

Clinical Pharmacology Review

| | |
|-------------------------|---|
| PRODUCT (Generic Name): | Esomeprazole Magnesium |
| PRODUCT (Brand Name): | Nexium |
| DOSAGE FORM: | Delayed-Release Granules for Oral Suspension |
| DOSAGE STRENGTH: | 10 mg (in a packet) |
| NDA: | 22-101 |
| PROPOSED INDICATIONS: | Short-term Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD) and Healing of Erosive Esophagitis (EE) once daily for 8 Weeks |
| TARGET POPULATION: | Pediatric Patients 1-11 Years Old |
| NDA TYPE: | Original |
| SUBMISSION DATE: | September 27, 2006, December 06, 2006, and May 16, 2007 |
| SPONSOR: | AstraZeneca LP |
| REVIEWER: | Tien-Mien Chen, Ph.D. |
| TEAM LEADER: | Sue-Chih Lee, Ph.D. |
| OCP DIVISION: | DCP III |
| OND DIVISION: | Division of Gastroenterology Products (HFD-180) |

1. Executive Summary

Esomeprazole magnesium (hereafter referred to as esomeprazole) is the pure S-enantiomer of the racemic omeprazole. It is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the H/K⁺-ATPase in the gastric parietal cell. The first oral Nexium (esomeprazole) formulation on the market was the delayed-release (DR) capsules (20 and 40 mg) approved for adult patients on 02/20/01 under NDA 21-153 for the treatment of GERD (gastroesophageal reflux disease) and gastric-acid related gastrointestinal (GI) disorders.

Pediatric written request (PWR) for Nexium was issued by the Agency initially on 12/31/01 with subsequent revisions. The PWR requires that the sponsor conduct studies in pediatric patients of all ages (neonates and preterm infants, 1-11 months, 1-11 yrs, and 12-17 yrs). Nexium DR capsules (20 and 40 mg) were approved for adolescent patients 12-17 years old under NDA 21-153/S-022 on 04/28/06.

The second oral Nexium formulation approved by the Agency was DR granules for oral suspension (20 and 40 mg) which was approved for use in patients 12 years of age and older under NDA 21-957 on 10/20/06. The approval was based on bioequivalence (BE) assessment in an *in vivo* pharmacokinetic (PK) study comparing it with the approved DR capsules without clinical trials. The study results showed that the formulation of DR granules for oral suspension was BE to DR capsule formulation.

In this NDA, the sponsor is pursuing the approval of a lower strength (10 mg) of Nexium DR granules for oral suspension for use in pediatric patients 1-11 years of age. Four studies were provided in the NDA: **1)** a multiple-dose, Phase-1 PK study in pediatric patients 1-11 years old (D9614C00099), **2)** a multicenter randomized double-blind parallel-group dose-response trial in pediatric patients 1-11 years old (D9614C00097), **3)** an *in vivo* PK study for assessing the BE between Nexium DR granules for oral suspension and DR capsules in healthy adult subjects (D9612C00032), and **4)** a supportive pediatric study in patients aged 1-24 months (SH-NEC-001).

The *in vivo* BE study (D9612C00032) had been reviewed under NDA 21-957 and the Phase III dose-response trial (D9614C00097) is being reviewed by the medical officer of HFD-180. Therefore, this review covers the multiple-dose PK study in patients 1-11 years old (D9614C00099) and the supportive PK, pH-monitoring, and safety study in patients aged 1-24 months (SH-NEC-0001).

A. Recommendation:

NDA 22-101 for Nexium DR granules for oral suspension 10 mg has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). The NDA is found acceptable from OCP perspective provided that a mutually satisfactory agreement regarding the package insert can be reached between the sponsor and the Agency. The labeling comments (p. 17) should be conveyed to the sponsor.

B. Comments

1. Regarding the sponsor's proposed dosing regimens for patients aged 1-11 years:

The proposed dosing regimens of 10 mg QD (for all patients in the specified age range) and 20 mg QD (for healing of erosive esophagitis in patients weighing \geq 20 kg) are reasonable based on the PK findings from Study D9614C00099. The appropriateness of the above proposed dosing regimens based on the dose-response trial is being evaluated by the Medical Officer of HFD-180.

2. Regarding whether the studies submitted can be used to fulfill the PWR requirements):

For the age group of 1-11 years, the PWR requires that the sponsor conduct a single-dose and a multiple-dose PK studies. The multiple-dose PK study as conducted by the sponsor was consistent with the terms delineated in the PWR except that the dose was not guided by the single-dose study, since the sponsor did not conduct a single-dose study first. Instead, the sponsor stated that they planned to conduct such a study in 2007. Conducting the single-dose study at this time is not as meaningful as it was originally proposed in the PWR.

C. Phase IV Commitments: None

05/14/07, 07/02/07

Tien-Mien Chen, Ph.D.

Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 05/16/07, 07/02/07

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III. Summary of Clinical Pharmacology Findings

This review covers the multiple-dose Phase I PK study in patients aged 1-11 years (D9614C00099) and the supportive PK, pH-monitoring, safety study in infants aged 1-24 months (SH-NEC-001). The dose-response trial (D9614C00097) is being reviewed by the Medical Officer of HFD-180.

Multiple-dose PK Study (D9614C00099):

In this study, Nexium DR granules for oral suspension was administered once daily to patients aged 1-11 years with GERD or symptoms of GERD for 5 days. The 5 and 10 mg doses were chosen for patients aged 1-5 years and 10 and 20 mg doses for patients aged 6-11 years. The PK parameters on Day 5 are shown in the table below:

Summary of PK Parameters in Pediatric Patients 1-11 Years Old

| Statistic | Age 1-5 years | | | | | | Age 6-11 years | | | | | |
|---------------------------------|-------------------|-----------|------|--------------------|-----------|------|--------------------|-----------|------|--------------------|-----------|------|
| | Esomeprazole 5 mg | | | Esomeprazole 10 mg | | | Esomeprazole 10 mg | | | Esomeprazole 20 mg | | |
| | N | Geo. mean | SD | N | Geo. mean | SD | N | Geo. mean | SD | N | Geo. mean | SD |
| AUC (µmol*h/L) | 5 | 0.74 | 0.36 | 8 | 4.83 | 2.56 | 7 | 3.70 | 2.05 | 6 | 6.28 | 2.71 |
| AUC _(0-t) (µmol*h/L) | 6 | 0.63 | 0.37 | 8 | 4.67 | 2.23 | 7 | 3.55 | 1.90 | 6 | 6.09 | 2.64 |
| C _{max} (µmol/L) | 6 | 0.62 | 0.38 | 8 | 2.98 | 0.69 | 7 | 1.77 | 0.96 | 6 | 3.73 | 1.21 |
| t _{1/2λz} (h) | 5 | 0.42 | 0.13 | 8 | 0.74 | 0.36 | 7 | 0.88 | 0.35 | 6 | 0.73 | 0.21 |
| CL/F/kg (L/h/kg) | 5 | 1.01 | 0.30 | 8 | 0.39 | 0.17 | 7 | 0.25 | 0.21 | 6 | 0.31 | 0.18 |

AUC is area under the plasma concentration-time curve from 0 to infinity; AUC_(0-t) is area under the plasma concentration-time curve from 0 to t; CI is confidence interval; C_{max} is maximum plasma (peak) drug concentration; Geo. mean is geometric mean; t_{1/2λz} is half life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; CL/F/kg is the apparent clearance normalized by body weight

For children aged 1-5 years, the AUC, AUC_(0-t), and C_{max} were 5- to 7-fold higher for the 10 mg dose group compared to the 5 mg dose group. The reason for this observation is unknown. The sponsor is not pursuing the 5 mg dose in this NDA. For children aged

6-11 years, these parameters were approximately twice as high for the 20 mg dose group compared to the 10 mg dose group. Mean body weight (BW) normalized apparent clearance (CL/F/kg) was slightly higher in children aged 1-5 years who received the 10-mg dose than in those aged 6 to 11 years who received either the 10-mg or 20-mg dose. However, high intersubject variability (%CV: 44-84%) was observed in all age and dose groups.

Comparison of Systemic Exposure Among Different Age/Dose groups:

The systemic exposure observed in this study is compared to historical data in adults and adolescents (see Table below). The findings are:

- 5 mg dose/1-5 year olds: Mean AUC (0.74 µmol.h/L) was much lower than that for any other dose/age groups shown in the table below. The reason for this observation is unknown. As such, the efficacy of the 5 mg dose in patients aged 1-5 years is uncertain in view of the PK findings.
- 10 mg dose/1-5 year olds: Mean AUC (4.8 µmol.h/L) was similar to that observed for the 20 mg dose in adults (4.2 µmol.h/L). It was in between those for the 10 mg dose in the 6-11 year olds (3.7 µmol.h/L) and 20 mg dose in the 6-11 year olds (6.3 µmol.h/L).
- 10 mg dose/6-11 year olds: Mean AUC (3.7 µmol.h/L) was the same as that for the 20 mg dose in adolescents (3.7 µmol.h/L).
- 20 mg dose/6-11 year olds: Mean AUC (6.3 µmol.h/L) was higher than that observed for the 20 mg dose given to adolescents (3.7 µmol.h/L) or adults (4.2 µmol.h/L), but much lower than that observed with the 40 mg dose given to adolescents (13.9 µmol.h/L) or adults (12.6 µmol.h/L). As such, none of the pediatric doses tested in this study showed their plasma AUC values close to those observed with the 40 mg dose in adults and adolescents.
- Based on the above findings, the proposed dosing regimens of 10 mg QD (for all patients aged 1-11 years) and 20 mg QD (for healing of erosive esophagitis in patients weighing ≥ 20 kg) is reasonable.

Comparisons of Esomeprazole Dose and Systemic Exposure Among Different Age groups

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

^a Data derived from Study D9614C00099 CSR, Module 5.

^b Data derived from Study D9614C00094 CSR, NDA 21-153/S-022.

^c Data derived from NEXIUM (AstraZeneca, Sweden) Label in Physicians' Desk Reference, 57th edition. Montvale, New Jersey: Thompson PDR, 2003, which was based on data from Astra Hassle Clinical Study Report SH-QBE-0008.

^d Median weight 62.5 kg (CSR D9614C00094, Table 9).

^e Median weight 81.0 kg (CSR SH-QBE-0008, Appendix 1 to Statistical Report, Table 1.1).

Supportive PK/PD study (SH-NEC-0001):

The PWR does not require a PK/PD study for the age group of 1-11 years old. This was a single blind, randomized, parallel-group, single-center, PK and pH-monitoring of esomeprazole in infants up to 24 months of age. Two dose levels were employed, 0.25 and 1.0 mg/kg QD for 7 or 8 days. The study as a whole showed that there was a trend of increased mean % of time with intragastric pH>4 with the higher dose compared to the lower dose. However, the sample size for the 5 mg dose was too small (N=6) to derive any meaningful supporting evidence for this age group.

Dose-Response Trial (D9614C00097):

This study is being evaluated by the Medical Officer of HFD-180. Only a brief summary will be provided here. It should be noted that the findings described below are pending review by the Medical Officer.

This was a multicenter, randomized, double-blind parallel-group study to evaluate the safety and clinical outcome of once daily esomeprazole for the treatment of GERD in pediatric patients 1-11 years old. No control group was included in this trial. The doses of 5 and 10 mg were selected for lower weight children (<20 kg) and 10 and 20 mg for higher weight children (≥20 kg), which were similar to the doses chosen for the multiple-dose PK study discussed above. The duration of treatment was 8 weeks. The sponsor showed that the first sustained resolution (defined as the first day that started a string of 7 consecutive entries of “none” for combined symptoms (heartburn, acid regurgitation, and epigastric pain) was achieved faster in the higher weight children (≥20 kg) than in the lower weight children (<20 kg). The median time to reach first sustained resolution was 42 days in the 5 mg (<20 kg) treatment group, 36 days in the 10 mg (<20 kg) group, 18 days in the 10 mg (≥20 kg) group, and 16 days in the 20 mg (≥20 kg) group.

According to the sponsor’s analysis, the follow-up endoscopies of patients who had erosive esophagitis (EE) at baseline by endoscopy showed that EE was improved or healed in the majority of patients after 8 weeks of esomeprazole treatment. Overall, 93.3% (42) of the 45 patients who had EE at baseline and had a follow-up endoscopy showed improvement in their final endoscopy results. In most of these patients (88.9%, 40/45), the EE was resolved and their erosions had healed. The 11 patients (1-5 years of age in the 5 mg treatment group) who had EE were all reported healed.

Conclusion:

The multiple-dose PK study as submitted in this NDA fulfills the requirements for the repeated-dose PK study as stipulated in PWR for the age group of 1-11 year olds. The proposed doses for pediatric patients 1-11 years old are reasonable based on the PK findings. The appropriateness of these doses based on the clinical trial results are being evaluated by the Medical Officer of HFD-180.

IV. Question Based Review

A. General Attributes

Drug Substance:

Esomeprazole magnesium (hereafter referred to as esomeprazole) is the pure S-enantiomer of the racemic omeprazole. It is also the drug substance used for the approved DR capsules (20 and 40 mg).

Formulation:

For Nexium DR granules for oral suspension, esomeprazole is manufactured as pellets and is identical to that for the approved DR capsules. The contents of DR granules for oral suspension in packet contain esomeprazole pellets and excipient granules (please see Table 6 on p. 16 of this review). The 20 and 40 mg strengths were approved by the Agency on 10/20/06 for use in patients aged 12 years and older (NDA 21-957).

The composition/formulation for the 10 mg strength is the same as that for the approved 20 and 40 mg strengths. The different product strengths are obtained by filling varying amounts of esomeprazole pellets and excipient granules into the packet. The exact amount of esomeprazole pellets in the packet is based on the content of the active drug in the pellets.

Mechanism of Action:

Esomeprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. Esomeprazole is protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity and leading to inhibition of gastric acid secretion.

B. General Clinical Pharmacology

Proposed Indication and Dosing Regimen:

For pediatric patient 1-11 years old, the proposed indication and dosing regimen are shown below:

Recommended Dosage Schedules of Nexium

| <u>Indication</u> | <u>Dose</u> | <u>Frequency</u> |
|--|--------------------|------------------------------|
| For pediatric Use (1-11 Years Old): | | |
| Short-term treatment of symptoms of GERD | 10 mg | Once Daily for up to 8 weeks |
| Healing of Erosive Esophagitis | | |

| | | |
|---------------|-------------------|------------------------|
| Weight <20 kg | 10 mg | Once Daily for 8 weeks |
| Weight ≥20 kg | 10 mg or 20 mg | Once Daily for 8 weeks |

The contents of the packet are to be mixed with water and the suspension can be left for up to 30 minutes before administration.

Pediatric Studies in patients aged 1-11 years as listed in the PWR:

The pathophysiology of GERD in children older than 1 year of age is considered to be similar to that in adults. As in adults, the acidic nature of the refluxate and the presence of activated pepsin are considered to be the principal irritants causing mucosal inflammation, resulting symptomatology, and other potential long-term outcomes associated with GERD. It is generally accepted that the clinical course and manifestation of GERD in the 1 to 17 year old pediatric population is similar to that of adult populations.

The PWR for Nexium was first issued by the Agency initially on 12/31/01 with subsequent amendments. The first group studied in the Nexium pediatric program consisted of adolescent patients aged 12 to 17 years old, inclusive (Study 5 in PWR). Data on the usage of the approved DR 20 and 40 mg capsules for this age group was approved by the Agency under NDA 21-153/S-022 on 04/28/06.

The second age group studied in the Nexium pediatric clinical program consisted of pediatric patients 1 to 11 years old, inclusive, the subject of this NDA submission. It is designed to support the used on Nexium DR granules (in packet) for oral suspension in pediatric patients 1-11 years old as indicated in the PWR (Study 4). In addition, a supportive pediatric study was also submitted to assess the PK of esomeprazole and its efficacy in controlling intragastric pH in pediatric patients 12-24 months.

The study in patients aged 1-11 years as delineated in the PWR (revised as of 03/29/07) is shown below:

STUDY 4: PHARMACOKINETIC, EXPOSURE/RESPONSE, AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 YEARS OF AGE

Pharmacokinetic Component:

Part 1 (single dose)

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of esomeprazole magnesium. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose)

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive and (b) have symptomatic GERD. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of esomeprazole magnesium. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

To support the Exposure/Response Component (under Study 4) for this age group as shown below, a Phase III, multicenter, randomized, double-blind, parallel-groups study was also submitted.

Exposure/Response Component

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

This will be a randomized, double blind, dose-ranging study of esomeprazole magnesium. The dosages of esomeprazole magnesium used in this study will be selected as dosages likely to be therapeutically effective and safe, based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Eligible patients will be randomized in approximately equal proportions to one of at least two dose levels of esomeprazole magnesium. After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 40 patients 1 to 5 years of age and 40 patients 6 to 11 years of age will complete at least 8 weeks treatment.

The sponsor requested a deferral for submission of pediatric studies **1**) in perterm and neonates and **2**) in 1-11 months inclusive which are to be planned for submission in 2008.

Q1. How were the doses selected for the pediatric studies?

Based on work done with previously available omeprazole and esomeprazole data using appropriate modeling techniques and a thorough review of pediatric PK and PD literature, the esomeprazole exposure (AUC) and the response (efficacy and safety) relationship in a pediatric population were established via a comprehensive PK and population PK modeling analysis of the omeprazole data in pediatric and adult patients and the esomeprazole data in adult patients.

Assuming 7 to 60 kg of body weight for children 1-11 years old, the proposed 5 mg dose would have a reasonable chance to show efficacy and acceptable safety for children weighing 7 to 25 kg, the 10 mg dose for children weighing 7 to 60 kg, and the 20 mg dose for children weighing 12 to 60 kg (children between the ages of 1 and 5 years old, inclusive have a typical body weight between 7 and 20 kg and 6-11 years old between 20 and 60 k.). Thus, 5 and 10 mg doses were selected for pediatric patients 1-5 years old (or BW <20 kg) and 10 and 20 mg doses were for pediatric patients 6-11 years old (or BW ≥ 20 kg). The doses selected for PK (based on age) and Phase III trials are consistent (based on BW) as shown below:

| Dose Selected | PK Study | Phase III Trial |
|---------------|----------------|-----------------|
| 5 and 10 mg | 1-5 years old | BW < 20 kg |
| 10 and 20 mg | 6-11 years old | BW ≥ 20 kg |

Q2. What are the pharmacokinetic characteristics of esomeprazole in pediatric patients aged 1-11 years?

A PK study (No. D9614C00099) entitled “A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Multiple Doses of Esomeprazole Magnesium in a Pediatric Population of 1 to 11 Year olds with Gastroesophageal Reflux Disease (GERD) or Symptoms of GERD” was conducted. The study design and results are shown below in Scheme 1 and Table 1, respectively:

Scheme 1. Study Design



Table 1. Summary of PK Parameters in Pediatric Patients 1-11 Years Old

| Statistic | Age 1-5 years | | | | | | Age 6-11 years | | | | | |
|---|-------------------|-----------|------|--------------------|-----------|------|--------------------|-----------|------|--------------------|-----------|------|
| | Esomeprazole 5 mg | | | Esomeprazole 10 mg | | | Esomeprazole 10 mg | | | Esomeprazole 20 mg | | |
| | N | Geo. mean | SD | N | Geo. mean | SD | N | Geo. mean | SD | N | Geo. mean | SD |
| AUC ($\mu\text{mol}\cdot\text{h/L}$) | 5 | 0.74 | 0.36 | 8 | 4.83 | 2.56 | 7 | 3.70 | 2.05 | 6 | 6.28 | 2.71 |
| AUC _(0-t) ($\mu\text{mol}\cdot\text{h/L}$) | 6 | 0.63 | 0.37 | 8 | 4.67 | 2.23 | 7 | 3.55 | 1.90 | 6 | 6.09 | 2.64 |
| C _{max} ($\mu\text{mol/L}$) | 6 | 0.62 | 0.38 | 8 | 2.98 | 0.69 | 7 | 1.77 | 0.96 | 6 | 3.73 | 1.21 |
| t _{1/2λz} (h) | 5 | 0.42 | 0.13 | 8 | 0.74 | 0.36 | 7 | 0.88 | 0.35 | 6 | 0.73 | 0.21 |
| CL/F/kg (L/h/kg) | 5 | 1.01 | 0.30 | 8 | 0.39 | 0.17 | 7 | 0.25 | 0.21 | 6 | 0.31 | 0.18 |

AUC is area under the plasma concentration-time curve from 0 to infinity; AUC_(0-t) is area under the plasma concentration-time curve from 0 to t; CI is confidence interval; C_{max} is maximum plasma (peak) drug concentration; Geo. mean is geometric mean; t_{1/2λz} is half life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; CL/F/kg is the apparent clearance normalized by body weight

The AUC, AUC_(0-t), and C_{max} were several-fold lower for 5 mg esomeprazole compared with 10 mg esomeprazole in children aged 1 to 5 years, while the same parameters were approximately 2 times lower for 10 mg esomeprazole compared with 20 mg esomeprazole in children aged 6 to 11 years. One factor that may have contributed to this difference may be the higher weight for 5 mg treatment group (21.0 ± 5.8 kg) vs. 10 mg treatment group (14.7 ± 3.3 kg) and thus lower actual (mg/kg) esomeprazole doses in children receiving the 5 mg dose. The above weight difference could only explain partially the 5- to 7-fold difference in PK parameters. However, the exact reason for this is not known.

Q3. How Do PK Parameters in Pediatric Patients Aged 1-11 Years Compare with Those in Adolescent and Adult Patients? Are the Proposed Dosing Regimens for Patients Aged 1-11 Years Reasonable Based on the PK Findings?

The PK parameters obtained from this study in 1 to 11 year old children were compared with those from adolescent 12 to 17 year old and from adult studies as shown below:

Table 2. Comparison of Esomeprazole Dose and Systemic Exposure Among Different Age groups

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

^a Data derived from Study D9614C00099 CSR, Module 5.

^b Data derived from Study D9614C00094 CSR, NDA 21-153/S-022.

^c Data derived from NEXIUM (AstraZeneca, Sweden) Label in Physicians' Desk Reference, 57th edition. Montvale, New Jersey: Thompson PDR. 2003, which was based on data from Astra Hassle Clinical Study Report SH-QBE-0008.

^d Median weight 62.5 kg (CSR D9614C00094, Table 9).

^e Median weight 81.0 kg (CSR SH-QBE-0008, Appendix 1 to Statistical Report, Table 1.1).

The 10 mg dose in the 1 to 5 year old children resulted in a similar exposure to the 20 mg dose in adults. The 10 mg dose in the 6 to 11 year old children resulted in a similar exposure to the 20 mg dose in adolescents and adults. The 20 mg dose in the 6 to 11 year old children resulted in a higher exposure than the 20 mg dose given to adolescents and adults, but a lower exposure than 40 mg esomeprazole given to adolescents and adults. Therefore, the proposed dosing regimens of 10 mg QD (in all patients) and 20 mg QD (in patients weighing at least 20 kg) are reasonable based on the PK findings.

Again, the 5 mg dose in the 1 to 5 year old children resulted in an exposure far below what was observed after 10 mg esomeprazole in the 1 to 11 year old children and after labeled doses (20 mg and 40 mg) in adolescents and adults, and therefore, the therapeutic effect of the 5 mg dose may be questionable.

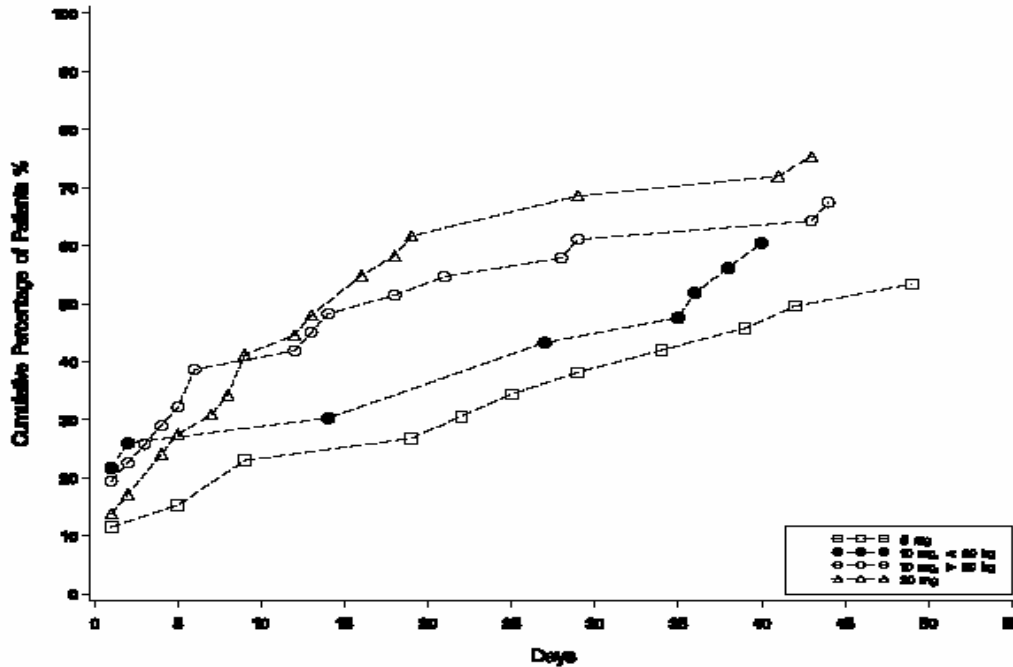
Q4. What was the dose-response relationship in pediatric patients aged 1-11 years?

The results summarized here are from clinical trial 9614C00097 following a discussion with Dr. Wen-Yi Gao, Medical Office of HFD-180. Two efficacy outcome measures (the first sustained resolution and improvement in erosive esophagitis) were presented here, however, no control/comparator group was employed in this study. Dr. Gao will present detailed evaluation of this study in his review.

The first sustained resolution:

The first sustained resolution is defined as the first day that started a string of 7 consecutive entries of “none” for combined symptoms; heartburn, acid regurgitation, and epigastric pain. This measure was achieved faster in the higher weight children (≥ 20 kg) receiving 10 or 20 mg dose than in the lower weight children (< 20 kg) receiving 5 or 10 mg dose. However, no clear dose-response was observed. The median time to reach first sustained resolution was 42 days in the esomeprazole 5 mg (< 20 kg) treatment group, 36 days in the 10 mg group (< 20 kg) group, 18 days in the 10 mg (≥ 20 kg) group, and 16 days in the 20 mg (≥ 20 kg) group as shown below in Figure 1.

Figure 1. Cumulative Percentage of Patients and Number of Days to First Sustained Resolution of the Combined GERD Symptoms Heartburn, Acid Regurgitation, and Epigastric Pain—ITT population



Data derived from [Table 11.2.6.3](#).

Improvement in EE:

Patients were considered to be improved if they were better than they were at baseline. Patients were resolved if their final endoscopy showed no signs of erosions. Analysis of the follow-up endoscopies of patients in Phase III trial who had EE at baseline by endoscopy showed that EE was improved or healed in the majority of patients after 8 weeks of esomeprazole treatment. Overall, 93.3% (42) of the 45 patients who had EE at baseline and had a follow-up endoscopy showed improvement in their final endoscopy results. In most of these patients (88.9%, 40/45), the EE was resolved and their erosions had healed. Eleven patients (1-5 years old in the 5 mg treatment group) who had EE, however, were all reported healed as shown below in Table 3. No clear dose-response was observed with this outcome measure. Again, no control/comparator group was employed in this study.

Table 3. Summary of Clinical Outcome for Patient who had EE at Baseline and had Follow-up Endoscopy –ITT Population

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

Wt is weight.

Table is derived from Table 11.2.7.1.

Note: For safety assessment, it is reported that the adverse event (AE) profile of esomeprazole in pediatric patients aged 1 to 11 years did not raise any new safety concerns. In general, the AEs reported were consistent with the known safety profile of esomeprazole. No new safety signals were identified in this population of 1 to 11 year old pediatric patients and AE occurrences did not appear to be dose related.

Q5. What information from Study No.SH-NEC-0001 can be used to support the proposed dosing regimens in Patients Aged 1-11 years?

The supportive study No. SH-NEC-0001 was conducted in 50 pediatric patients 1-24 months employing repeated dose of 0.25 mg/kg (n=26) or 1.0 mg/kg (n=24) for 7-8 days. PK and intragastric and intraesophageal pH values were obtained. The study results provided some evidence of positive trend of dose vs. mean change in % of time with intragastric pH > 4 and with intraesophageal pH <4 as shown below in Tables 4 (1-24 months; n=22) and 5 (only for 12-24 months; n=6). Because of the small sample size of patients aged 12-24 months (n=6), the data from this study are not deemed useful.

Table 4. Mean Percentage of Time with Intragastric pH>4 and Intraesophageal pH<4 at Baseline and After One Week of Treatment (Day 7/8) for Patient. 1-24 Months

| Pharmacodynamic Parameters | 0.25 mg/kg | | | 1.0 mg/kg | | |
|---|----------------|----------------|----------------|----------------|---------------------|-------------------------------------|
| | Baseline | Day 7/8 | Change | Baseline | Day 7/8 | Change |
| % of Time with Intragastric pH >4 in 24 hr | 30.5 (n=22) | 47.9 (n=22) | 14.0 (n=21) | 28.6 (n=22) | 69.3 (n=22) | 40.6; (26.6) ² (n=21) |
| p value | ----- | ----- | ----- | ----- | 0.0009 ¹ | <0.0001 ³ |
| % of Time with Intraesophageal pH <4 in 24 hr | 11.6 (n=23) | 8.4 (n=23) | -3.5 (n=23) | 12.5 (n=22) | 5.5 (n=22) | -6.7; (-3.3) ² (n=21) |
| p value | ----- | ----- | ----- | ----- | 0.171 ¹ | 0.0615 ³ |

¹. Comparison on Day 7/8 between two dose levels (and significant if p<0.05).

². Comparison of change/improvement on Day 7/8 from baseline between two dose levels.

³. Significantly different if p<0.05.

Table 5. Mean Percentage of Time with Intra gastric pH>4 and Intraesophageal pH<4 at Baseline and After One Week of Treatment (Day 7/8) for Patients > 12 and < 24 Months

| Pharmacodynamic Parameters | 0.25 mg/kg | | | 1.0 mg/kg | | |
|---|---------------|---------|--------|---------------|---------------------|-----------------------------|
| | Baseline | Day 7/8 | Change | Baseline | Day 7/8 | Change |
| % of Time with Intra gastric pH >4 in 24 hr | 18.6 (n=4) | 25.7 | 6.7 | 19.8 (n=2) | 76.1 | 55.4 (48.7) ² |
| p value | ----- | ----- | | ----- | 0.0204 ¹ | 0.0535 ³ |
| % of Time with Intraesophageal pH <4 in 24 hr | 10.0 (n=4) | 2.9 | -7.4 | 9.5 (n=2) | 5.3 | -5.1 (2.2) ² |
| p value | ----- | ----- | ----- | ----- | 0.455 ¹ | 0.538 ³ |

¹. Comparison on Day 7/8 between two dose levels (and significant if p<0.05).

². Comparison of change/improvement on Day 7/8 from baseline between two dose levels.

³. Significantly different if p<0.05.

Q6. Are the Proposed Dosing Regimens for Pediatric Patients 1-11 Years Old Reasonable based on the Study Data Submitted to This NDA?

The proposed dosing regimens (10 mg QD for all patients aged 1-11 years and 20 mg QD for EE patients weighing at least 20 kg) are reasonable based on the PK results presented in this NDA. The appropriateness of the proposed doses based on clinical study results are being evaluated by the Medical Officer.

Q7. Did the PK study of esomeprazole in Pediatric Patients 1-11 Years Old (No. D9614C00099) comply with the PWR?

It is stated in the PWR that for this age group, the PK after single and repeated doses are to be determined (p.7 of this review). Study No. D9614C00099 provided PK data in 1 to 11 year old children after repeated doses of esomeprazole and therefore, fulfilled the Part 2 requirements for Study 4 in patients aged 1-11 years as delineated in the PWR.

The sponsor considered that 1) esomeprazole is a well-known chemical entity and 2) repeated dosing results in greater exposure (AUC) than single dose administration, therefore, a repeated-dose PK study would be sufficient for assessment of esomeprazole PK profile and for the purposes of a label extension for Nexium use in pediatric patients aged 1 to 11 years. The sponsor, however, indicated that a study to support single-dose PK (part 1) of this age group will be completed in 2007.

C. Intrinsic Factors:

It appears that esomeprazole PK in adolescents are similar to those in adults. However, PK in younger children (<12 years) appear to be different from those aged 12 years and above as suggested by the following:

Comparison of AUC between the age groups of 6-11 years and 12-17 years:

- AUC was similar between the 10 mg dose in the 6-11 yr olds (mean dose: 0.34 mg/kg) and 20 mg dose in the 12-17 yrs olds (mean dose: 0.32 mg/kg). However, AUC for the 20 mg dose in the 6-11 yr olds (mean dose: 0.71 mg/kg) was less than half of that for the 40 mg dose in the 12-17 yrs olds (mean dose: 0.64 mg/kg).

D. Extrinsic Factors: N/A

E. General Biopharmaceutics:

The composition/formulation of esomeprazole granules (in packet) for oral suspension 10 mg plus the 2.5 and 5 mg tested clinically are compositionally the same and proportionally similar as the approved 20 and 40 mg granules (NDA 21-957) as shown below in Table 6.

Table 6. The Composition/Formulation of Esomeprazole Granules in Packet for Oral Suspension

| Esomeprazole pellets ^a | 2.5 | 5.0 | 10 | 20 | 40 | Active substance | AstraZeneca |
|-----------------------------------|-----|-----|------|------|-------|------------------|-------------|
| Esomeprazole | | | | 22.3 | 44.5 | | |
| Glycerol monostearate 40-55 | | | | | | | |
| Hydroxypropyl cellulose | | | | | | | |
| Hydroxypropyl methylcellulose | | | | | | | |
| Magnesium stearate | | | | | | | |
| Methacrylic acid copolymer type C | | | | | | | |
| Polysorbate 80 | | | | | | | |
| Sugar spheres | | | | | | | |
| Talc | | | | | | | |
| Triethyl citrate | | | | | | | |
| Weight of esomeprazole pellets | | | 42.7 | 85.8 | 171.6 | | |

The initial esomeprazole DR pellets in granule formulation was developed in capsule form and used in the earlier supportive study No. SH-NEC-0001. The contents of capsules were dispersed on applesauce or emptied into a funnel pan and administered through a specially designed adapter (>1 to <3 months of age). The capsule dosage form was also used in pediatric patients in the other two studies, Nos. D9614C00099 and

D9614C00097 and for those who could not swallow intact capsules, contents sprinkled on applesauce were used. Because the granules containing the active ingredient in the proposed formulation are identical to granules in the DR capsules and the *in vitro* comparative dissolution data were comparable as reviewed previously under NDA 21-957, no differences in PK performance between DR granules and DR capsules are expected.

F. Analytical Section

For study No. D9614C00099, plasma samples for determination of esomeprazole were analyzed at DMPK & Bioanalytical Chemistry, AstraZeneca R&D Mölndal, Sweden using validated [REDACTED] liquid chromatography and LC/MS/MS according to method No. BA-410-01, “Analytical Method for Determination of Esomeprazole or Omeprazole, in Human Heparin Plasma by LC-MS/MS”, (AstraZeneca R&D Mölndal Analytical Method No. BA-410-01, 7 September 2004). The nominal concentrations of esomeprazole performed ranged from 20-20000 nmol/L with the limit of quantification (LOQ) of 20 nmol/L for esomeprazole. The quality control (QC) samples, 59.1 (n=12), 626 (n=12), and 16000 nmol/L (n=12), showed precision with coefficient of variation (CV%) of 2.1-4.8% and an overall mean of accuracy of 98.9 – 105.9%.

For study No. SH-NEC-0001, the same method was used. The nominal concentrations of esomeprazole performed ranged from 5-5000 nmol/L with the limit of quantification (LOQ) of 5 nmol/L for esomeprazole. The quality control (QC) samples, 44.7-54.2 (n=14), and 960-1100 nmol/L (n=14), showed precision with coefficient of variation (CV%) of 1.6-4.8% and an overall mean of accuracy of 99.6 – 107.1%. The above two assay methods were reviewed and found acceptable.

V. Detailed Labeling Recommendations

The following CP labeling recommendations should be conveyed to the sponsor; sponsor’s addition (double underlined), Agency’s addition (blue and underline), and deletion (~~red and double strikethrough~~)

[REDACTED]

[REDACTED]

[REDACTED]

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

VI. Appendices

1. Proposed Package Insert (Original and Annotated)
2. Individual Study Review
3. Cover Sheet and OCPB Filing/Review Form

**NDA 22-101 for Nexium (Esomeprazole Magnesium)
Granules in Packet for Oral Suspension**

Appendix 1

Sponsor's Proposed PI (Annotated; 01/17/2007 version)

34 Page(s) Withheld

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 X Draft Labeling

 Deliberative Process

**NDA 22-101 for Nexium (Esomeprazole Magnesium)
Granules in Packet for Oral Suspension**

Appendix 2

Individual Study Review

| | | |
|--|-----------------|-----------------------------------|
| Drug Substance(s) Esomeprazole magnesium | SYNOPSIS | (For national authority use only) |
| Study Code D9614C00099 | | |
| Date 10 March 2005 | | |

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Multiple Doses of Esomeprazole Magnesium in a Pediatric Population of 1 to 11 Year olds with Gastroesophageal Reflux Disease (GERD) or Symptoms of GERD

Investigator

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Study center(s)

This study was conducted in 1 center in the United States.

Study dates

First subject enrolled 22 March 2004
 Last subject completed 31 July 2004

Phase of development

Clinical pharmacology (I)

Objectives

Primary Objective: To determine the area under the curve (AUC) of esomeprazole after multiple oral doses of 5 mg, 10 mg, and 20 mg esomeprazole magnesium in 1 to 11 year olds, inclusive with GERD or symptoms of GERD.

Secondary Objectives:

- To determine the $AUC_{(0-t)}$, C_{max} , t_{max} , $t_{1/2z}$, apparent oral clearance (CL/F), apparent volume of distribution during terminal phase ($V_{\lambda z}/F$) and apparent volume of distribution at steady state (V_{ss}/F) of esomeprazole after multiple oral doses of 5 mg, 10 mg, and 20 mg esomeprazole in 1 to 11 year olds, inclusive with GERD or symptoms of GERD.
- To determine AUC, $AUC_{(0-t)}$, C_{max} , t_{max} , $t_{1/2z}$ of the 5-hydroxy and sulphone metabolites of esomeprazole after multiple oral doses of 5 mg, 10 mg, and 20 mg esomeprazole magnesium in 1 to 11 year olds, inclusive with GERD or symptoms of GERD. (Note:

The PK parameters of the 5-hydroxy metabolite were not determined because it could not be separated from the 3-hydroxy metabolite on the HPLC chromatogram.)

- To assess the safety and tolerability of esomeprazole in 1 to 11 year olds, inclusive with GERD or symptoms of GERD.

Study design

This was a randomized, open label study to evaluate the pharmacokinetics, safety, and tolerability of esomeprazole 5 mg, 10 mg, and 20 mg when given as repeated doses to subjects aged 1 to 11 years, inclusive with GERD or symptoms of GERD.

Target subject population and sample size

The target subject population was male and female children, aged 1 to 11 years inclusive, who suffered from GERD or symptoms of GERD and were candidates for acid suppression therapy.

The target sample size of 24 evaluable subjects (minimum) was selected to provide data sufficient to describe the PK profile for esomeprazole in the population, while at the same time minimizing the number of subjects that needed to be enrolled. Eighteen 1 to 5 year old subjects were enrolled in order to obtain at least 12 evaluable subjects, 6 in each dosage group of 5 mg and 10 mg esomeprazole magnesium. Thirteen 6 to 11 year old subjects were enrolled in order to obtain 12 evaluable subjects, 6 in each dosage group of 10 and 20 mg esomeprazole magnesium. This sample size was not based on any power calculations.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Esomeprazole magnesium blue clinical image capsules formulated as 5 mg, 10 mg, and 20 mg were used for 5 days of oral administration as either an intact capsule with water or as an opened capsule mixed with applesauce followed by water.

Duration of treatment

Each 1 to 5 year old subject was exposed to either 5 mg or 10 mg esomeprazole magnesium for 5 days and each 6 to 11 year old subject was exposed to either 10 mg or 20 mg esomeprazole magnesium for 5 days.

Variables

Pharmacokinetic: Blood samples were analyzed to determine the pharmacokinetics of esomeprazole magnesium (AUC, AUC_(0-t), C_{max}, t_{max}, t_{1/2,z}, CL/F, V_{1,z}/F and V_{ss}/F) and the pharmacokinetics of its sulphone metabolite (AUC, AUC_(0-t), C_{max}, t_{max}, t_{1/2,z}) in the specified population.

Safety: Safety and tolerability were assessed by means of incidence and severity of all adverse events, vital signs, laboratory parameters and physical examinations.

Statistical methods

Subjects were analyzed based on the actual dose they received. Summaries of PK parameters were based on the subjects who had PK parameter estimates available (AUC, $AUC_{(0-t)}$, or C_{max}). Summary of esomeprazole plasma concentrations and safety data were based on the subjects who participated in the study and received at least one dose of drug.

Esomeprazole and the sulphone metabolite plasma concentrations were summarized by dose group and reported as descriptive statistics. For esomeprazole, the following PK parameters were summarized: AUC, $AUC_{(0-t)}$, C_{max} , t_{max} , $t_{1/2z}$, CL/F, V_{1z}/F , and V_{2z}/F . For the esomeprazole sulphone metabolite, the following PK parameters were summarized: AUC, $AUC_{(0-t)}$, C_{max} , t_{max} , and $t_{1/2z}$.

Descriptive statistics were used to evaluate vital signs and clinical laboratory assessments. Clinical chemistry and hematology values outside the laboratory reference range were flagged. No formal statistical comparisons were made.

All adverse event data were listed individually and summarized using MedDRA terminology.

Subject population

In the overall study population of 1 to 11 year old pediatric subjects, the percentages of males and females were similar (17 males, 14 females). Within the 1 to 5 year old age groups, the 5 mg dose group was predominantly female (6/9, 66.7%) and the 10 mg dose group was predominantly male (6/9, 66.7%). Within the 6 to 11 year old age groups, the 10 mg dose group was predominantly male (5/7, 71.4%) and the 20 mg dose group was evenly distributed between males and females (50.0% each).

The race of most participants in the study was classified as Caucasian (12/31, 38.7%) or Other (11/31, 35.5%). The breakdown of race within the dose groups varied.

The mean weight and height of the 1 to 5 year old subjects in the 10 mg esomeprazole group were less than the weight and height of the subjects in the 5 mg group; however, the mean BMIs were similar in both groups (10 mg: 17.1, 5 mg: 18.2). The mean weight, height, and BMI were similar in both the 6 to 11 year old subject groups (10 and 20 mg).

Thirty-one (31) subjects were randomized in this study. Four (4) of these subjects discontinued prematurely and 27 subjects completed the study, receiving all assigned doses of esomeprazole. Of the 4 subjects who discontinued early, 3 were withdrawn by their parents due to the blood draws required by the study and 1 subject was discontinued because he refused to take the drug. All subjects who discontinued were in the 1 to 5 year old dose groups.

Summary of pharmacokinetic results

[Table S1](#) summarizes the primary PK parameter (AUC) and secondary PK parameters ($AUC_{(0-t)}$, C_{max} , $t_{1/2z}$, and apparent clearance normalized by body weight) of esomeprazole for all dose groups. The results were as follows:

- The AUC, AUC_(0-t), and C_{max} were several-fold higher for 10 mg esomeprazole compared with 5 mg esomeprazole in children aged 1 to 5 years, while the same parameters were approximately twice as high for 20 mg esomeprazole compared with 10 mg esomeprazole in children aged 6 to 11 years.
- The t_{1/2,z} was approximately twice as long for the 10 mg dose compared with the 5 mg dose in children aged 1 to 5 years, while the t_{1/2,z} was similar for 20 mg dose compared with 10 mg dose in children aged 6 to 11 years.
- Overall, children aged 1 to 5 years seemed to have a higher apparent clearance than those aged 6 to 11 years in terms of per kilogram of body weight (CL/F/kg).

Table S1 Summary of esomeprazole PK results

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

AUC is area under the plasma concentration-time curve from 0 to infinity; AUC_(0-t) is area under the plasma concentration-time curve from 0 to t; CI is confidence interval; C_{max} is maximum plasma (peak) drug concentration; Geo. mean is geometric mean; t_{1/2,z} is half life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve; CL/F/kg is the apparent clearance normalized by body weight (shown only for 10 mg for comparison between 2 different age groups with the same dose).

Summary of safety results

Esomeprazole doses of 5 and 10 mg were well tolerated in pediatric subjects ages 1 to 5 years. Doses of 10 and 20 mg were well tolerated in pediatric subjects ages 6 to 11 years. There were no deaths, DAEs, or OAEs in this study. There was 1 SAE (skin laceration), which was unrelated to study medication. There were 2 AEs (excoriation, faeces discoloured) and both AEs were of mild intensity.

There were no clinically important findings and trends in haematology, clinical chemistry, urinalysis, or vital signs observed across or within treatment groups.

Reviewer's Comments:

For CP comments, please see the QBR section of this review.

A Single-Blind, Randomised, Parallel-Group, Single-Centre Pharmacokinetic and pH-Monitoring Study of Esomeprazole in Infants up to 24 Months of Age

Investigator

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Study centre

This was a single-centre study conducted in Australia at the Centre for Paediatric and Adolescent Gastroenterology, Women's and Children's Hospital, North Adelaide, Australia.

Study dates

First subject enrolled 6 June 2002
Last subject completed 23 March 2005

Phase of development

Therapeutic exploratory

Objectives

The primary objective of this study was to assess the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants.

The secondary objectives were:

- to assess the efficacy of esomeprazole in controlling esophageal acid exposure
- to assess the safety and tolerability of esomeprazole in infants
- to assess the ability of esomeprazole to reduce gastroesophageal reflux disease (GERD) symptoms in infants.

Study design

A single-centre, randomised, single blind, two-arm parallel, repeated dose design was used in this study. Subjects were given a 1 week regimen of esomeprazole 0.25 mg/kg or esomeprazole 1.0 mg/kg administered orally once daily (od).

Target subject population and sample size

The subject population comprised outpatient infants up to 24 months of age with symptoms of GERD where the diagnosis was confirmed by 24-hour pH-monitoring.

The aim was to have about 30 evaluable subjects for the pharmacokinetics (PK) in the study of which at least 24 subjects (12/treatment arm) had to be <12 months, including at least 2 subjects aged between 1 to 3 months. Thus, taking into account a dropout from the PK evaluation of some subjects, 40-50 subjects were estimated to be randomised. However, if infants eligible for inclusion were difficult to recruit, the study was to be terminated when 24 (12/treatment arm) PK evaluable subjects <12 months had been reached with at least 2 subjects aged between 1 to 3 months.

Investigational product: dosage, mode of administration and batch numbers

Each subject was randomised to receive 1 of 2 possible doses of the study drug (hereafter referred to as investigational product), ie esomeprazole 0.25 mg/kg or esomeprazole 1.0 mg/kg orally once daily (od) in the morning for a period of 7 or 8 days (hereafter referred to as 7/8 days). The pellets were dispersed in approximately 1 teaspoon of apple sauce (subjects ≥ 3 months of age) or emptied into a funnel pan and administered through a specially designed adapter (subjects ≥ 1 month to <3 months of age). Four different capsules (1.5 mg, 2.5 mg, 5 mg and 10 mg) were used in combination to achieve a dose as accurate as possible.

Batch numbers were H1539-01-01-01, H1538-01-01-01, H1504-01-01-02 and H1221-02-01-05 for the 1.5 mg, 2.5 mg, 5 mg and 10 mg esomeprazole capsules, respectively.

Duration of treatment

Once daily oral doses of the investigational product were given during 7/8 days.

Variables

- Pharmacokinetic

- AUC_{τ} the area under the plasma concentration versus time curve during a dosage interval (24 hours) (*primary variable*)
- AUC_t the area under the plasma concentration versus time curve from zero to the last quantifiable concentration, calculated by log/linear trapezoidal method (*primary variable*)
- C_{SSmax} the observed maximum plasma concentration (*primary variable*)

- t_{\max} the time to reach C_{\max}
 - $t_{1/2}$ the plasma elimination half-life, calculated by $\ln 2/\lambda$
- **Pharmacodynamic**
- The percentage of time with intragastric pH >4 during the 24-hour period (*primary variable*)
 - Median intragastric pH during the 24-hour period
 - The percentage of time with intra-esophageal pH <4 during the 24-hour period
 - Number of reflux episodes during the 24-hour period. The reflux episode is defined as an intra-esophageal pH <4 lasting longer than 5 seconds, or if pH is already below 4, a further drop of at least 1 pH unit
 - Number of reflux episodes longer than 5 minutes during the 24-hour period
 - Gastroesophageal reflux (GER) score (number of reflux episodes + 4 x number of reflux episodes longer than 5 min)
 - Symptom scores for vomiting, crying and gagging, respectively and combined
 - Visual analogue scale for overall symptom intensity
 - Weight
- **Safety**
- Adverse Events (AEs), laboratory measurement, weight, height, head circumference, pulse and breathing rate

Statistical methods

The conclusions of the pharmacodynamic and pharmacokinetic analyses are based on the intention to treat (ITT) population.

Pharmacokinetic variables

The log transformed variables AUC, AUC_t , C_{\max} and $t_{1/2}$ were analysed using an ANOVA model. The estimates, ratios (difference between treatments) and 95% confidence intervals for the true geometric means are presented.

The metabolites were analysed in the same way as the main compound and the ratios between esomeprazole and its metabolites are also given.

The relationship between exposure (AUC_t and C_{max}) and age, weight, intragastric pH and dose as well as the relationship between the ratio of esomeprazole and its metabolites and age and weight were investigated.

Individual values and descriptive statistics are given for all pharmacokinetic variables.

Pharmacodynamic variables

The percentage of time with intragastric pH >4 during the 24-hour period following drug administration was analysed using an ANOVA model.

The change in percentage of time with intragastric pH >4 during the 24-hour period from pre-entry to that after 1 week of treatment was analysed using an ANOVA model, with the pre-entry values used as a covariate.

The percentage of time with esophageal pH <4 during the 0 to 24-hour period following drug administration was analysed in the same way as intragastric pH.

Symptoms recorded on the diary cards are presented descriptively.

The results of the parent's assessment of the global severity of the child's symptoms are presented as the proportion of subjects with improved health.

Individual values and descriptive statistics are given for all pharmacodynamic variables.

Safety evaluation

Adverse events, laboratory variables, weight, height, head circumference, pulse and breathing rate are presented descriptively for the safety population.

Subject population

Number of subjects:

- enrolled = 107
- randomised = 50 (43 were ≤ 12 months of age [9 were <3 months of age], 7 were >12 months of age)
- completed = 45 (39 were ≤ 12 months of age, 6 were >12 months of age)
- discontinued = 5

The baseline demographics for randomised subjects in the 2 dosage groups were comparable.

Summary of pharmacokinetic results

The median time to reach the maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. There was a large interindividual variability in AUC_t , AUC_τ and C_{SSmax} of esomeprazole for both the 0.25 mg/kg and 1.0 mg/kg doses, and the variability seemed to be larger in the younger children. Numerically there was a larger than proportional increase in AUC_t , AUC_τ and C_{SSmax} with dose, even though not statistically significant (Table S 1). The geometric mean half-life was similar for the 2 dose-groups, 0.8 and 1 hours for the 0.25 mg/kg and 1.0 mg/kg dose, respectively.

Table S 1 Estimated geometric mean and 95% CI for pharmacokinetic variables, esomeprazole, ITT

| Variable | | Estimated | 95% confidence interval | |
|---|--|-----------|-------------------------|-------|
| | | Mean | Lower | Upper |
| AUC_t ($\mu\text{mol}\cdot\text{h/L}$)* | Esomeprazole 0.25 mg/kg (n=17) | 0.24 | 0.12 | 0.48 |
| | Esomeprazole 1.0 mg/kg (n=18) | 1.79 | 0.90 | 3.56 |
| | Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg | 7.62 | 2.85 | 20.40 |
| AUC_τ ($\mu\text{mol}\cdot\text{h/L}$) | Esomeprazole 0.25 mg/kg (n=9) | 0.65 | 0.27 | 1.57 |
| | Esomeprazole 1.0 mg/kg (n=7) | 3.51 | 1.28 | 9.59 |
| | Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg | 5.42 | 1.42 | 20.73 |
| C_{SSmax} ($\mu\text{mol/L}$) | Esomeprazole 0.25 mg/kg (n=17) | 0.17 | 0.09 | 0.31 |
| | Esomeprazole 1.0 mg/kg (n=17) | 0.85 | 0.45 | 1.60 |
| | Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg | 5.08 | 2.09 | 12.35 |
| $t_{1/2}$ (h) | Esomeprazole 0.25 mg/kg (n=9) | 0.77 | 0.55 | 1.08 |
| | Esomeprazole 1.0 mg/kg (n=8) | 0.95 | 0.66 | 1.35 |
| | Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg | 1.23 | 0.75 | 2.00 |

*In the 0.25 mg/kg dose group there is 1 subject with all samples below LOQ and therefore no PK-variables could be calculated. This subject is therefore not included in the calculation of the estimated geometric means or ratios between doses.

Summary of pharmacodynamic results

The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group on Day 7/8. Statistically, the increase was significantly higher with the esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose.

At baseline, the mean percentage of time with intra-esophageal pH <4 was 11.6% in the esomeprazole 0.25 mg/kg dose group and 12.5% in the 1.0 mg/kg dose group. After 7/8 days of treatment with esomeprazole 0.25 mg/kg or 1.0 mg/kg, these values decreased to 8.4% and 5.5%, respectively. There was no statistically significant difference in the decrease in the percentage of time with intra-esophageal pH <4 between the 2 dosage groups.

The proportion of subjects improving after 1 week's treatment (as assessed by the parent) was 77% and 62% in the 0.25 mg/kg and 1.0 mg/kg group, respectively.

Summary of pharmacokinetic/pharmacodynamic correlations

A positive correlation between both AUC_t and C_{SSmax} of esomeprazole and the percentage of time with an intragastric $pH > 4$ could be seen in the study.

Summary of safety results

Esomeprazole in doses of 0.25 mg/kg and 1.0 mg/kg was well tolerated. The occurrence of adverse events was similar in the treatment groups. One subject discontinued use of the investigational product due to an adverse event (DAE), irritability. No serious adverse events (SAEs) were reported. There were no clinically important trends within or between treatment groups with respect to laboratory variables, vital signs or physical findings.

Reviewer's Comments:

For CP comments, please see the QBR section of this review.

**NDA 22-101 for Nexium (Esomeprazole Magnesium)
Granules in Packet for Oral Suspension**

Appendix 3

Cover Sheet and OCPB Filing/Review Form

OFFICE OF CLINICAL PHARMACOLOGY

New Drug Application Filing and Review Form

General Information About the Submission

| | Information | | Information |
|-----------------------------------|---------------------------|-------------------------|--|
| NDA Number | 22-101 | Brand Name | Nexium |
| OCPB Division (I, II, III) | DCP III | Generic Name | Esomeprazole magnesium |
| Medical Division | GI and Dermatology | Drug Class | PPI |
| OCPB Reviewer | Tien-Mien Chen, Ph.D. | Indication(s) | GERD and gastric-acid related GI disorders |
| OCPB Team Leader | Sue-Chih Lee, Ph.D. | Dosage Form | Granules in Packet Formulation for Oral Suspension |
| | | Dosing Regimen | 10 or 20 mg granules QD up to 8 weeks |
| Date of Submission | 09/27/06 | Route of Administration | Oral |
| Estimated Due Date of OCPB Review | 05/22/07 | Sponsor | AstraZeneca |
| Medical Division Due Date | 06/13/07 | Priority Classification | S |
| PDUFA Due Date | 07/27/07 | | |

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. | X | █ | █ | |
| Tabular Listing of All Human Studies | X | █ | █ | |
| HPK Summary | | █ | █ | |
| Labeling | X | █ | █ | |
| Reference Bioanalytical and Analytical Methods | X | █ | █ | Additional information was requested |
| 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- | X | █ | █ | █ |
| single dose: | | | | |
| multiple dose: | 1 | 1 | | |
| 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: | X | 1 | | A supportive PK and PD monitoring in pediatric patients 1-24 months |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | X | 1 | | Already reviewed previously under NDA 21-957 |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 3 | 2 | |
| | | | | |
| Filability and QBR comments | | | | |
| | "X" if yes | <i>Comments</i> | | |
| Application filable ? | X | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? | | |
| Comments sent to firm ? | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. Additional information on validation of analytical methods was requested | | |
| QBR questions (key issues to be considered) | Do the PK and supportive PK/PD studies submitted support the proposed dose and also support the pediatric study listed in the pediatric exclusivity written request for the use of Nexium in this pediatric population 1-11 years old? | | | |
| Other comments or information not included above | | | | |
| Primary reviewer Signature and Date | Tien-Mien Chen, Ph.D., 03/15/07 | | | |
| Secondary reviewer Signature and Date | Shue-Chih Lee, Ph.D., 03/15/07 | | | |

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

/s/

Tien-Mien Chen
7/3/2007 02:29:54 PM
BIOPHARMACEUTICS

Sue Chih Lee
7/3/2007 02:49:13 PM
BIOPHARMACEUTICS