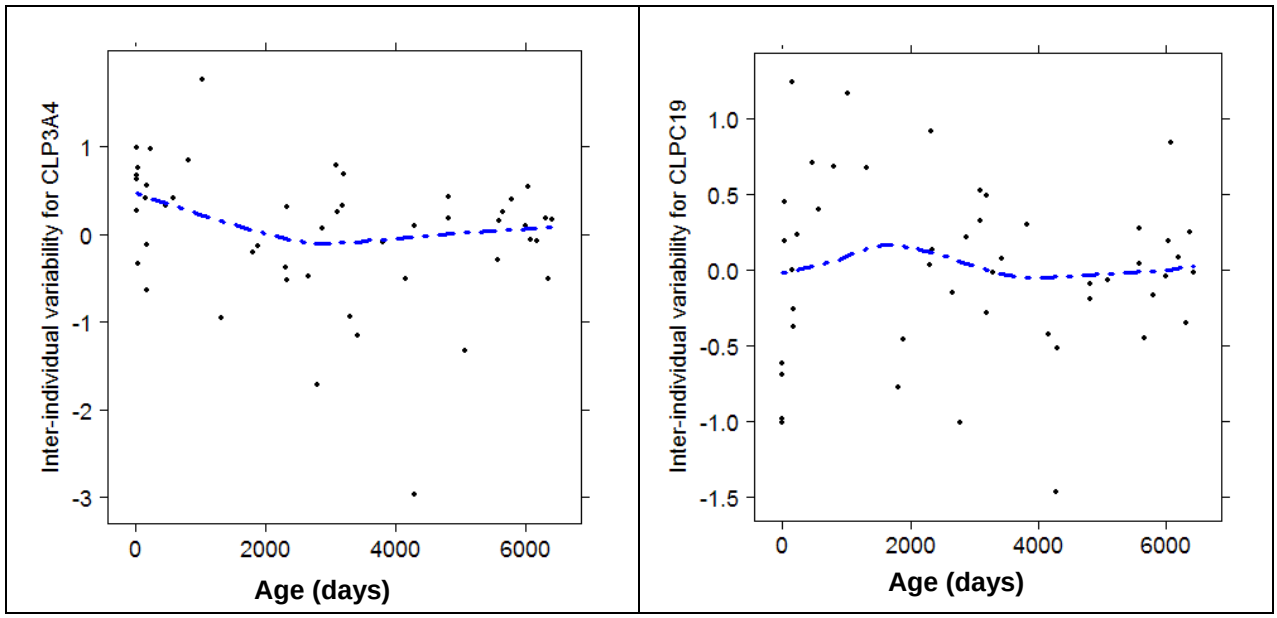
4.2.5.1 Esomeprazole IV Population Pharmacokinetics in Pediatrics

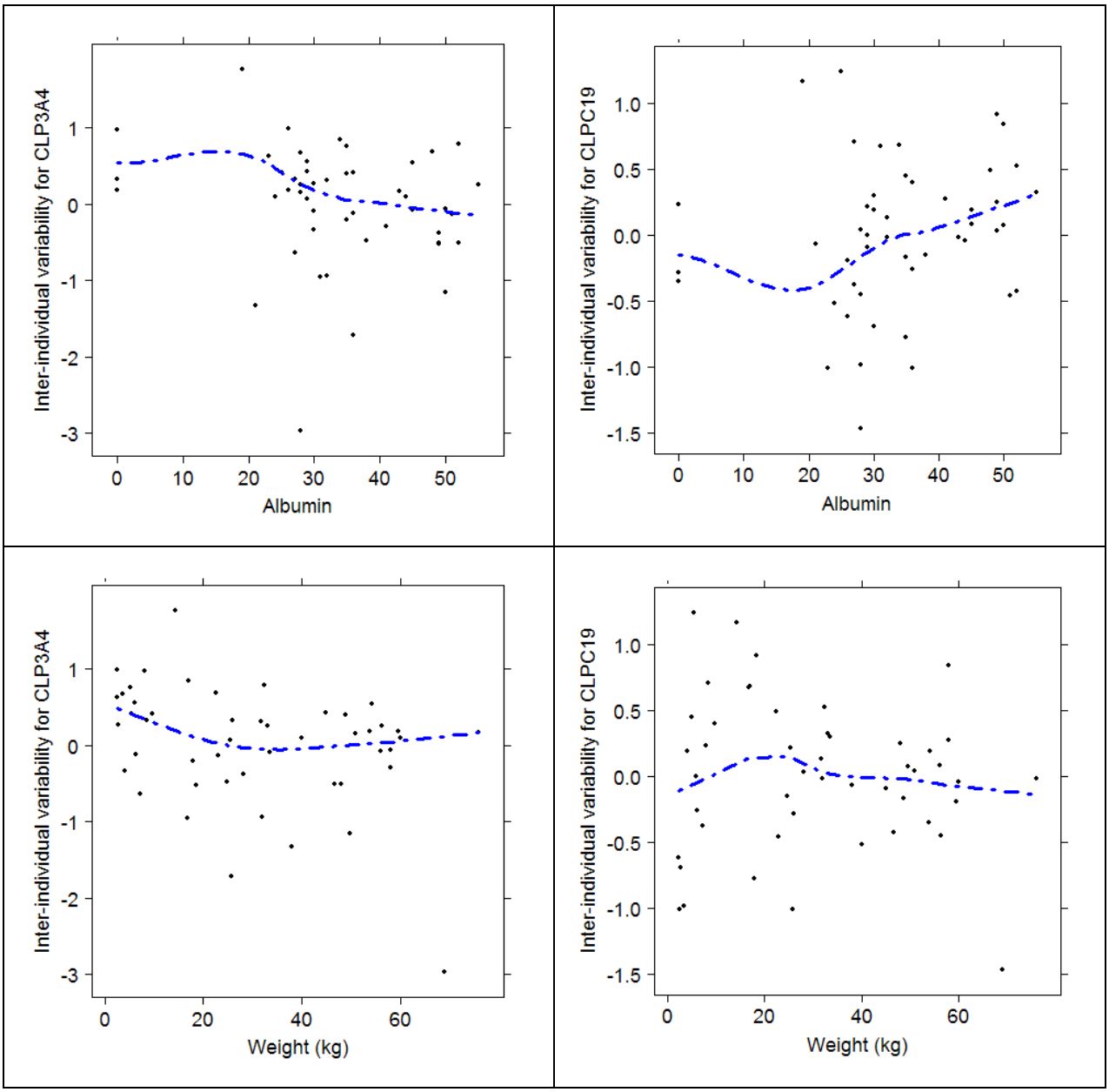
The sponsor's population PK model for the pediatric IV data is acceptable.

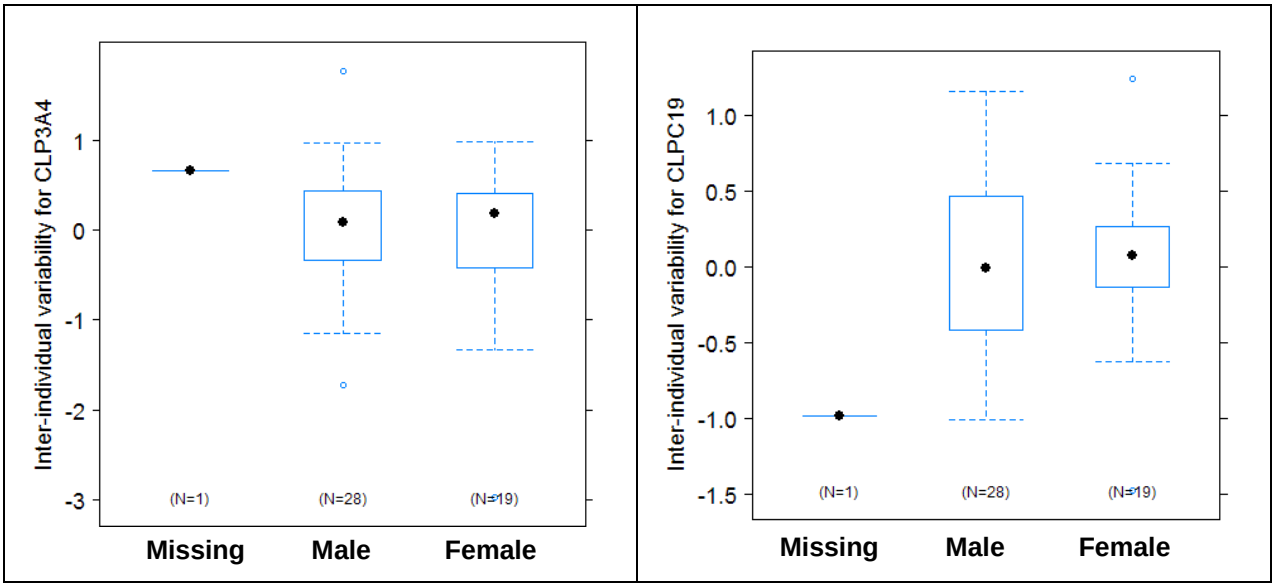
Body weight was identified as a covariate on all esomeprazole volume and clearance parameters. The allometric scaling coefficient for body weight was fixed to 0.75 and 1.0 for the clearance and volume parameters. The relationship between esomeprazole clearance and body weight is shown in Figure 13.

Figure 18 shows no trends exist between clearance of esomeprazole by either CYP3A4 or CYP2C19 with age, albumin, or gender. Body weight is also shown in Figure 18, after being included in the model, to indicate that the fixed allometric scaling coefficient reasonably captured the effect of body weight on the clearance of esomeprazole. There were not enough patients of different ethnicities to test race as a covariate on the clearance of esomeprazole.

Figure 18. No covariate relationships were evidenced with the final IV population PK model for age, albumin, or gender. The left and right columns show plots of inter-individual variation in the clearance of esomeprazole by the CYP3A4 and CYP2C19 pathways against age, albumin, body weight, or gender.




Inter-individual variability for CLP3A4
Albumin
Inter-individual variability for CLPC19
Albumin
Inter-individual variability for CLP3A4
Weight (kg)
Inter-individual variability for CLPC19
Weight (kg)

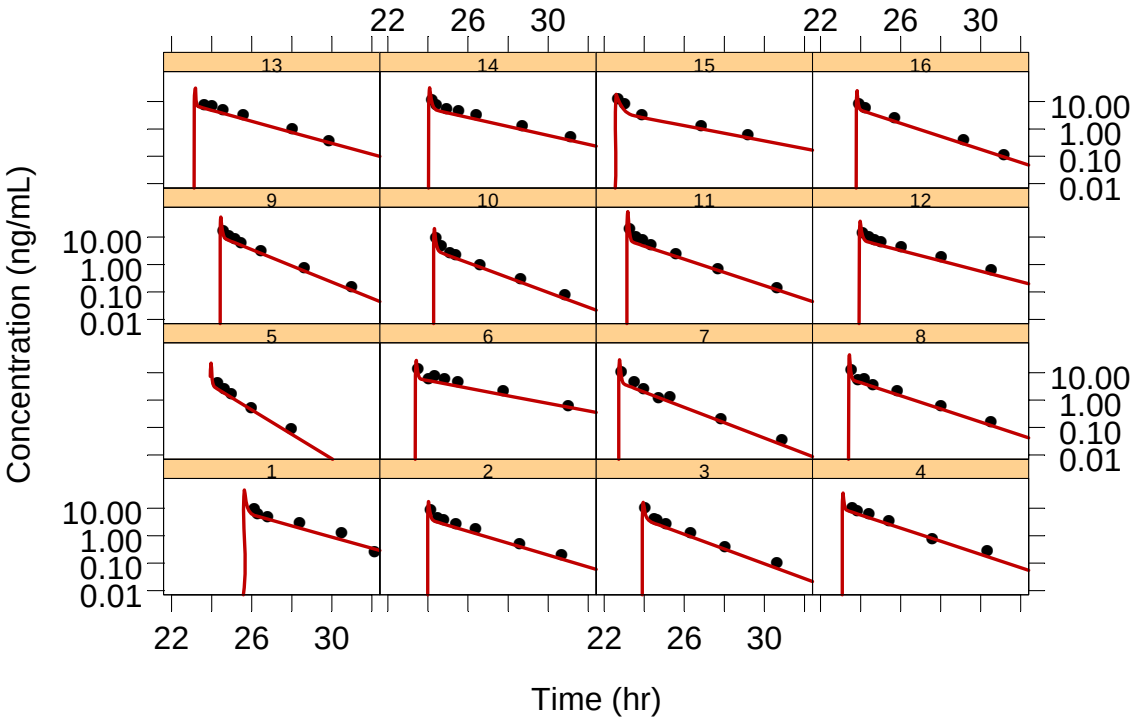


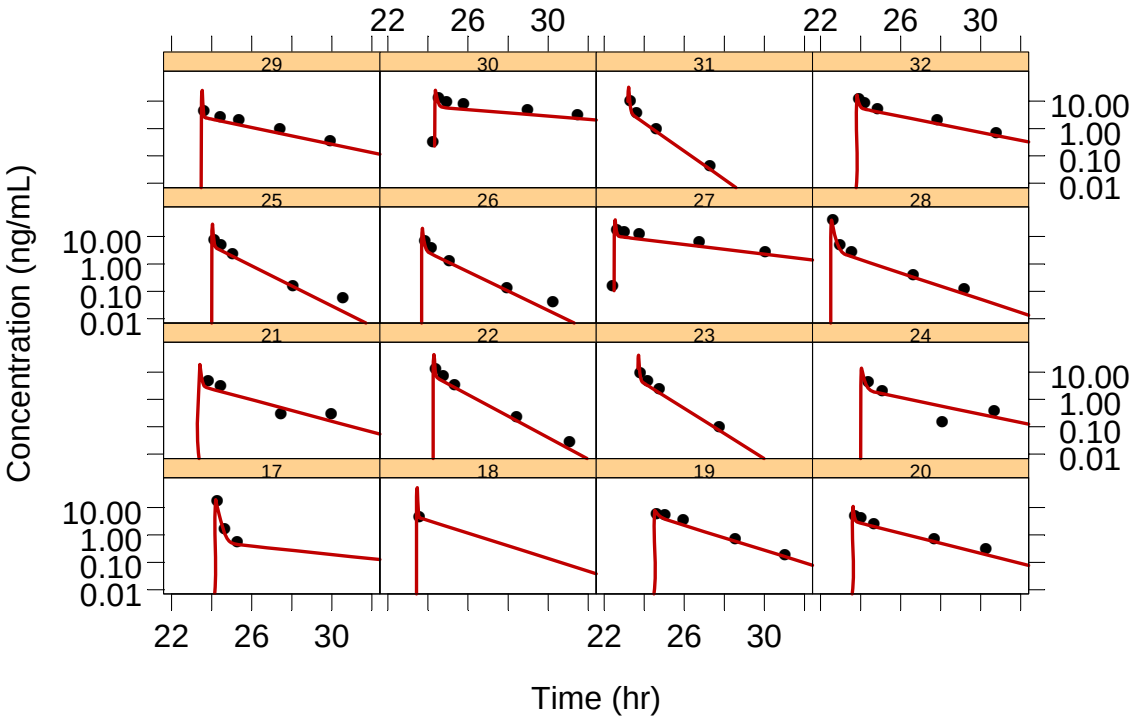
4.3 Listing of Analyses Codes and Output Files

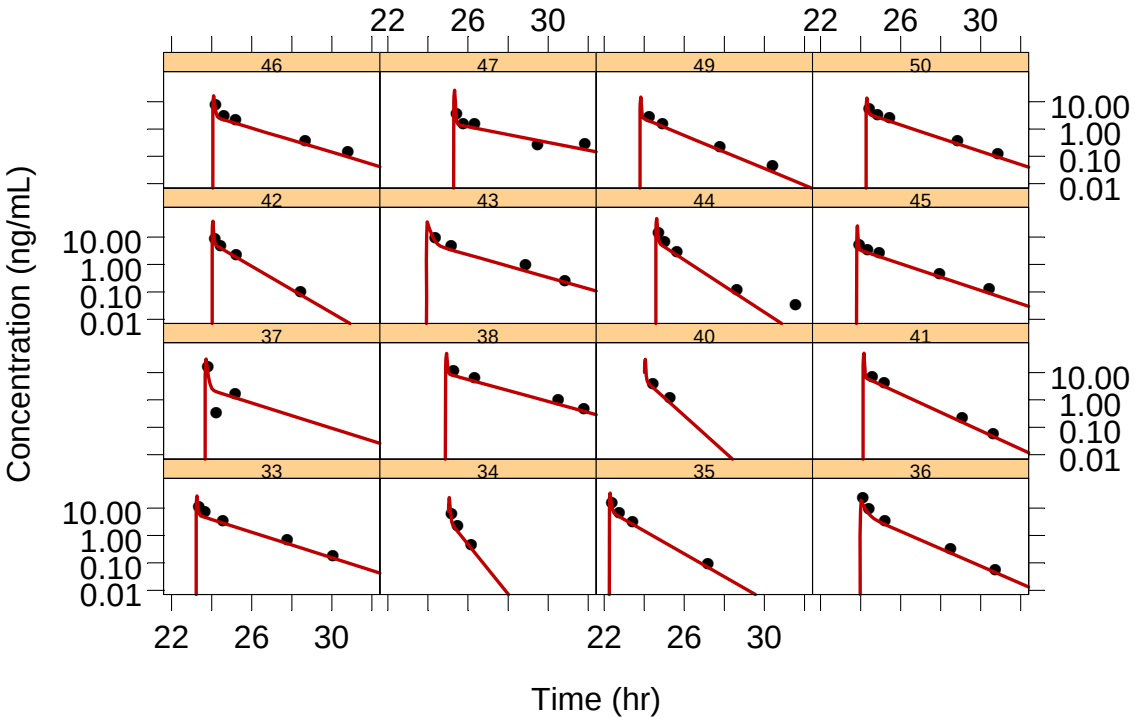
File Name	Description	Location in \\cdsnas\pharmacometrics\
NeonateLabelValues.ssc	Determines Label Values for Neonates	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
PK Data Convert Study 21 IVOnly.ssc	Converts XPT file to NONMEM Compatible .CSV file for study 21 NONEM Analysis	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
PK Data Convert.ssc	Converts XPT file to NONMEM Compatible .CSV file for joint IV, PO NONEM Analysis	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
PKCheck*...*.ssc	Files used for exposures matching different dosing scenarios	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
SIM_*...*.tab	NONMEM Simulation Output for PK data in each pediatric patient for different dosing scenarios	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
Sim_*...*.ssc	Files used to create NONMEM input file for simulation for different dosing scenarios	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
SIM_*...*.csv	NONMEM Input file for simulation for different dosing scenarios	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\
TimetoSimilarExposures10min.ssc	Median Timecourse for 10-min infusion with the final dosing scenario	Reviews\PM Review Archive\2011\Nexium_NDA21689_JCE\PK Analyses\

4.4 APPENDIX to Pharmacometric Review: Sponsor's Final IV Model Fittings of Individual Pediatric IV Data.

Subject IDs are shown at the top of each panel. Subjects with ID < 38 are older than 1yr. Subjects 38, 40-44,47 are 1 month – 11 months old. Subjects 45, 46, 49, 50 are neonates < 1 month old.







5 COVER SHEET AND OCP FILING/REVIEW FORM

General Information About the Submission

	Information		Information
NDA/BLA Number	**21-689**	**Brand Name**	**Nexium I.V.**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**esomeprazole sodium**
Medical Division	**GIEM**	**Drug Class**	**PPI**
OCP Reviewer	**Kris Estes**	**Indication(s)**	**Treatment of GERD**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**IV injection**
Pharmacometrics Reviewer	**Justin Earp**	**Dosing Regimen**	(b) (4)
Date of Submission	**31 MAR 2010**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review		**Sponsor**	**AstraZeneca**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**31 JAN 2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the	X			

	pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kristina Estes 25 MAY 2010

Reviewing Clinical Pharmacologist Date

Sue Chih Lee

Team Leader/Supervisor Date

6 CITED REFERENCES

None.

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

/s/

JUSTIN C EARP
04/04/2011

KRISTINA E ESTES
04/04/2011

CHRISTINE E GARNETT
04/05/2011

SUE CHIH H LEE
04/05/2011

EDWARD D BASHAW
04/05/2011