CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-689

MEDICAL REVIEW

03/23/05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 23, 2005

TO: Division Files: **NDA 21-689**
NEXIUM® (esomeprazole) I.V. for Injection

APPLICANT: AstraZeneca Pharmaceuticals [AZ]

LIST OF REVIEWED SUBMISSIONS [BY DIVISION REVIEWERS]:

Original	September 10, 2003
Amendment	March 29, 2004
Amendment	April 01, 2004
Second Cycle	Document Date
Amendment BC	August 05, 2004
Amendment (response to the approvable letter)	September 23, 2004
Amendment AZ	September 30, 2004

Proposed Indications(s): Short-term treatment (up to 10 days) of _____ (GERD) as an alternative to oral therapy in patients when therapy with NEXIUM Delayed Release Capsules is not possible or appropriate

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader [Gastrointestinal Drugs]
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

SUBJECT: **Recommendations for Regulatory Action, including labeling revisions**

I. BACKGROUND/INTRODUCTION

Esomeprazole is the single S-enantiomer of the proton pump inhibitor (PPI) omeprazole. All PPIs act through inhibition of the proton pump enzyme H^+/K^+-ATPase located in the parietal cells of the gastric mucosa.

Esomeprazole (Nexium®) Delayed Release Capsule (20 and 40 mg) was approved in the US in February 2001 for three indications: 1) treatment of erosive esophagitis (EE), at the recommended dosages of 20 mg or 40 mg once daily; 2) maintenance of healed EE to prevent relapse, at the recommended dose of 20 mg once daily; and 3) short-term treatment of symptomatic GERD [s-GERD], at the recommended dose of 20 mg once daily.

Through NDA 21-689, AZ is requesting approval of Nexium® I.V. [redacted]

NDA 21-689 consisted of 14 studies; 13 clinical pharmacology studies evaluating the PK and PD aspects and a single clinical study evaluating the safety and efficacy of I.V. esomeprazole. In the 4 critical studies, male and female GERD patients, with a history of EE received esomeprazole (20 mg in studies SH-NEP-0012 & D9615C00014, and 40 mg in studies SH-NEP-0011 & D9615C00013) as either an oral capsule or an I.V. infusion (3 min injection in studies D9615C00013 & D9615C00014, and 15-min infusion in studies SH-NEP-0011 & SH-NEP-0012) QD for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for basal acid output (BAO) measurement. Thereafter, pentagastrin (6 μg/kg) S.C. was administered and four 15-min samples were collected for maximal acid output (MAO) measurement. The main PD findings are summarized in Tables 1 and 2.

Table 1
Estimates of mean MAO values after administration of 20 mg doses as either a 3 min injection or P.O. for 10 days (study D9615C00014)

	E20 oral (n=42)		E20 IV inj (n=42)		Ratio (IV/Oral)	
Acid output	LS geometric mean (95% CI)	Arith. Mean (SD)	LS geometric mean (95% CI)	Arith. Mean (SD)	LS geometric mean	1-Sided 95% upper confidence limit [a]
MAO (mmol/h)	3.18 (2.18 to 4.65)	5.27 (5.39)	3.44 (2.36 to 5.00)	5.86 (5.41)	1.08	1.44

Table 2
Estimates of mean MAO values after administration of 40 mg doses as either a 3 min injection or P.O. for 10 days (study D9615C00013)

	E40 oral (N=50)		E40 IV inj (N=50)[a]		Ratio (IV/Oral)	
Acid output	LS geometric mean (95% CI)	Arith. Mean (SD)	LS geometric mean (95% CI)	Arith. Mean (SD)	LS geometric mean	1-Sided 95% upper confidence limit[b]
MAO (mmol/h)	2.75 (1.97 to 3.85)	4.41 (3.11)	3.88 (2.76 to 5.47)	5.06 (3.90)	1.41	1.82

From the PK/PD viewpoint, the conclusions arrived at were:

- Administration of esomeprazole I.V. at doses of 20 and 40 mg QD results in markedly higher Cmax and AUC values relative to comparable P.O. doses. However, consistent PD differences of a smaller magnitude are observed between I.V. and P.O. esomeprazole following multiple dose administration. The clinical relevance of such PD differences is unknown. Moreover, administration of esomeprazole I.V. infusions ranging in duration from 3 to 30 min results in similar PD profiles.
- According to the Biopharmaceutics reviewer, overall, the sponsor has adequately characterized the clinical pharmacology and biopharmaceutics-related aspects of the drug product. From their viewpoint, NDA 21-689 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert.
- The findings of study SH-NEP-0003 suggest that I.V. infusions of esomeprazole given over a period as short as 3 min and as long as 30 min are likely to yield similar PD profiles.

The Chemistry review identified a long list of specific issues regarding the compatibility of the I.V. proposed formulation in various diluents and delivery systems. They also requested of the sponsor to add a heavy metals specification (test and limits of [redacted] to the drug substance and drug product proposed specifications. The rationale for this request is that [redacted] in the manufacturing process and some batches were tested and found to contain some low amounts of [redacted]

The Clinical/Statistical reviewers analyzed results of Study SH-NEP-006, a randomized, double-blind [during the first 7 days?], multiple placebo, parallel group study of Nexium® I.V. as a 3-min injection [n = 79], 30-min infusion [n = 81] or oral [n = 86]. The study population consisted of patients with endoscopically documented erosive esophagitis, assessed according to the LA classification. Each patient received this blinded therapy for 7 days then was switched to oral Nexium for the next 3 weeks. Endoscopy was performed at the end of 4 weeks of therapy. The main constraints with interpretation of the healing results in this study are: lack of a concurrent placebo control, lack of prospectively specified equivalence boundary, and unblinded assessments during the oral treatment [actually the trial may have been unblinded during the entire 4 weeks]. The results of this trial support the safety of the Nexium® formulations and are

hypothesis-generating: adequately designed studies are needed to support the notion that Nexium® I.V. can be used *de novo.*

There were no issues raised by the Pharmacology/Toxicology reviewers. They recommended approval of the application.

On July 9, 2004 an approvable letter was sent to the sponsor. The letter included a long list of Chemistry deficiencies regarding to the sponsor's proposed drug product specifications, description of impurities and degradants for the drug substance, drug product and reconstituted solutions, at different time points and other requests regarding expiring dating for the drug substance. Another issue regarding approvability was an agreement between the Division and the sponsor on the wording to be included in the various sections of the package insert.

II. CONCLUSIONS FROM CHEMISTRY REVIEW

In his review, completed on March 17, 2005, Dr. Ali Al-Hakim addressed all the chemistry deficiencies included in the Division's approvable letter of April 23, 2004. Dr. Al-Hakim's review included a list of all related supporting documents, ONDC status, detailed description of the drug product, detailed description of the drug substance, a description of how the drug product is intended to be used and the basis for his recommendations for regulatory action.

The application is recommended for approval from CMC point of view. According to Dr. Al;-Hakim, the sponsor provided satisfactory responses to the Agency's Information Request letter dated April 23, 2004. Specifically, the basis for the Chemist's recommendation is that the sponsor provided satisfactory Reponses to the deficiencies delineated in the Chemistry review number 1. The responses were related to the CMC issues regarding compatibility studies with other diluents and I.V. bags and other CMC queries. Dr. Al Hakim notes that this drug product will be used in hospital emergency setting. From CMC risk management point of view, the compatibility study for this type of product is a critical requirement for this application.

III. LABELING REVISIONS [Table 3]

The sponsor's proposed labeling revisions have been considered at several multi-diciplinary intramural meetings. The FDA proposed revisions are reflective of the fact that esomeprazole is safe and effective for the sought indication. Our proposed revisions are also reflective of other facts, notably the following: 1) in the pharmacokinetic/pharmacodynamic trials that form the basis for approval of the current application, the study population consisted of patients with a history of EE who had GERD symptoms; 2) the data in NDA 21-689 support the approval of the use of esomeprazole for short-term [up to 10 days] in those patients that are unable to continue taking the oral form of the drug; 3) no adequate data have been submitted demonstrating that the I.V. formulation can be used *de novo* in GERD patients, an indication that differs from to the one being granted to AstraZeneca. The *de novo* indication has been granted to manufacturers of other PPIs that submitted results of adequate and well controlled pharmacodynamic and clinical data demonstrating that, under certain circumstances, the intravenous form of the PPI could be used from the start, as an initial form of therapy in either EE or s-GERD patients.

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

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

/s/

Hugo Gallo Torres
3/23/05 03:10:53 PM
MEDICAL OFFICER

07/09/04

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 7/8/2004

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: **Director (Deputy) Summary Approval Comments**
NDA 21-689

APPLICANT: AstraZeneca Pharmaceuticals

DRUG: Nexium®(esomeprazole) IV for Injection

DIVISION RECOMMENDATION:
The Division finds that this application is approvable pending resolution of CMC issues and negotiation of the final labeling.

The deficiencies listed in the action letter are as follows:

1. "Regarding your proposed drug product specifications:

    a- Your proposed acceptance criteria for total and individual impurities appear to be broad. Tighten the limits for total and individual impurities based on your real time stability test data (refer to your long term stability test data after —months which are submitted in amendment dated April 01, 2004).

    b- Your proposed acceptance criteria for residual solvents are broad. Tighten the limits based on your batch test data.

2. Provide information describing the structural elucidation of the impurities and degradants for your drug substance, drug product and reconstituted solutions. Of particular concern is the new impurity—— which was discovered and reported in a recent amendment dated April 01, 2004. Reference standards are needed to support the proposed structures for the impurities and degradants.

3. Provide data documenting the level of degradants during reconstitution studies at different time points (please refer to the meeting minutes sent you by the Agency on May 26, 2004).

4. If the data (from question 1) confirms that Nexium IV is chemically unstable in Lactated Ringer's Injection and Dextrose Injection then further testing with these diluents is not required. The drug will need to be appropriately labeled in concordance with the data.

5. Additional compatibility studies using saline as your diluent and employing IV bags of all commercial compositions should be conducted and include the tubing, connectors, syringes, etc. supplied by these different manufacturers.

6. On-going compatibility studies for the drug product with various diluents, indicate that heavy metal specifications (test and limits of) need to be added to the drug substance and drug product specifications."

I. BACKGROUND:

Esomeprazole is the S-enantiomer of omeprazole and is an inhibitor of gastric acid secretion. It is currently available as an oral dosage form of Nexium 20 mg and 40 mg Delayed Release Capsules. In the US, the recommended dosages for the GERD indication are: 20 mg or 40 mg once daily for the treatment of erosive esophagitis (EE), 20 mg once daily for the maintenance of healed EE to prevent relapse, and 20 mg once daily for the short-term treatment of symptomatic GERD (sGERD).

Currently, there are 2 proton pump inhibitors (PPI) that are available as an intravenous formulation: Protonix IV (pantoprazole); Prevacid IV (lansoprazole). These formulations have been approved for the following indications:

"Protonix IV for Injection is indicated for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative to oral therapy in patients who are unable to continue taking PRTONIX (pantoprazole sodium) Delayed-Release Tablets. Safety and efficacy of PRIOTONIX IV for Injections as an initial treatment for GERD have not been demonstrated."

"When patients are unable to take the oral formulations, PREVACID IV for Injections is indicated as an alternative for the short-term treatment (up to 7 days) of all grades of erosive esophagitis. Once the patient is able to take medications orally, therapy can be switched to an oral formulation of Prevacid for a total of 6 to 8 weeks. The safety and efficacy of PREVACID IV for Injection as an initial treatment of erosive esophagitis have not been demonstrated."

It is the Sponsor's intention seek approval for an indication that would permit patients to switch from current oral esomeprazole treatment to IV esomeprazole, and continue with oral esomeprazole when oral administration as appropriate.

In the current application, the sponsor has developed an I.V. formulation of Nexium to be used as an alternative to Nexium Capsules. The I.V. formulation is intended for short-term (10 days) treatment of gastroesophageal reflux disease. The label specifically states that In addition, the applicant is requesting labeling for the injection (no less than 3 minutes) or the infusion (10 to 30 minutes) for both doses (20mg and 40mg).

Finally, AztraZeneca proposes that only 0.9% sodium chloride solution be used to prepare and deliver this formulation. It appears that they have not studied the effect of other commonly used diluants and intravenous bags and tubing with regard to the formation of precipitants and degradation products. This is an important class issue in the formulation of intravenous proton pump inhibitors. The stability of esomeprazole sodium in aqueous solution is strongly dependent on the pH. The rate of degradation increases with decreasing pH. (For further discussion see Chemistry review).

The proposed IV formulation contains an esomeprazole sodium salt, in place of the esomeprazole magnesium salt in the oral formulation. The sodium salt was selected because the water solubility of esomeprazole magnesium was insufficient for the IV formulation. Each dose of esomeprazole contains —— of sodium.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

DDMAC and DMETS found the proprietary name of Nexium IV acceptable. DDMAC made some suggestions regarding the label. The input is appreciated, however, the label will be negotiated during the next cycle and these comments will be considered then in light of the final decision regarding the acceptability of giving the initial therapy indication.

B. Chemistry:

Chemistry identified specific issues regarding the compatibility of this formulation in various diluents and delivery systems. This issue was transmitted tot he applicant in the FILLING COMMUNICATION Letter (10/20/03). The issue was stated as follows:

> *"Conduct additional compatibility studies using IV bags of all commercial compositions (e.g. PVC, Polyolefin, etc.). These studies should include the tubing, connectors, syringes, etc. supplied by different manufacturers and commonly used diluents (e.g. Lactated Ringer's Injection, 5% Dextrose Injection, etc.) even if they are not identified in the proposed drug product labeling. The studies should include testing for potency (assay), pH, impurities and —— particulates at different time point within 24 hours."*

During the review this chemistry issue was discussed with AstraZeneca (refer specifically to minutes from teleconference held on April 28, 2004.) AstraZeneca proposed a strategy for approval of Nexium IV ——— The Agency responded that due to safety concerns this approach is not acceptable and that we are treating all agents within this drug class the same and holding them to the same requirements and reiterated the desire to see all infusion sets and IV bags tested with all diluents. The Agency stated that the use of an incorrect diluent is not uncommon and the data are needed to insure the safe use of the product. The Agency indicated that this point was non-negotiable and is consistent with their position on other agents in this drug class.

The Agency requested that compatibility testing be performed using Lactated Ringer's and Dextrose in IV bags and infusion or extension sets of representative commercial compositions and manufacturers. This additional testing should be based on the saline compatibility protocol with additional time points. The Agency feels that full compatibility testing is necessary for Lactated Ringer's and Dextrose. The Agency indicated that Lactated Ringer's and Dextrose should be tested at 0, 1, 2, 4, 6, 12, and 24 hours. Furthermore, the Agency is requesting both subvisible particulate and chemical stability data be collected at all time points for a full characterization. The test results from these additional studies must be submitted to the NDA.

The Sponsor agreed to perform this additional testing and notified the Agency of the anticipated timing for submission of the data would be in September of 2004.

Finally the Chemistry reviewers added one more issue. They are requesting the applicant to include a heavy metals specification (test and limits of ——— be added to the drug substance and drug product proposed specifications. This is because ——— is a catalyst in the manufacturing process and some batches were tested and found to contain some low amounts of ———

MICROBIOLOGY REVIEW found this formulation acceptable.

C. Pharmacology/Toxicology:
Several pharmacology studies and toxicology studies were performed. There were no issues raised by the reviewer and this application was for approval from at pharm/tox perspective. However, if additional chemistry study results reveal significant impurities, then additional toxicology testing may be considered.

D. Biopharmaceutics:

AstraZeneca submitted several studies comparing oral Nexium to intravenous Nexium, (injection or infusion). Overall, the results are supportive and demonstrate that this formulation has very similar properties to the oral formulation. Both formulations very potently suppress gastric acid. However, from a strict bioequivalence standpoint based upon pharmacokinetics they are not bioequivalent. Additional pharmacodynamic studies demonstrate similarity and there are no fixed definitions for defining "bioequivalence" based upon pharmacodynamic parameters. Therefore, it is important to consider this data from a clinical prospective and in light of clinical information presented in study SH-NEP-006 (see below).

The pharmacokinetics of Nexium IV 20-mg and 40-mg were studied as either a 3-minute injection or as an infusion ranging from 15 to 30 minutes. The pk was compared to oral Nexium. The results of the 40-mg IV dose demonstrated Cmax and AUC values which were higher on day 1 by 128% and 66%, respectively

compared to the oral capsule, and by day 5 these values had decreased to 63% and 29% higher relative to the oral 40 mg capsule. The results of the 40-mg IV dose demonstrated Cmax and AUC values which were higher on day 1 by 324% and 82%, respectively compared to the oral capsule, and by day 5 these values had decreased to 146% and 31% higher relative to the oral 40 mg capsule. Thus they were not bioequivalent based upon the strict definition.

Pharmacokinetic Parameters of NEXIUM Following I.V. Dosing for 5 days

Parameter	NEXIUM I.V. 20 mg	NEXIUM I.V. 40 mg
AUC (μmol*h/L)	5.11 (3.96:6.61)	16.21 (14.46:18.16)
C_{max} (μmol/L)	3.86 (3.16:4.72)	7.51 (6.93:8.13)
$t_{1/2}$ (h)	1.05 (0.90:1.22)	1.41 (1.30:1.52)

Values represent the geometric mean (95% CI)

The pharmacodynamic data reveal similar results between the two formulations measured by MAO and %time gastric pH >4. AstraZeneca prespecified the upper bound of the 95% confidence interval for the ratio of 1.25 (MAO iv/MAO oral) to be the limit for claiming equivalence. The studies did not demonstrate equivalence based upon this prespecified criterion. The results of several studies where MAO was collected were somewhat unexpected based upon the pk data (for complete details see biopharmaceutics review). The table below displays a portion of this data. It is of interest to note that while the LS geometric means for BAO and MAO of the intravenous formulation are somewhat less active than the oral formulation, this slight difference may not represent a clinically meaningful difference. The data from the clinical trial of erosive esophagitis supports this possibility. Finally, data previously submitted regarding MAO in these types of patients treated with placebo reveals untreated levels of 28, which are substantially higher than any of the values obtained in these PD studies.

Mean (SD) BAO and MAO measured 22-24 hours post-dose following once daily oral and intravenous administration of esomeprazole for 10 days in GERD patients with or without a history of erosive esophagitis

Study	Dose in mg	intravenous administration method	BAO in mmol H/h		MAO in mmol H/h	
			Intravenous	Oral	Intravenous	Oral
1 (N=42)	20	3-minute injection	0.71 (1.24)	0.69 (1.24)	5.96 (5.41)	5.27 (5.39)
2 (N=44)	20	15-minute infusion	0.78 (1.38)	0.82 (1.34)	5.95 (4.00)	5.26 (4.12)
3 (N=50)	40	3-minute injection	0.36 (0.61)	0.31 (0.55)	5.06 (3.90)	4.41 (3.11)
4 (N=47)	40	15-minute infusion	0.36 (0.79)	0.22 (0.39)	4.74 (3.65)	3.52 (2.86)

In addition, review of the % time gastric acid > 4 does lends further support to the activity of this intravenous formulation (see below). In fact the % time is somewhat greater for the intravenous formulation.

Estimates of geometric means of the % time pH > 4 after I.V. and oral administration of 40 mg multiple doses of esomeprazole

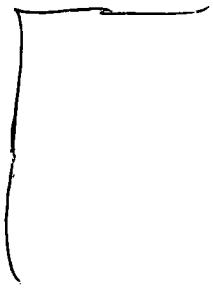
Study Day	Treatment	Estimate	95% CI	
			Lower	Upper
1	40 mg iv	42.1	35.2	49.1
	40 mg po	36.5	29.6	43.5
	40 mg iv - 40 mg po	5.6	1.2	10.0
5	40 mg iv	66.2	62.4	70.0
	40 mg po	63.6	59.7	67.4
	40 mg iv - 40 mg po	2.6	-0.5	5.8

The biopharmaceutics review found that while the IV and oral formulations were not strictly bioequivalent based upon the pharmacokinetic profile, the formulations were similar based upon the pharmacodynamic evaluations.

E. Clinical Efficacy/Safety:

Study SH-NEP-006 is a randomized, double blind, multiple placebo, parallel-group study design. In this study the patients were given Nexium IV 40-mg as a 3 minute injection (79 patients), 30 minute infusion (81 patients) or orally (86 patients). Each of these treatments had a matched placebo. Patients enrolled in this study were patients with endoscopically documented erosive esophagitis. Patients were excluded if they had taken a PPI for more than 10 days within 28 days prior to entry into the study. Each patient received this blinded therapy for 7 days then was switched to oral Nexium 40-mg for the next 3 weeks. Endoscopy was performed at the end of 4 weeks of therapy. Oral esomeprazole is labeled for a minimum treatment duration of 4 weeks for erosive esophagitis patients.

The sponsor performed this study primarily as a safety study and stated that the efficacy results were secondary endpoints.



Safety:
Review of the safety profile of short-term administration of intravenous Nexium (20-mg or 40-mg) did not reveal any new safety issues. Since concerns regarding blurry vision were documented in the past, ophthalmologic evaluation was undertaken in this safety study. Overall, the ophthalmic examinations did not indicate any safety concerns regarding visual acuity at long and reading distances, or in the visual field after treatment with iv esomeprazole 40 mg.

The results regarding potential injection/infusion site reactions are not specifically commented on by AstraZeneca. It is not included in the overall summary of safety. Further queries as to the frequency and nature of these types of adverse events is important for the practitioner. This type of information should be included in the label and discussed at future labeling negotiations.

In conclusion, the results of pk/pD testing and clinical, endoscopic response in erosive esophagitis generally support the indication for treating this entity with Nexium IV, for short-term treatment. Symptomatic GERD was not studied.

This will have to be considered in light of the PD data. This application is approvable pending resolution of CMC issues and negotiation of label.

III. PHASE 4 COMITTMENTS:

None have been identified at this time. The Division will revisit this issue in the next cycle.

IV. LABELING:

Final labeling will be negotiated in the next cycle of review. The major issue to be considered then is will the indication be restricted to oral-to-iv switch. In addition consideration as to how to represent the PK/PD data will be important.

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

/s/

Joyce Korvick
7/9/04 01:38:22 PM
MEDICAL OFFICER

06/16/04

CLINICAL REVIEW

Medical Officer Review of NDA 21-689
Nexium® (Esomeprazole) I.V. for Injection

Date Submitted: September 10, 2003
Date Completed: June 16, 2004

Applicant: AstraZeneca
1800 Concord Pike
Wilmington, DE 19803-8355

Proprietary name: Nexium I.V. ®

Drug Class: Proton pump inhibitor

Formulation: Intravenous solution of esomeprazole sodium

Route of Administration: Injection or Infusion

Material Reviewed: Results of studies assessing pharmacokinetic/pharmacodynamic effects and a study evaluating short-term safety

Medical Team Leader, GI Drugs: Hugo E. Gallo-Torres, MD, PhD, PNS

Medical Reviewer: Gail I. Moreschi, MD, MPH, FACP

Table of Contents

Clinical Review for NDA 21-689

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Based on the long established safety and efficacy of Nexium capsules and on the efficacy presented in this review of the pharmacokinetics and pharmacodynamics of Nexium I.V., this Medical Reviewer recommends that of Nexium I.V. is approvable for adults with GERD [redacted] It is indicated for short term use [redacted] Approval should only occur after the C.M.C. issues are resolved and when the label is agreed upon between the Sponsor and the Agency. Clinically at this time, Nexium I.V. is not recommended for de novo use or for maintenance (longer than 10 days). Since the 40 mg i.v. dose does not appear statistically quite as efficacious as the oral dose, no pharmacodynamic equivalence was established using the MAO data, this should be delineated in the label.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

None.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Nexium is currently approved as an orally administered drug for the treatment of the following indications: Treatment of acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, acute treatment of symptomatic gastroesophageal reflux disease (GERD), and combined with the appropriate antibacterial regimen for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

In this application the Sponsor is seeking approval for the short-term treatment (up to [redacted] 10 days) of [redacted] GERD [redacted] erosive esophagitis when [redacted]. In addition to the wording related to the sought indication, the Sponsor proposed [redacted]

However, data in support of these labeling revisions are inadequate.

Nexium is the third proton pump inhibitor for which approval of an intravenous formulation has been requested. Protonix (pantoprazole) and Prevacid (lanzoprazole) have intravenous formulations approved by the Agency.

Nexium is not currently approved for use in children.

B. Efficacy

The findings of the clinical pharmacology studies indicate that while higher peak plasma concentration (Cmax) and the plasma concentration-time curve (AUC) were observed with i.v. administration of esomeprazole relative to p.o. administration, the two drug products were nearly comparable in their PD (acid suppression) profiles. Moreover, administration of esomeprazole i.v. 20 or 40 mg over an infusion period of 3 to 30 min does not result in substantial PD differences relative to the Nexium capsule.

Administration of esomeprazole I.V. at doses of 20 and 40 mg daily (qd) results in markedly higher Cmax and AUC values relative to comparable p.o. doses. However, despite the large PK differences, no substantial PD differences are observed between i.v. and p.o. esomeprazole following multiple dose administration. In addition, administration of esomeprazole i.v. infusions ranging in duration from 3 to 30 min resulted in similar PD profiles

C. Safety

As a class of drugs, the proton pump inhibitors (PPIs) are perceived as safe. This includes esomeprazole.

The safety information from the design of the study attempts to stimulate what may happen in the clinic. The reviewer agrees with the Sponsor's conclusions as follows:

- The safety profiles of esomeprazole 40 mg given once daily for 1 week either as an injection or an infusion were similar to oral administration. The safety of oral esomeprazole has been well established. Neither the Adverse Event (AE) pattern nor any of the other safety assessments implied any safety concerns for i.v. administration of esomeprazole.
- The safety profiles of esomeprazole 40 mg given once daily for 1 week either as an injection, infusion or by oral administration and followed by 3 weeks of once daily oral administration of esomeprazole 40 mg were similar.

D. Dosing

Nexium I.V. is indicated for the short-term treatment (up to 10 days) of [redacted] (GERD) [redacted] in patients when therapy with Nexium Delayed-Release Capsules is not possible or appropriate. When oral therapy is possible or appropriate, intravenous therapy with Nexium I.V. should be discontinued and the therapy should be continued orally.

The recommended adult dose as an alternative to oral dosing, is either 20 or 40 mg esomeprazole given once daily by injection (no less than 3 minutes) or infusion (10 to 30 minutes).

E. Special Populations

Geriatric

No data from geriatric patients given the intravenous from are available. However, in oral studies, the AUC and Cmax values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric

The pharmacokinetics of esomeprazole, whether orally or intravenously administered, have not been studied in patients < 18 years of age.

Gender

In oral studies, the AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Similar differences were seen for intravenous administration of esomeprazole. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

In the labeling for oral esomeprazole no dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded. The same recommendations apply for intravenously administered esomeprazole.

Renal Insufficiency

The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of the administered esomeprazole dose is excreted unchanged in urine.

Clinical Review

I. Introduction and Background

The inability of patients to take medication orally can result from various causes such as major abdominal surgery, surgery in the ear-nose-throat region, major trauma, septic shock, or severe burns. Other conditions causing dysphagia, nausea, vomiting, or gastrointestinal bleeding may also interfere with oral drug intake.

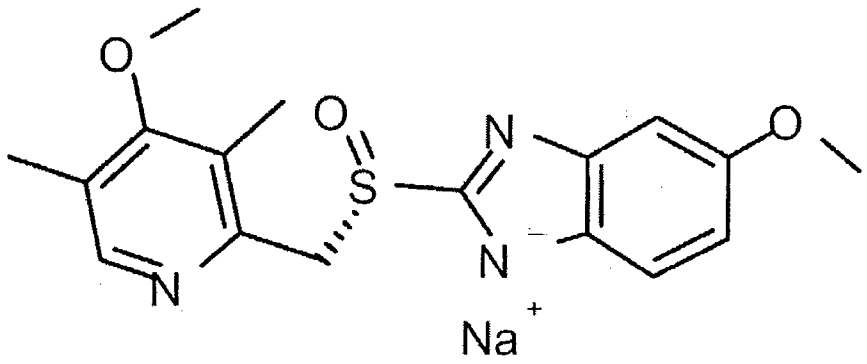
In this New Drug Application (NDA) the Sponsor is seeking approval for an intravenous (i.v.) form of esomeprazole for patients who are unable to take the oral formulation. Situations that prevent patients from oral intake are generally of short duration. Most patients are expected to be able to switch from i.v. back to oral esomeprazole within a week.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

In 2001 Nexium®, esomeprazole magnesium was approved in 20 or 40 mg delayed-release capsules for the following indications:

- Treatment of acute healing of erosive esophagitis
- Maintenance of healing of erosive esophagitis
- Acute treatment of symptomatic gastroesophageal reflux disease (GERD)
- Combined with appropriate antibacterial regimen for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

Esomeprazole is a proton pump inhibitor with the following structural formula.



Esomeprazole is the single (*S*)-enantiomer of the proton pump inhibitor (PPI) omeprazole. It acts through inhibition of the proton pumping enzyme H+/K+-ATPase located in the parietal cells of the gastric oxyntic mucosa, thus inhibiting hydrochloric acid secretion to the gastric lumen. The Sponsor has developed an i.v. formulation of esomeprazole to be used as an alternative to the oral formulation. The i.v. formulation is intended for short-term (up to 10 days) ——————————(GERD). patients ——— oral ——————is not possible or not appropriate. The proposed i.v. formulation contains an esomeprazole sodium salt, in place of the esomeprazole magnesium salt in the oral formulation. The sodium salt was selected because the water solubility of esomeprazole magnesium was insufficient for the i.v. formulation.

The Sponsor has submitted pharmacokinetic/pharmacodynamic studies (4 using MAO/BAO as the evaluation parameter and 2 using intragastric pH) and one safety study in support of Nexium I.V. This new drug application for injectable esomeprazole sodium is for the short-term treatment (up to 10 days) of patients ——————————(GERD) as an alternative to oral therapy in patients when therapy with Nexium Delayed-Release Capsules is not possible or appropriate. When oral therapy is possible or appropriate, intravenous therapy with Nexium I.V. should be discontinued and the therapy should be continued orally.

Nexium I.V. contains esomeprazole sodium 21.3 or 42.5 mg equivalent to esomeprazole 20 or 40 mg. Nexium I.V. is formulated 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.

The recommended doses as an alternative to oral medication for ——10 days

are either 20 or 40 mg esomeprazole given once daily by injection (no less than over 3 minutes) or by infusion (over 10 to 30 minutes).

The Sponsor proposes

Medical Officer comment:
The precise indication is for *The proposed* *is not within the realm of this new drug application as this drug is indicated only for* *10 days*

Preparation for use:

- Injection (20 or 40 mg)
  The freeze-dried powder should be reconstituted in 5.0 mL of 0.9% sodium chloride solution. Withdraw 5.0 mL of the reconstituted solution and administer as an injection over no less than 3 minutes.

- Infusion (20 or 40 mg)
  A solution for infusion is prepared by dissolving the content of one vial 50 mL 0.9% sodium chloride infusion over a period from 10 to 30 minutes.

Medical Officer comment:
The availability of both the injection and the infusion forms is an asset for medical practice.

Nexium I.V. should not be administered concomitantly with any other medications through the same intravenous site or tubing. The intravenous line should always be flushed both prior to and after administration of Nexium I.V.

The Sponsor is proposing that the i.v. formulation of esomeprazole be made available for use as an injection and an infusion, providing greater flexibility to the medical staff. In addition, some patients may require reduced fluid intake because of conditions such as cirrhosis with ascites, congestive heart failure, or renal impairment, and would benefit from the smaller volume (5 mL) used for injection, compared to the larger volume (50 mL) used for infusion.

B. State of Armamentarium for Indication(s)

The first i.v. proton pump inhibitor application to the Agency was for [redacted] in 1990 which was not approved for Chemistry, Manufacturing, and Controls (C.M.C.) reasons. Currently there are two i.v. proton-pump inhibitors available for short-term use for Gastroesophageal Reflux Disease (GERD) with erosive esophagitis in the U.S., pantoprazole and lansoprazole. They were approved as an alternative to oral therapy for short-term (7 to 10 days) in patients who are unable to continue to take their oral medication. This is the same indication being sought by this Sponsor. The efficacy of these i.v. forms has not been demonstrated in the initial treatment of patients with GERD.

Pantoprazole (Protonix®) was the first i.v. proton pump inhibitor to receive FDA approval. Originally, Protonix needed to be administered with a special filter. Recently the Sponsor received FDA approval for a small amount of EDTA to be added in lieu of the filter. Recently i.v. lansoprazole (Prevacid®) was approved.

Most European countries have approved the 40 mg dose of [redacted] for both injection and infusion. The [redacted] has been on the market for more than 14 years and according to the Sponsor, an estimated 145 million doses have been utilized as of September 2002.

Prior to the development of the proton pump inhibitors, the H_2-receptor antagonists were developed and continue to be available. Pepcid® (famotidine) Injection, supplied as a premixed solution or a concentrated solution for intravenous injection, is indicated in some hospitalized patients for the following conditions:

- Short-term treatment of active duodenal ulcer.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.
- Short-term treatment of active benign gastric ulcer.
- Short-term treatment of gastroesophageal reflux disease (GERD) and the short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy.
- Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).

Zantac® (ranitidine) Injection and Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

Parental Tagamet® (cimetidine hydrochloride) has been FDA approved for hospitalized patients with pathological hypersecretory conditions or intractable ulcers. However, the parental doses and regimen for patients with GERD have not been established.

[redacted] may be available in Japan for parental use. These data are not available at this time.

There are limited data comparing the i.v. proton pump inhibitors (oral or i.v.) to the H2-recetor antagonists (oral or i.v.). Therefore, conclusions regarding comparative efficacy cannot be made.

C. Important Milestones in Product Development

A background package was submitted to IND 53,733 on October 25, 2001, which included information on the proposed clinical and nonclinical programs regarding an intravenous formulation of Nexium. A Type B meeting was held on December 6, 2001, at the FDA with the Sponsor. The Sponsor confirmed that the indication to be pursued was an alternative to oral therapy in patients with gastroesophageal reflux disease (GERD) and not in patients with ulcer disease. The proposed indication was stated as follows:

- Nexium (esomeprazole sodium) for injection is indicated for short-term treatment (up to 10 days) of GERD as an alternative to oral therapy in patients when [redacted] therapy is not possible or appropriate.

After the indication, the following important explanation was proposed:

- When oral therapy is possible or appropriate, intravenous therapy with Nexium should be discontinued and the therapy should be continued orally.

Both the Sponsor and the Agency concurred that short-term treatment (up to 10 days) of GERD was the indication to be pursued. Therefore, it was mutually agreed that 90-day intravenous studies toxicity studies were not necessary.

However, the Agency did request that the submission also contain adequate data to describe how this intravenous formulation should be used in GERD patients who do not have a history of previous exposure to the oral formulation (i.e., in patients naive to Nexium). Also, separate studies were to be conducted for the 20 mg and 40 mg strengths.

D. Other Relevant Information

The international workshop in Genval, Belgium in 1999 issued guidelines on gastro-esophageal reflux disease (Dent, 2002). Treatment should begin in patients with GERD with the most effective therapy which is a proton pump inhibitor. Long term safety and tolerability for orally administered proton pump inhibitors has been well established and documented.

However, proton pump inhibitors, especially [redacted] have been implicated in adverse reactions of the eye. This is true for both oral and i.v. [redacted] preparations[1]. An ophthalmology consult[2] recommended and HFD-180 agreed that the [redacted] label should include blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy (AION), optic neuritis and double vision. To date this has not been included in the [redacted] label. However, in 1995 the Federal Institute for Drugs and Medical Devices in Germany cancelled the marketing of the two available i.v. [redacted] formulations. Today the i.v. [redacted] is available in the European Union but was not originally approved by the FDA for C.M.C. reasons.

It is interesting that the possible etiology for AION may be through proton pump inhibitors blocking a vascular H+K+ATPase and therefore possibly inducing vasoconstriction and ischemia in the end arteries such as the retinal artery. (McCabe &Young)

E. Important Issues with Pharmacologically Related Agents

The following information was obtained from the 2 PPI labels already approved for i.v. use:

- Protonix I.V. ® (pantoprazole sodium) is indicated for short-term treatment (7 to 10 days) of patients having gastroesophageal reflux disease (GERD) with a history of erosive esophagitis, as an alternative to oral therapy in patients who are unable to continue oral medication. The safety and efficacy of pantoprazole as an initial treatment of patients having GERD with a history of erosive esophagitis have not been demonstrated. This i.v. formulation is also indicated for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions. Treatment with i.v. pantoprazole should be discontinued as soon as the patient is able to resume treatment with oral medication. Because the data comparing proton pump inhibitors (oral or i.v.) or H2 receptor antagonists (oral or i.v.) are limited; no conclusions

[1] Dr. Robert Prizont, Medical Officer, DGCDP, CDER, FDA, [redacted]

[2] Dr. Wiley Chambers

regarding comparative efficacy or safety can be made. The recommended adult dose, as an alternative to continued oral therapy, is 40 mg pantoprazole given once daily by intravenous infusion for 7 to 10 days. Safety and efficacy as a treatment of patients having GERD with a history of erosive esophagitis for more than 10 days have not been demonstrated. Data on the safe and effective dosing for conditions other than those described, such as life-threatening upper gastrointestinal bleeds, are not available.

- Prevacid I.V.® (lansoprazole) is indicated for patients who are unable to take oral formulations for the short-term treatment (up to 7 days) of all grades of erosive esophagitis. Once the patient is able to take medications orally, therapy should be switched to an oral formulation. The safety and efficacy of i.v. lansoprazole as an initial treatment of erosive esophagitis has not been demonstrated. Lansoprazole i.v. admixtures should be administered intravenously using the in-line filter provided. The filter must be used to remove precipitates that may form when the reconstituted drug product is mixed with i.v. solutions.

Medical Officer comment:
Thus, the safety and efficacy of the two approved PPIs as an initial treatment of patients having GERD have not been demonstrated.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are CMC issues, related to prevention of drug precipitation in containers used for i.v. administration that need to be resolved. (See CMC review.) For preclinical pharmacology and toxicology issues see Dr.Yash M. Chopra's review.

III. Human Pharmacokinetics and Pharmacodynamics

A biopharmacological review by Dr. S. Al-Fayoumi has been completed. Since the current medical officer review is primarily based on PD data, this information is discussed under VI. Integrated Review of Efficacy.

IV. Description of Clinical Data and Sources

A. Overall Data

The submission consisted of four PK/PD studies (SH-NEP-0002, SH-NEP-0003, SH-NEP-0004, SH-NEP-0008); four pharmacodynamic studies comparing the oral and i.v. routes (SH-NEP-0011, SH-NEP-0012, D9615C00013, D9615C00014); a tolerability study comparing the 3 minute infusion to the 20 minute infusion (SH-NEP-0001); a PK study comparing 40 mg given at differing rates to 20 mg (SH-NEP-0009); and a clinical trial (SH-NEP-0006) designed to support safety.

B. Tables 1 to 3 Listing the Clinical Trials

Table 1 Clinical Trials

Type of study	Study Code	Study design	Primary objective	Dosage Regimen; Route of administration	Treatment Duration	Number of subjects randomised	Healthy subjects or Patients	Study status
PK	SH-NEP-0001	Randomised dose-escalation study. Double-blind and placebo-controlled at each dose step. Washout of at least 10 days.	To study the tolerability and safety of esomeprazole after intravenous administration.	Esomeprazole and corresponding Placebo: 40 mg iv 20-min infusion; 40 mg iv 3-min injection; 80 mg iv 20-min infusion; 100 mg iv 20-min infusion; 100 mg iv + 100 mg iv (12h apart) 20-min infusion.	Single dose	12	Healthy subjects	Complete
PK	SH-NEP-0009	Randomised, open, 3-period, 5-treatment, 6-sequence crossover with washout period of at least 6 days	To evaluate the PK after iv single-dose administration of esomeprazole 40 mg given over 10, 15, 20 or 30 minutes or esomeprazole 20 mg given over 3 minutes	40 mg iv 30-min infusion 40 mg iv 20-min infusion 40 mg iv 15-min infusion 40 mg iv 10-min infusion 20 mg iv 3-min injection	Single dose	24	Healthy subjects	Complete
PD	SH-NEP-0002	Randomised, double-blind (double-dummy), 2-way crossover with washout period of at least 13 days	To estimate any difference in effect on intragastric acidity on day 5 of once daily iv and oral administration of esomeprazole 40 mg by assessment of percentage of time with intragastric pH>4.	Esomeprazole 40 mg iv 30-min infusion Esomeprazole 40 mg oral capsule	5 days per arm	40	Healthy subjects	Complete

Table 2 Clinical Trials

Type of study	Study Code	Study design	Primary objective	Dosage Regimen; Route of administration	Treatment Duration	Number of subjects randomised	Healthy subjects or Patients	Study status
PD	SH-NEP-0004	Randomised, open, 2-way crossover with washout period of at least 13 days	To estimate the difference in effect on intragastric acidity on day 5 of once-daily iv and oral administration of esomeprazole 40 mg, by assessment of percentage of time with intragastric pH>4	Esomeprazole 40 mg iv 30-min infusion Esomeprazole 40 mg oral capsule	5 days per arm	12	Healthy subjects	Complete
PD	SH-NEP-0003	Randomised, double-blind (double-dummy), 2-way crossover with washout period of at least 13 days	To estimate any difference in effect on intragastric acidity on days 1 and 10 of once daily administration of 40 mg esomeprazole given intravenously over a period of 3 or 30 minutes, by assessment of percentage of time with intragastric pH>4	Esomeprazole 40 mg iv 30-min infusion Esomeprazole 40 mg iv 3-min injection	10 days per arm	42	Healthy subjects	Complete
PD	SH-NEP-0008	Randomised, open, 2-way crossover with washout period of at least 13 days	To estimate the difference in effect on intragastric acidity of day 5 of once-daily iv and oral esomeprazole 20 mg by assessment of percentage of time with intragastric pH>4	Esomeprazole 20 mg iv 30-min infusion Esomeprazole 20 mg oral capsule	5 days per arm	24	Healthy subjects	Complete

Table 3 Clinical Trials

Type of study	Study Code	Study design	Primary objective	Dosage Regimen; Route of administration	Treatment Duration	Number of subjects randomised	Healthy subjects or Patients	Study status
PD	SH-NEP-0011	Open label, randomised, two-way crossover	To compare the maximal acid output (MAO) during pentagastrin stimulation after 10 days of oral dosing with esomeprazole to the MAO after 10 days of iv dosing as a 15-minute infusion.	Esomeprazole 40 mg iv 15-minute infusion, oral	10 days per arm	53	Patients with GERD	Complete
PD	SH-NEP-0012	Open label, randomised, two-way crossover	To compare the maximal acid output (MAO) during pentagastrin stimulation after 10 days of oral dosing with esomeprazole to the MAO after 10 days of iv dosing as a 15-minute infusion	Esomeprazole 20 mg iv 15-minute infusion, oral	10 days per arm	50	Patients with GERD	Complete
PD	D9615C00013	Open label, randomised, two-way crossover	To compare the maximal acid output (MAO) during pentagastrin stimulation after 10 days of oral dosing with esomeprazole to the MAO after 10 days of iv dosing as a 3-minute injection	Esomeprazole 40 mg iv 3-minute injection, oral	10 days per arm	53	Patients with GERD	Complete
PD	D9615C00014	Open label, randomised, two-way crossover	To compare the maximal acid output (MAO) during pentagastrin stimulation after 10 days of oral dosing with esomeprazole to the MAO after 10 days of iv dosing as a 3-minute injection	Esomeprazole 20 mg iv 3-minute injection, oral	10 days per arm	50	Patients with GERD	Complete
Safety and efficacy	SH-NEP-0006	Double-blind, randomised, 1 week, followed by 3 week's open-label treatment with oral esomeprazole 40 mg once daily	To evaluate safety after 1 week's once daily treatment with iv injection, infusion and oral esomeprazole administration, respectively	Esomeprazole 40 mg iv 3-min injection, 30-min infusion, oral	1 week + 3 week	246	Patients with erosive reflux esophagitis	Complete

C. Postmarketing Experience

The Sponsor upon request from the Agency has submitted, May 12, 2004, a Post-Marketing Safety Update Report (PSUR). Nexium I.V. was first approved in Sweden and marketing began in September 2003. Since then, no case reports on the intravenous formulation have met the inclusion criteria for serious or unexpected adverse reactions in this country. Nexium is approved in Europe for the following indications: "Nexium is indicated for gastroesophageal reflux disease in patients with esophagitis and/or severe symptoms of reflux as an alternative to oral therapy when oral intake is not appropriate."

D. Literature Review

Relevant literature publications were consulted to support scientific principles involved in this review.

V. Clinical Review Methods

- The labor was divided so that the clinician incorporates the issues addressed in the biopharmaceutical review in her medical officer review. All disciplines of the reviews for the previously approved i.v. formulations (pantoprazole and lansoprazole) were carefully considered. The Sponsor's described methods to evaluate data quality and integrity are adequate. From the available information the studies were conducted in accordance with acceptable ethical standards.
- The information provided by the Sponsor reveals no financial improprieties.

VI. Integrated Review of Efficacy

This section of the review incorporates findings and conclusions in Dr. I. Al-Fayoumi's biopharmacological review. The Sponsor has submitted thirteen clinical pharmacology (PK/PD) studies assessing the comparability of esomeprazole P.O. and I.V. using 24-hr intragastric pH in healthy subjects and pentagastrin-stimulated gastric acid output in GERD patients.

A. Brief Statement of Conclusions

While higher peak plasma concentration (Cmax) and the plasma concentration-time curve (AUC) were observed with i.v. administration of esomeprazole relative

to oral (p.o.) administration, the two drug products are comparable on their PD (acid suppression) profiles. Moreover, administration of esomeprazole i.v. 20 or 40 mg over an infusion period of 3 to 30 min does not result in substantial PD differences relative to Nexium capsule.

The basal acid output (BAO) and the maximal acid output (MAO) after pentagastrin stimulation were measured in patients with GERD, with or without erosive esophagitis. This assessment was carried out at 22 to 24 hours post-dose following once daily administration of oral or intravenous administration of esomeprazole for 10 days. There were two studies each for both the 20 mg and the 40 mg doses.

B. General Approach to Review of the Efficacy of the Drug

Of 13 clinical pharmacology studies submitted by the Sponsor, three (SH-QBE-0006, SH-QBE-0045 & SHQBE-0061) were not addressed by the biopharmacological reviewer as they were originally submitted and reviewed under NDA 21-153 (Nexium Delayed Release Capsule).

C. Detailed Review of Trials by Indication

The sponsor conducted a total of 13 PK/PD studies to assess the comparability of esomeprazole p.o. and i.v.

Four studies (SH-NEP-0011, SH-NEP-0012, D9615C00013 & D9615C00014) evaluated the comparability of esomeprazole p.o. and i.v. (3 min injection and 30-min infusion) on pentagastrin-stimulated gastric acid output in GERD patients. These four studies employed identical study designs.

Male and female GERD patients, with or without a history of EE received esomeprazole (20 mg in studies SH-NEP-0012 & D9615C00014, and 40 mg in studies SH-NEP-0011 & D9615C00013) as either an oral capsule or an i.v. infusion (3 min injection in studies D9615C00013 & D9615C00014, and 15-min infusion in studies SH-NEP-0011 & SH-NEP-0012) qd for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22 to 24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for basal acid output (BAO) measurement. Thereafter, pentagastrin (6 μg/kg) Subcutaneously (sc) was administered and four 15-min samples were collected for maximal acid output (MAO) measurement.

Study SH-NEP-0003 evaluated the comparative PK/PD profiles of a 40 mg esomeprazole i.v. infusion administered over either a 3 min or 30 min period. Healthy male and female subjects (n = 41, age 28.5 ± 6.7 years, wt 73.2 ± 10.0 kg) received 40 mg esomeprazole as either a 3 min or 30 min i.v. infusion qd for

10 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole PK up to 24 hrs post-dose. Twenty-four-hr pH monitoring was conducted on days 1 and 5 of each treatment using a microelectrode attached to a Mark III Gastrograph data-logger.

Administration of a 40 mg dose of esomeprazole as a 3 min injection resulted in Cmax values that are higher by 117% and 93% on days 1 and 10, respectively relative to a 30-min infusion. The PD profiles however were similar following administration of 40 mg doses of esomeprazole as either a 3-min or 30-min infusion.

The findings of study SH-NEP-0003 suggest that i.v. infusions of esomeprazole given over a period as short as 3 min and as long as 30 min are likely to yield similar PD profiles.

Studies SH-NEP-0002 and SH-NEP-0008 evaluated the comparative PK and PD aspects of esomeprazole following p.o. and i.v. administration based on 24-hr intragastric pH in healthy subjects. Identical study designs were employed in the two studies. Healthy male and female subjects received esomeprazole (20 mg dose in study SH-NEP-0008 and 40 mg in study SH-NEP-0002) as a 30 min i.v. infusion or an oral capsule QD for 5 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole PK up to 24 hrs post-dose, while 24-hr intragastric pH monitoring was conducted on days 1 and 5 of each treatment using a [redacted] microelectrode.

The results of study SH-NEP-0008 (20 mg) indicate that administration of esomeprazole I.V. results in Cmax and AUC values on day 1 that are higher by 128% and 66%, respectively relative to the oral capsule, decreasing to 63% and 29%, respectively on day 5. The results of study SH-NEP-0002 (40mg) indicate that administration of esomeprazole i.v. resulted in Cmax and AUC values on day 1 that are higher by 324% and 82%, respectively relative to the oral capsule, decreasing to 146% and 31%, respectively on day 5. The results of the two studies indicated that the PD profiles following administration of similar doses of i.v. and oral esomeprazole are nearly comparable in healthy subjects.

Pharmacokinetics

Absorption

The pharmacokinetic profile of Nexium I.V. 20 mg and 40 mg was determined in 24 healthy volunteers for the 20 mg dose and 38 healthy volunteers for the 40 mg dose following once daily administration of 20 mg and 40 mg of Nexium I.V. by constant rate over 30 minutes for five days. The results are shown in the following table:

Table 4 Pharmacokinetic Parameters of Nexium Following I.V. Dosing for 5 days

Parameter	NEXIUM I.V. 20 mg	NEXIUM I.V. 40 mg
AUC (µmol*h/L)	5.11 (3.96:6.61)	16.21 (14.46:18.16)
C_{max} (µmol/L)	3.86 (3.16:4.72)	7.51 (6.93:8.13)
$t_{1/2}$ (h)	1.05 (0.90:1.22)	1.41 (1.30:1.52)

Values represent the geometric mean (95% CI)

Medical Officer comment:
Although AUC, C_{max}, and even $t_{1/2}$ are higher/longer with the 40 mg i.v. Nexium, these PK dissimilarities did not result in consistent PD differences.

Special Populations

Geriatric
In oral studies, the AUC and Cmax values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state.

Dosage adjustment based on age is not necessary.

Pediatric
The pharmacokinetics of esomeprazole, whether orally or intravenously administered, have not been studied in patients < 18 years of age.

Gender
In oral studies, the AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Similar differences were seen for intravenous administration of esomeprazole. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

In the labeling for oral esomeprazole, no dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded. The same recommendations apply for intravenously administered esomeprazole.

Renal Insufficiency
The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of the administered esomeprazole dose is excreted unchanged in urine.

Pharmacodynamics

Clinical Studies
Pentagastrin-Stimulated Gastric Acid Suppression in GERD
Four multicenter, open-label, two-period crossover studies were conducted to compare the pharmacodynamic efficacy of the intravenous formulation of esomeprazole (20 mg and 40 mg) to that of Nexium delayed-release capsules at corresponding doses in patients with symptoms of GERD, with or without erosive esophagitis. The patients (n=206, 18 to 72 years old; 112 female; 110 Caucasian, 50 Black, 10 Oriental, and 36 Other Race) were randomized to receive either 20 or 40 mg of intravenous or oral esomeprazole once daily for 10 days (Period 1), and then were switched in Period 2 to the other formulation for 10 days, matching their respective dose level from Period 1. The intravenous formulation was administered as a 3-minute injection in two of the studies, and as a 15-minute infusion in the other two. BAO and MAO were determined 22 to 24 hours post-dose on Period 1, Day 11; on Period 2, Day 3; and on Period 2, Day 11. BAO and MAO were estimated from 1-hour continuous collections of gastric contents prior to and following (respectively) subcutaneous injection of 6.0 μg/kg of pentagastrin.

After 10 days of once daily administration, the intravenous dosage forms of Nexium 20 mg and 40 mg were somewhat similar to the corresponding oral dosage forms in their ability to suppress BAO and MAO in the GERD patients (see table below). While the mean BAO and MAO values for the intravenous formulation were generally slightly higher than those for the oral formulation, both formulations showed marked reductions from published mean values for untreated GERD patients, which range from 1.7 to 4.0 mmol H+/h for BAO and from 18.7 to 34.9 mmol H+/h for MAO. Both formulations were associated with a pronounced acid-suppressive effect.

Table 5 Mean (SD) BAO and MAO measured 22 to 24 hours post-dose following once daily oral and intravenous administration of esomeprazole for 10 days in GERD patients with or without a history of erosive esophagitis

Study	Dose in mg	intravenous administration method	BAO in mmol H/h		MAO in mmol H/h	
			Intravenous	Oral	Intravenous	Oral
1 (N=42)	20	3-minute injection	0.71 (1.24)	0.69 (1.24)	5.96 (5.41)	5.27 (5.39)
2 (N=44)	20	15-minute infusion	0.78 (1.38)	0.82 (1.34)	5.95 (4.00)	5.26 (4.12)
3 (N=50)	40	3-minute injection	0.36 (0.61)	0.31 (0.55)	5.06 (3.90)	4.41 (3.11)
4 (N=47)	40	15-minute infusion	0.36 (0.79)	0.22 (0.39)	4.74 (3.65)	3.52 (2.86)

Medical Officer comment:
It appears from the above table that in patients with GERD, 40 mg of oral esomeprazole after 10 days of administration is somewhat more efficacious than 40 mg administered i.v. as demonstrated in the MAO values. The clinical significance of this finding is not known.

Antisecretory Activity

The effect of intravenous esomeprazole on intragastric pH was determined in two separate studies. In the first study, 20 mg of Nexium I.V. for Injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Twenty-two healthy subjects were included in the study. In the second study, 40 mg of Nexium I.V. for Injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Thirty-eight healthy were included in the study.

Data comparing Nexium I.V. to other proton pump inhibitors (oral or intravenous) or receptor antagonists (oral or intravenous) are limited, and therefore, are inadequate to support any conclusions regarding comparative clinical efficacy.

Individual Studies

SH-NEP-0001: "Tolerability and Pharmacokinetics of Esomeprazole after Intravenous Administration to Healthy Subjects"

Intravenous administration of esomeprazole as single 20-minute infusions of 40 mg to 100 mg, two consecutive 20-minute infusions of two 100 mg separated by 12 hours, and as a single 3-minute injection of 40 mg in healthy male subjects were well tolerated at all dose-levels.

Administration of escalating i.v. doses of esomeprazole resulted in greater-than-proportional increases in AUC and a decrease in total clearance (CL). These results point to non-linear PK at the studied dose range. Also, it appears that 100 mg doses were well tolerated.

SH-NEP-0002: "A double-Blind, randomized, two-way cross-over comparative study of 40 mg oral and intravenous esomeprazole regarding the effect on 24-hour intragastric pH and pharmacokinetics during once daily administration for 5 days in healthy male and female subjects".

The comparative PK/PD profiles of 40 mg esomeprazole administered as either i.v. solution or oral capsule were assessed.

Administration of esomeprazole i.v. resulted in Cmax and AUC values on day 1 that were higher by 128% and 66%, respectively relative to the oral capsule, decreasing to 63% and 29%, respectively on day 5. The absolute bioavailability of the oral capsule increased from 60% on day 1 to 78% on day 5. The PD data indicate that the PD profiles following administration of similar doses of I.V. and oral esomeprazole were comparable.

SH-NEP-0003: "A double-Blind, randomized, two-way cross-over comparative study of 40 mg esomeprazole given intravenously over a period of 3 or 30 minutes regarding the effect on 24-hour intragastric pH and pharmacokinetics during once daily administration for 10 days in healthy male and female subjects".

The comparative PK/PD profiles of 40 mg i.v. infusion administered over either a 3 min or 30 min period were assessed.

Administration of a 40 mg dose of esomeprazole as a 3 min injection resulted in Cmax values that were higher by 117% and 93% on days 1 and 10, respectively relative to a 30-min infusion.

The PD data indicate that the PD profiles are similar following administration of 40 mg doses of esomeprazole as either a 3-min or 30-min infusion.

SH-NEP-0004: "A pilot Study to compare 40 mg oral and intravenous esomeprazole regarding the effect on 24-hour intragastric pH and pharmacokinetics during once daily administration for 5 days in healthy male and female subjects".

The comparative PK/PD profiles of 40 mg esomeprazole i.v. infusion administered as either i.v. solution or oral capsule were assessed.

Administration of esomeprazole i.v. resulted in Cmax and AUC values on day 1 that were higher by 167% and 90%, respectively relative to the oral capsule, decreasing to 70% and 37%, respectively on day 5. The absolute bioavailability of the oral capsule increased from 53% on day 1 to 73% on day 5.

The PD data indicate that the PD profiles following administration of similar doses of i.v. and oral esomeprazole were similar.

Medical Officer comment:
On day 5 no substantial differences were observed in PK values between i.v. and oral dosing.

SH-NEP-0008: "A open, randomized, two-way cross-over comparative study of 20 mg oral and intravenous esomeprazole regarding the effect on 24-hour intragastric pH and pharmacokinetics during once daily administration for 5 days in healthy male and female subjects".

The comparative PK/PD profiles of 20 mg esomeprazole administered as either 30 min. i.v. infusion or oral capsule were assessed.

The results indicate that administration of esomeprazole i.v. results in Cmax and AUC values on day 1 that are higher by 324% and 82%, respectively relative to the oral capsule, decreasing to 146% and 31%, respectively on day 5. The absolute bioavailability of the oral capsule increased from 55% on day 1 to 77% on day 5.

The PD data indicated that the PD profiles following administration of similar doses of i.v. and oral esomeprazole were comparable.

SH-NEP-0009: "A single-center, open, randomized, three-period, 5-treatment, 6-sequence cross-over study of the pharmacokinetics after intravenous single dose administration of 40 mg esomeprazole given at different infusion rates or 20 mg esomeprazole given as an injection in male and female subjects".

The PK profiles following single dose administration of 40 mg esomeprazole i.v. given over 10, 15, 20 or 30 min or 20 mg esomeprazole i.v. given over 3 min. were assessed.

Administration of 40 mg single doses of esomeprazole as i.v. infusions of varying lengths resulted in similar AUC values. However, Cmax decreased with the length of infusion.

SH-NEP-0011: "An open, randomized, two-way crossover study comparing the effect of 40 mg esomeprazole administered orally and intravenously as a 15-minute infusion on basal and pentagastrin-stimulated acid output in patients with symptoms of GERD".

The MAO during pentagastrin stimulation after 10 days of oral dosing with esomeprazole was compared to the MAO after 10 days of i.v. dosing as a 15-minute infusion at a daily dose of 40 mg.

Medical Officer comment:
As stated above, it appears from the BAO and MAO data in Table 5 shown above that in patients with GERD, 40 mg i.v. as demonstrated in the MAO values is not quite as efficacious as 40 mg of oral esomeprazole after 10 days of administration.

SH-NEP-0012: "An open, randomized, two-way crossover study comparing the effect of 20 mg esomeprazole administered orally and intravenously as a 15-minute infusion on basal and pentagastrin-stimulated acid output in patients with symptoms of GERD".

The MAO during pentagastrin stimulation after 10 days of oral dosing with esomeprazole was compared to the MAO after 10 days of i.v. dosing as a 15-minute infusion at a daily dose of 20 mg.

Medical Officer comment:
Administration of 20 mg esomeprazole either as a 15-min i.v. infusion or p.o. resulted in fairly comparable MAO and BAO values.

Study D9615C00013: "An open, randomized, two-way crossover study comparing the effect of 40 mg of esomeprazole administered orally and intravenously as a 3-minute injection on basal and pentagastrin-stimulated acid output in patients with symptoms of GERD".

The MAO during pentagastrin stimulation after 10 days of oral dosing with esomeprazole was compared to the MAO after 10 days of i.v. dosing as a 3-minute infusion at a daily dose of 40 mg.

Medical Officer comment:
Again, it appears from Table 5 shown above with the BAO and MAO data that in patients with GERD, 40 mg i.v. is not as efficacious as 40 mg of oral esomeprazole after 10 days of administration as demonstrated in the MAO values.

Study D9615C00014: "An open, randomized, two-way crossover study comparing the effect of 20 mg of esomeprazole administered orally and intravenously as a 3-minute injection on basal and pentagastrin-stimulated acid output in patients with symptoms of GERD".

The MAO during pentagastrin stimulation after 10 days of oral dosing with esomeprazole was compared to the MAO after 10 days of i.v. dosing as a 3-minute infusion at a daily dose of 20 mg.

Medical Officer comment:
Administration of 20 mg esomeprazole either as a 15-min i.v. infusion or p.o. resulted in fairly comparable MAO and BAO values.

D. Efficacy Conclusions

From the view point of the Office of Clinical Pharmacology and Biopharmaceutics, the proposed new drug submission regarding Nexium I.V. is acceptable provided that a satisfactory agreement is reached between the Agency and the Sponsor with respect to the proposed language in the package insert.

Medical Officer comments:
The efficacy of oral esomeprazole has been well established. With the above studies it is apparent that the 40 mg i.v. dosing is, pharmacodynamically, somewhat less effective than the oral formulation. This conclusion is based on the MAO evaluations which are the most meaningful and relevant.

This NDA submission includes duplicate efficacy studies which appear to document reproducible data.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The Sponsor has submitted one clinical study, SH-NEP-006, in order to address safety issues. According to the Sponsor regarding the safety of Nexium I.V.:

- The safety profiles of esomeprazole 40 mg given once daily for 1 week either as an injection or an infusion were similar to oral administration. The safety of oral esomeprazole has been well established. Neither the Adverse Event (AE) pattern nor any of the other safety assessments implied any safety concerns for i.v. administration of esomeprazole.
- The safety profiles of esomeprazole 40 mg given once daily for 1 week either as an injection, infusion or by oral administration and followed by 3 weeks of once daily oral administration of esomeprazole 40 mg were similar.

B. Description of Patient Exposure

In order to provide safely data the Sponsor has completed one clinical trial, SH-NEP-006, in subjects with erosive esophagitis. This was a double-blind, randomized, multicenter study to evaluate the safety of esomeprazole 40 mg given intravenously or orally once daily (qd) for 1 week, followed by 3 weeks' open oral treatment with esomeprazole 40 mg qd. The study was conducted in South Africa.

The primary objective of the study was:

- To evaluate safety after 1 week's treatment with intravenous (i.v.) injection, i.v. infusion and oral esomeprazole administration, respectively. The evaluation was done by assessment of adverse events (AEs), physical examination, laboratory measurements, blood pressure (BP), pulse, electrocardiogram (ECG) and ophthalmic examination (visual acuity test and visual field).

The secondary objectives of the study were:

- To evaluate safety after 4 weeks' treatment with esomeprazole:
  - 1 week's i.v. injection followed by 3 weeks' oral administration of esomeprazole
  - 1 week's i.v. infusion followed by 3 weeks' oral administration of esomeprazole
  - 4 weeks' oral esomeprazole intake.

The evaluation was done by assessment of AEs, physical examination, laboratory measurements, BP, pulse and ophthalmic examination (visual acuity test and visual field).

Medical Officer comment:
Although of some interest, results of these secondary safety evaluations are not critical to the evaluation of safety of the newly proposed 40 mg i.v. form. Therefore the results of the secondary evaluations are only briefly summarized.

C. Methods and Specific Findings of Safety Review

Double-blind treatment period:
Esomeprazole powder for solution for injection, 40 mg/placebo, dissolved in 5.2 ml of sodium chloride solution (9 mg/mL), was given qd as a 3-minute injection for 1 week.
or
Esomeprazole powder for solution for infusion, 40 mg/placebo, dissolved in 5.2 ml of sodium chloride solution (9 mg/mL) and diluted to a final volume of 100 mL, which was administered intravenously over 30 (±10) minutes qd for 1 week.

Duration of treatment
During the double-blind period, esomeprazole 40 mg was given qd for 1 week either as i.v. injection (3 minutes), i.v. infusion over 30 (±10) minutes or orally.

Main Variables
Safety

- Primary variables: Frequency and nature of AEs, physical examination, laboratory measurements, BP and pulse, ECG and ophthalmic examination (visual acuity and visual field) after 1 week's treatment.

- Secondary variables: Frequency and nature of AEs, physical examination, laboratory measurements, BP, pulse and ophthalmic examination (visual acuity and visual field) after 4 weeks' treatment.

Statistical methods
All safety variables data were presented descriptively.

Subject population
A total of 246 subjects were randomized. All 246 were included in the Intention to Treat (ITT)/Safety population.

The subject population and disposition are given in the following table.

Table 6 Study SH-NEP-006, Subject population and disposition

		Esomeprazole 40 mg once daily[a]			
		3-min injection	30-min infusion	oral	Total
Population					
N randomised		79	81	86	246
Demographic characteristics					
Gender (n and % of subjects)	Male	35 (44.3%)	34 (42.0%)	47 (54.7%)	116 (47.2%)
	Female	44 (55.7%)	47 (58.0%)	39 (45.3%)	130 (52.8%)
Age (years)	Mean (SD)	47.7 (12.1)	43.8 (12.2)	45.7 (12.9)	45.7 (12.4)
	Range	22 to 70	18 to 71	19 to 79	18 to 79
Race (n and % of subjects)	Caucasian	41 (51.9%)	38 (46.9%)	47 (54.7%)	126 (51.2%)
	Black	7 (8.9%)	7 (8.6%)	9 (10.5%)	23 (9.3%)
	Oriental	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	Other	30 (38.0%)	36 (44.4%)	30 (34.9%)	96 (39.0%)[b]
Disposition					
N (%) of subjects who	completed	78 (98.7%)	81 (100%)	83 (96.5%)	242 (98.4%)
	discontinued	1 (1.3%)	0 (0.0%)	3 (3.5%)	4 (1.6%)
N analysed for ITT/Safety		79	81	86	246
N analysed for PP		74	75	75	224

[a] Refers to treatment during the 1-week period of randomised treatment (all three treatments were followed by 3 weeks of open treatment with oral esomeprazole 40 mg).

[b] Other comprised of mixed race (33%), Malay (1%) and coloured (5%).

Medical Officer comments:
Very few Black patients and no Asians or Hispanic patients were included. Therefore, this study does not match the population for which it is intended in the United States.

The proportion of subjects who had important protocol deviations leading to exclusion from the per protocol analysis was generally similar across treatment groups. Overall, the treatment groups were comparable in terms of demographic characteristics and baseline values.

Safety results

A summary of adverse events in each category during 1 week's treatment is given in the following table.

Table 7 Number of subjects who had an adverse event and total number of adverse events in any category during 1 week's treatment (safety population)

Category of adverse events	Esomeprazole 40 mg once daily		
	3-min injection	30-min infusion	oral
	n=79	n=81	n=86
	N of subjects who had an adverse event in each category[a]		
Any adverse events	29	28	29
Serious adverse events	0	0	1
Discontinuations of study treatment due to adverse events	0	0	1
Other significant adverse event	0	0	0
Severe adverse events	1	1	4
	Total number of adverse events		
Any adverse events[b]	44	51	52
Serious adverse events[b]	0	0	1
Discontinuations adverse events[b]	0	0	2
Other significant adverse event[b]	0	0	0
Severe adverse events	1	1	5

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

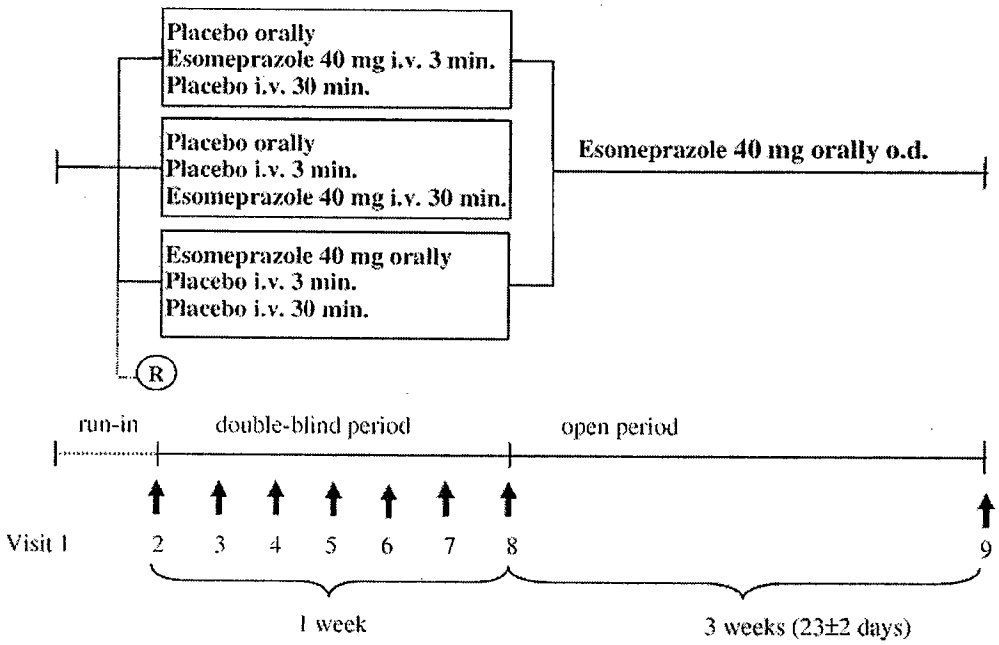
[b] Events are counted by preferred term, ie, for subjects with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

In this safety study, i.v. treatment with esomeprazole 40 mg administrated as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole 40 mg in subjects with erosive reflux esophagitis. The AE patterns were similar among the 3 treatment groups. Headache and flatulence were the most commonly reported AEs. The safety evaluation of serious adverse events (SAEs), discontinuations due to AEs or the other safety parameters, including ophthalmic examination have not raised any safety concerns. No clinically relevant trends in the laboratory values were observed and

no clinically relevant changes in vital signs, ECG and physical examination were found. When evaluating the individual safety data and the grouped safety data separately, no safety concerns were raised.

The study comprised 3 periods and started with a run-in period of 3 days, followed by a double-blind (by multiple-placebo technique), randomized treatment period of 1 week with 3 parallel arms and an open treatment period of 3 weeks.

Figure 1 Study design



Medical Officer comments:
The design of this study is quite limited as all patients received esomeprazole orally for 3 weeks only after receiving the study medication

Also, all patients were required to be able to take oral medicines, yet the indication is for individuals when they cannot take oral medications. This study design is not very helpful.

The following table summarizes the study procedures and assessments conducted at each time point.

Table 8 Study plan Best Available Copy

Visits Study days	Pre-study assessment[1]	1 Day 1	2 Day 4	3-7 Day 5-9	8 Day 10	9 Day 33(±2)
Endoscopy	X					X
Subject information and written informed consent		X				
Inclusion/exclusion criteria		X	X			
Randomisation			X[2]			
Medical/surgical history		X				
Physical examination		X			X	X
Weight and height[3]		X			X	X
Blood pressure/pulse		X			X	X
ECG[4]		X	X		X	
Laboratory measurements[5]		X			X	X
Ophthalmic examination[6]		X			X	X
Study drug administration			X	X	X	
Adverse events			(X)	X	X	X
Open treatment dispense					X	
Open treatment compliance						X

1 An endoscopically verified erosive reflux esophagitis, using the LA classification (A-D), done 0-11 days prior to enrolment (Visit 1), was mandatory for inclusion in the study.

2 For women of childbearing potential, a pregnancy test with a negative result was done before randomisation.

3 Height was measured only at Visit 1.

4 ECG was done at Visit 1 (as baseline) and at Visits 2 and 8 directly after the 3-minute iv injection and was followed by the 30-minute iv infusion.

5 At Visit 1, laboratory measurements were done as baseline measurements. For women of childbearing potential a pregnancy test (serum HCG) was also taken. At Visits 8 and 9 the laboratory measurements were made after administration of the study drug.

6 Ophthalmic examination comprised a visual acuity test and visual field test.

Study design, doses and control groups

This study had a parallel group design, allowing the evaluation of safety of 3 different modes of drug administration of esomeprazole 40 mg in subjects with erosive reflux esophagitis. According to the Sponsor the double-blind design ensured an unbiased documentation of the safety of i.v. injection, i.v. infusion and oral administration of esomeprazole. Both i.v. injection and i.v. infusion were studied, as i.v. treatment practices differ among countries.

Medical Officer comment:
It is convenient for medical practice to have both i.v. injection and i.v. infusion available.

Only subjects who were able to take oral medication were included since the comparator was esomeprazole by oral administration. The study also was blinded to avoid bias. To enable treatment with oral esomeprazole in the open, 3-week treatment period after the initial double-blind week with i.v. (injection or infusion) or oral esomeprazole, subjects eligible for the study had to be able to take oral medication and therefore they could not have any conditions preventing oral drug intake.

Medical Officer comment:
As stated above one of the flaws in the design of this study is the fact that all the patients needed to be able to take oral medications when indeed this i.v. form of the drug has been designed for individuals who are not able to take oral medications.

A treatment period of 7 consecutive days of i.v. administration was considered adequate for a comparison of the safety of i.v. versus oral administration of esomeprazole. Clinical situations preventing subjects from oral intake usually are of short duration. The inclusion and exclusion criteria were chosen to find a representative population with erosive reflux esophagitis. Esomeprazole 40 mg is the highest approved dose for treatment of GERD and was therefore chosen since studying safety was the primary objective of this study.

Medical Officer comment:
It may be that, in analogy to the oral formulation, a lower dose, i.e. 20 mg., would be adequate for intravenous administration.

Selection of study population
The target population for treatment with i.v. esomeprazole is patients with erosive GERD who for various reasons are unable to take PPI orally during a limited time period.

Medical Officer comment:
Although the Sponsor describes the eventual target population for i.v. esomeprazole, this study did not evaluate the effect of the drug in the target population.

Inclusion criteria
For inclusion, subjects had to fulfill the following criteria: erosive reflux esophagitis documented by endoscopy, be age 18 years or older, able to swallow,

capable of providing written informed consent, able to comply, and women of child-bearing potential must have a negative pregnancy test.

Medical Officer comment:
One of the inclusion criteria, as mentioned above, are the patients for whom this medication is designed for, i.e. able to swallow. As pointed out above, this is not the target population for i.v. esomeprazole.

Exclusion criteria
Any of the following were regarded as a criterion for exclusion from the study: any bleeding disorder or signs of gastrointestinal (GI) bleeding by endoscopy; "alarm symptoms" such as unintentional weight loss, hematemesis, melena, jaundice; Zollinger-Ellison syndrome, primary esophageal motility disorder(s), upper gastrointestinal malignancy, or any other significant medical problems. Also patients taking continuously the following medications were excluded:warfarin, diazepam, diphenylhydantoins, mephenytoin, anticholinergics for treatment of GI disorders, cisapride, non-steroidal anti-inflammatory drugs on a daily basis, acetylsalicylic acid except for cardiovascular prophylaxis. Patients were excluded for sensitivity to PPIs, lactation or pregnancy, any investigational compound within 28 days prior to the study, alcohol and/or drug abuse, or using a PPI for more than 10 days within 28 days prior to entry into to the study.

Antacids and H_2-receptor antagonists were allowed.

Medical Officer comment:
An interesting variable to include in this study would have been the kind and amount of antacids and H2-receptor antagonists used by the individual subjects.

Criteria for discontinuation
Subjects could be withdrawn from study treatment and assessments at any time at the discretion of the investigator(s).

Double-blind treatment period:
The study drugs were administered to the subjects at the investigational site by the study personnel.

Medical Officer comment:
The study design to directly administer the drugs to the patients at the study site during the first week which was blinded is an asset for this study.

Open treatment period:
Subject compliance with study drug dosing was determined by pill count. At Visit 8, the subject was dispensed the study medication. The subject was instructed to

take one capsule with a glass of water qd and to return the bottle and all unused medication at the subsequent visit.

The following table summarizes the safety variables assessed in this study and shows how they relate to the study objectives.

Table 9 Primary safety objectives and variables relating to each objective

Objective	Summary variables for analysis	Statistical analysis or presentation of data
Primary To evaluate safety after 1 week's treatment with iv injection, iv infusion and oral administration, respectively. Data captured after 1 week's treatment (Visit 8)	Frequency of - all AE - SAE - AE leading to withdrawal of study drug - AE with severe intensity Physical examination Laboratory measurements BP and pulse ECG Ophthalmic examination For all subjects eligible for safety evaluation	No formal statistical comparison Descriptive statistics

Medical Officer comment:
This design of including ECGs close to the time of medication is an asset to the study design as chest pain has been associated with proton pump inhibitors. Also patients with heart burn and angina can present with similar clinical histories.

Ophthalmic examination
An ophthalmic examination (visual acuity and visual field test) was done at Visit 1 (baseline) and again at visits 8 and 9. The following ophthalmic evaluations were included at each of these visits:

- **Sight examination - visual acuity/long distance:**

The subject was seated on a chair at a standardized distance of 20 ft (6 meters) from a letter chart of the Snellen type, and visual acuity was examined with the best possible correction, i.e., if the subject used corrective eyeglasses for nearsightedness, he/she had them on while being examined. The left eye was covered when examining the right eye, and vice versa. The scale on the letter chart was; 0.1, 0.2, 0.28, 0.4, 0.5, 0.6, 0.8, 1.00, 1.20, 1.54, 2.0.

- **Sight examination - visual acuity/reading distance:**

The subject was given a pre-printed handheld card of the Jaeger type (using reading glasses on if these were normally worn), and the light was turned on. The left eye was covered first and then the right. The scale on the handheld card was: J01, J02, J03, J04, J05, J06, J07, J08, J09.

- **Visual field - confrontation test:**

The examiner sat in front of the subject at a distance of 3 ft (1 meter). With one eye covered, the subject fixed his/hers eyes on the examiner's nose and vice versa. The examiner held up both palms at half the distance pointing outwards at a distance of approximately 8 inches (20 cm) from each other. The hands were shown to the subjects just above his/hers head, at eye level and at chest level. The subject was asked whether he/she could see them clearly.

Medical Officer comment:
The inclusion of these ophthalmic evaluations is important safety variables.

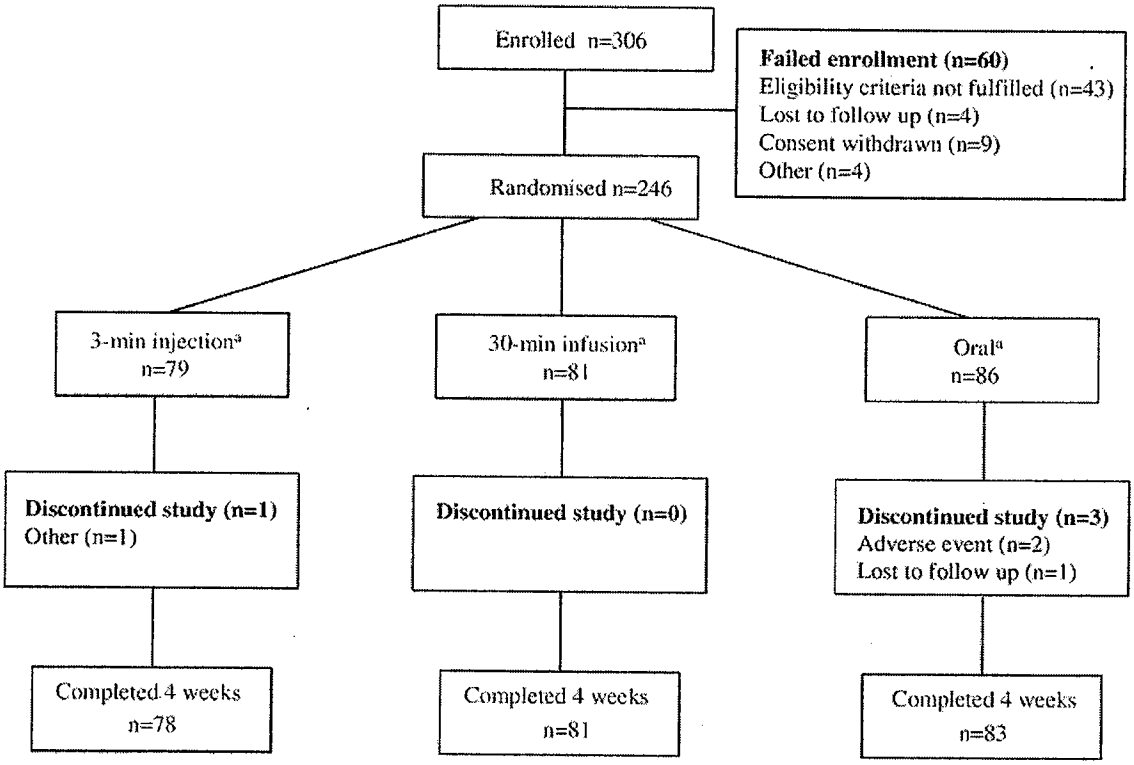
Primary evaluation:
No formal statistical analysis was done for the safety variables.
The primary endpoint was evaluated using data collected after 1 week's treatment.
Adverse event data were presented descriptively.

Determination of sample size
A sample size of 225 completed subjects (75 randomized subjects per group) was considered relevant to further document safety of the intravenous formulation. To allow for a dropout rate of approximately 10% during the study, it was planned to randomize 250 subjects.

Summary of the disposition of subjects
In total, 306 subjects were enrolled at 10 study sites and 246 were randomized to study treatment. One subject was enrolled twice in the study and received enrolment numbers E003010 and E003020. The subject was then randomized to study treatment (subject number 1107). The ITT/Safety and PP populations included 246 and 224 subjects, respectively. The first subject was enrolled on 28 February 2002 and the last subject completed the study on 28 June 2002.

The proportions of subjects who had important protocol deviations leading to exclusion from the per protocol analysis were generally similar across treatment groups. Overall, the treatment groups were comparable for demographic characteristics and baseline values.

Figure 2 Subject dispositions (completion or discontinuation)



[a]Refers to treatment during the 1-week period of randomized treatment (all three treatments were followed by 3 weeks of open treatment with oral esomeprazole 40 mg).

Table 10 Summary of subjects excluded from the ITT/Safety and PP populations

Population/reason for exclusion	Esomeprazole 40 mg once daily			Total
	3-min injection	30-min infusion	oral	
ITT and safety population	79	81	86	246
PP population	74	75	75	224
Excluded from PP population	5	6	11	22
Insufficient intake of study drug	4	3	9	16
Disallowed medication	1	3	2	6

Table 11 Treatment compliance between Visit 2 and Visit 9, ITT/Safety population

Compliance	Esomeprazole 40 mg once daily		
	3-min injection	30-min infusion	oral
	n=79	n=81	n=86
<75%	0(0.0%)	0(0.0%)	1(1.2%)
75%-<90%	1(1.3%)	1(1.2%)	2(2.3%)
≥90%	74(93.7%)	75(92.6%)	77(89.5%)
Unknown	4(5.1%)	5(6.2%)	6(7.0%)

Conclusions on study subjects

The demographic and baseline characteristics were comparable between treatment groups and are well in accordance with data observed in earlier studies on treatment of erosive reflux esophagitis. In conclusion, the subject population studied is representative of the general population with erosive reflux esophagitis.

Summary of safety

Among the 246 subjects, no deaths were reported, 4 subjects reported SAEs (all of which were unrelated to study treatment), and 3 subjects discontinued study treatment due to an AE. All 7 subjects were randomized to the oral treatment group.

During 1 week's treatment 1 subject reported 1 SAE and 1 subject discontinued study drug due to AE (the subject had 2 simultaneous AEs that both led to discontinuation). The other SAEs and AEs leading to discontinuation of a subject from the study were reported during the open treatment period.

Extent of exposure

A total of 246 subjects were randomized in the study, 116 males and 130 females. All of the randomized subjects received at least 1 dose of esomeprazole and/or placebo and had postdose information available. All randomized subjects were therefore included in the safety population. The subjects received esomeprazole 40 mg given blinded either intravenously as a 3-minute injection, a 30-minute infusion or orally for 1 week. Oral esomeprazole 40 mg was then given on an open basis to all subjects for 3 weeks.

The duration of treatment during week 1 is shown in the following table.

Table 12 Duration of treatment during week 1, safety population

	Esomeprazole 40 mg		
	3-min injection n=79	30-min infusion n=81	oral n=86
Duration of treatment (days)			
Mean (SD)	6.9 (0.6)	6.9 (0.3)	6.9 (0.6)
Range	2 - 7	6 - 7	1 - 7
Total	547	561	596

The duration of treatment in the safety population was similar in all three treatment groups during week 1.

Adverse events

A summary of adverse events in each category during 1 week's treatment is given in the following table and during 4 weeks' treatment in the subsequent table.

Table 13 Number of subjects who had an adverse event and total number of adverse events in any category during 1 week's treatment (safety population)

Category of adverse events	Esomeprazole 40 mg once daily		
	3-min injection	30-min infusion	oral
	n=79	n=81	n=86
	N of subjects who had an adverse event in each category[a]		
Any adverse events	29	28	29
Serious adverse events	0	0	1
Discontinuations of study treatment due to adverse events	0	0	1
Other significant adverse event	0	0	0
Severe adverse events	1	1	4
	Total number of adverse events		
Any adverse events[b]	44	51	52
Serious adverse events[b]	0	0	1
Discontinuations adverse events[b]	0	0	2
Other significant adverse event[b]	0	0	0
Severe adverse events	1	1	5

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Events are counted by preferred term, ie. only 1 occurrence of an event is counted for subjects with multiple events falling under the same preferred term.

The number of subjects with any AE and the total numbers of AEs were similar in all three treatment groups. One subject had an SAE (myocardial infarction) during week 1 in the oral treatment group.

During the four weeks of the study, essentially equal adverse events occurred in each of the study groups. Four SAEs were reported during the study. In addition to the myocardial infarction during the first week, three SAEs were reported during the following 3 weeks: chest pain, cerebrovascular disorder and dysentery.

Most common adverse events
The most common adverse events, as summarized in the following table.

Table 14 Number of subjects with the most commonly reported adverse events during 1 week's treatment, presented by preferred term and sorted by descending order of frequency as summarized over all treatment groups (safety population)

Preferred term[a]	Esomeprazole 40 mg once daily		
	3-minute injection (n=79)	30-minute infusion (n=81)	oral (n=86)
	n	n	n
Headache	9	9	13
Flatulence	5	3	5
Nausea	1	7	5
Diarrhoea	3	4	5
Abdominal pain	2	5	3
Constipation	4	2	2
Dizziness/vertigo	4	2	1
Mouth dry	2	1	2
Infection viral	2	1	1
Pharynx disorder	2	0	1
Pruritus	1	1	1
Vomiting	0	1	2
Accommodation abnormal	1	1	0
Eructation	0	0	2
Paraesthesia	0	1	1
Pharyngitis	1	1	0
Sinusitis	0	2	0
Sleep disorder	0	1	1
Vision abnormal	2	0	0

[a] Events are counted by preferred term, ie. only 1 occurrence of the event is counted for subjects with multiple events falling under the same preferred term.

This table uses a cut-off of 2 subjects.

The most common AEs during week 1 were: headache, flatulence, nausea, diarrhea, abdominal pain, constipation, dizziness/vertigo and dry mouth. No clinically relevant difference was observed among the treatment groups in the most commonly reported AEs. There was one report of injection site reaction (itching) which was of mild intensity and resolved within 3 hours.

During the entire four weeks of the study the most common AEs during the study were: headache, flatulence, nausea, abdominal pain, constipation, diarrhea, infection viral and dizziness/vertigo. No clinically relevant difference in the most commonly reported AEs was observed between the treatment groups.

Medical Officer comment:
Some of the occurring side effects are similar to the symptoms for which the patients take esomeprazole.

Discussion of adverse events
During week 1, the number of subjects who reported AEs, as well as the number of AEs reported, were similar in all treatment groups. The most common AEs were representative to what is known from oral PPI treatment. A large proportion of the AEs were reported during the first week. This is most likely a result of the more frequent assessments of AEs during the first 7 days in the study, when the subjects visited the study site once daily.

When comparing the treatment groups during 4 weeks' treatment relatively fewer AEs were reported in the groups treated with injection or infusion during week 1 compared to the oral treatment group. All SAEs reported emanated from the group treated with oral esomeprazole the first week. Both observations are probably a chance finding.

There were no indications of that the higher peak plasma concentration following intravenous administration compared to oral administration changed the pattern of AEs. No safety concerns were raised concerning the AEs reported during this study. Esomeprazole 40 mg qd i.v. for 7 days, as an injection or as an infusion, showed a similar AE-pattern as oral treatment with esomeprazole 40 mg qd for 7 days.

No deaths were reported in this study.

All subjects who had a serious adverse event other than death are listed in the following table.

Table 15 Listing of all subjects who had a serious adverse event other than death during 4 weeks' treatment (safety population)

Centre Subject	Treatment group	Sex Age	Treatment period	Dose of inv.drug	Treat. dur	Preferred term (Verbatim term)	Onset day	Duration of AE	Serious	Recovered	Causality Intensity	Action taken
3 1180	Oral	F 57	Esomeprazole capsule (open)	40 mg od	26	Dysentery (Dysentry, dysentery)	4	4	Yes	Yes	Not related Severe	Temporarily stopped
4 1159	Oral	M 41	Esomeprazole capsule (open)	40 mg od	95*	Chest pain (Atypical chest pain)	10	48	Yes	Yes	Not related Severe	None
4 2047	Oral	M 53	Esomeprazole capsule (open)	40 mg od	23	Cerebrovascular disorder (Cerebro infarction, cerebral infarction)	8	16	Yes	Yes	Not related Severe	None
9 2017	Oral	M 32	Esomeprazole capsule (double-blind)	40 mg od	7	Myocardial infarction (Myocardial infarct)	7	1	Yes	Yes	Not related Severe	Temporarily stopped

Headings
Treatment group: Refers to the treatment during the 1-week period of randomised treatment.
Treatment period: Indicates the treatment given during the period when the AE was recorded.
Treatment duration: Total duration of current treatment period (* This subject was lost to follow-up. The 95-day treatment duration is a result of the last contact with the subject having been a follow-up telephone contact that occurred about 2 months after the planned follow-up visit.)
Preferred term: AE coded term from Astra Adverse Event Dictionary.
Verbatim term: AE term used by investigator in the Case Report Form.
Onset day: Duration of treatment up to and including the day the event started (only calculated for the first treatment period when AE occurred). C = continued from previous period.
Duration of AE: Duration of AE (in days, if not otherwise specified) calculated from first onset in the study until the resolution of the event, or end of the current treatment period, whichever came first.

Discontinuations due to adverse events

All subjects who were discontinued from study treatment due to an adverse event are summarized in the following table.

Table 16 Listing of all subjects whose study treatment was discontinued owing to an adverse event during 4 weeks' treatment (safety population)

Centre Subject	Treatment group	Sex Age	Treatment period	Dose of inv.drug	Treat. dur	Preferred term (Verbatim term)	Onset day	Duration of AE	Serious	Recovered	Intensity	Action taken
3 1180	Oral	F 57	Esomeprazole capsule (open)	40 mg od	26	Abdominal pain (Abdominal cramp)	4	30	No	Yes	Severe	Drug stopped[a]
5 1024	Oral	F 51	Esomeprazole capsule (double-blind)	40 mg od	1	Diarrhoea (Diarrhoea)	1	>6	No	Yes	Severe	Drug stopped
			Esomeprazole capsule (double-blind)	40 mg od	1	Nausea (Nausea)	1	>6	No	Yes	Severe	Drug stopped
9 2014	Oral	M 39	Esomeprazole capsule (open)	40 mg od	25	Gastroenteritis (Gastroenteritis)	10	11	No	Yes	Moderate	Drug stopped
			Esomeprazole capsule (open)	40 mg od	25	Rash (Generalised skin rash)	12	9	No	Yes	Mild,	Drug stopped
			Esomeprazole capsule (open)	40 mg od	25	Headache (Headache)	12	9	No	Yes	Mild	Drug stopped

[a] The subject stopped study medication due to the AE at approximately the same time that she was scheduled to stop the study according to the protocol.

Headings
Treatment group: Refers to the treatment during the 1-week period of randomized treatment.
Treatment period: Indicates the treatment given during the period when the AE was recorded.
Treatment duration: Total duration of current treatment period.
Preferred term: AE coded term from Astra Adverse Event Dictionary.
Verbatim term: AE term used by investigator in the Case Report Form.
Onset day: Duration of treatment up to and including the day the event started (only calculated for the first treatment period when AE occurred). C =
continued from previous period.
Duration of AE: Duration of AE (in days, if not otherwise specified) calculated from first onset in the study until the resolution of the event, or end of the
current treatment period, whichever came first.

Discussion of deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events

A small number of SAEs and discontinuations due to adverse events were reported. No other significant adverse events were reported. The SAEs were assessed by the investigators as not causally related to the study drug.

Clinical laboratory evaluation

Clinical laboratory results are presented separately for hematology, clinical chemistry and urinalysis variables. For hematology and clinical chemistry, the results are examined in 3 ways: changes in mean values over time, changes in individual subjects over time, and individual clinically important abnormalities. For urinalysis the results are examined as changes over time.

Hematology
There were no hematological changes seen in the individual subjects when comparing baseline to after 1 week's treatment or baseline to after 4 weeks' treatment. No clinically important abnormal values in hematology tests were observed.

Clinical chemistry
Creatine kinase (CK) showed a decrease in median value in the injection and infusion groups whereas the mean values increased in all 3 treatment groups.

The ASAT and ALAT values were higher than the reference limit in 23 out of 242 and 64 out of 242 subjects, respectively, at baseline. Of the subjects with elevated ASAT values at baseline, 8 had normal values at 1 week and 10 had normal values at week 4. Of the ASAT values within the normal range at baseline, 9 were above the reference range after 1 week and 15 after 4 weeks of treatment. Of the raised ALAT values at baseline, 18 had normalized after 1 week and remained so after 4 weeks of treatment. Of the subjects with ALAT values within the normal range at baseline, 11 and 18 were above the normal range after 1 and 4 weeks of treatment, respectively.

Individual clinically important abnormalities in clinical chemistry
Abnormal CK values were observed in some subjects. At baseline 70 out of 243 (29%) subjects had elevated values of serum CK. In some of these subjects the values were markedly above the reference ranges. At Visit 8 the CK values in several of these subjects had normalized. In contrast, some of the subjects with normal baseline values showed raised values after the same treatment period. At Visit 9, still other subjects demonstrated an elevation or normalization of the CK values.

One of the laboratory values was reported as an AE. The subject had received oral treatment during week 1. At Visit 9 the ALAT value was 147 U/L (ref. range 1 to 39). At Visits 1 and 8 the value was within normal reference range. The AE was assessed by the investigator to be nonserious and of moderate intensity. No action was taken. The duration of the AE was 9 days. The same subject had 3 ½ weeks earlier experienced an animal bite in the left arm.

No clinically relevant changes in urinalysis in individual subjects over time were seen comparing baseline values with values after 1 week's treatment, and baseline values with values after 4 weeks' treatment. No individual clinically important abnormalities were observed in urinalysis in any of the treatment groups.

Analysis of the hematological parameters and urinalysis did not show any changes in the different treatment groups. The mean changes in vital signs were not considered clinically significant.

Some of the ECG measurements were assessed as abnormal at baseline or after treatment. No clinically relevant changes were seen after 1 and 7 days of treatment. No individual clinically important changes in vital signs and ECG were seen.

Physical examination
No major changes were seen after 1 and 4 weeks of treatment.

Ophthalmic examination
Long distance and reading distance
Changes in ophthalmic examination, long distance and reading distance, after 1 week's treatment are shown are shown in the following table and after 4 weeks' treatment in the subsequent table.

Table 17 Ophthalmic Examination - Long distance and reading distance after 1 week's treatment compared with baseline (safety population)

		Esomeprazole 40 mg once daily		
		3-min injection	30-min infusion	oral
		n=79	n=81	n=86
Long distance, right eye	Impairment[a]	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Unchanged	71 (89.9%)	76 (93.8%)	77 (89.5%)
	Improvement[a]	5 (6.3%)	4 (4.9%)	6 (7.0%)
	Not comparable	2 (2.5%)	1 (1.2%)	3 (3.5%)
Long distance, left eye	Impairment[a]	2 (2.5%)	0 (0.0%)	1 (1.2%)
	Unchanged	69 (87.3%)	76 (93.8%)	77 (89.5%)
	Improvement[a]	5 (6.3%)	4 (4.9%)	5 (5.8%)
	Not comparable	3 (3.8%)	1 (1.2%)	3 (3.5%)
Reading distance, right eye	Impairment[a]	2 (2.5%)	1 (1.2%)	0 (0.0%)
	Unchanged	73 (92.4%)	78 (96.3%)	78 (90.7%)
	Improvement[a]	2 (2.5%)	1 (1.2%)	0 (0.0%)
	Not comparable	2 (2.5%)	1 (1.2%)	8 (9.3%)
Reading distance, left eye	Impairment[a]	2 (2.5%)	1 (1.2%)	0 (0.0%)
	Unchanged	71 (89.9%)	78 (96.3%)	78 (90.7%)
	Improvement[a]	2 (2.5%)	1 (1.2%)	1 (1.2%)
	Not comparable	4 (5.1%)	1 (1.2%)	7 (8.1%)

[a] Two levels change were required for impairment and improvement.

Table 18 Ophthalmic Examination -Long distance and reading distance after 4 weeks' treatment compared with baseline (safety population)

		Esomeprazole 40 mg once daily		
		3-min injection	30-min infusion	oral
		n=79	n=81	n=86
Long distance, right eye	Impairment[a]	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Unchanged	70 (88.6%)	74 (91.4%)	77 (89.5%)
	Improvement[a]	5 (6.3%)	6 (7.4%)	5 (5.8%)
	Not comparable	3 (3.8%)	1 (1.2%)	4 (4.7%)
Long distance, left eye	Impairment[a]	3 (3.8%)	0 (0.0%)	1 (1.2%)
	Unchanged	68 (86.1%)	77 (95.1%)	76 (88.4%)
	Improvement[a]	4 (5.1%)	3 (3.7%)	5 (5.8%)
	Not comparable	4 (5.1%)	1 (1.2%)	4 (4.7%)
Reading distance, right eye	Impairment[a]	1 (1.3%)	0 (0.0%)	1 (1.2%)
	Unchanged	72 (91.1%)	76 (93.8%)	73 (84.9%)
	Improvement[a]	2 (2.5%)	0 (0.0%)	3 (3.5%)
	Not comparable	4 (5.1%)	5 (6.2%)	9 (10.5%)
Reading distance, left eye	Impairment[a]	1 (1.3%)	1 (1.2%)	1 (1.2%)
	Unchanged	71 (89.9%)	76 (93.8%)	75 (87.2%)
	Improvement[a]	2 (2.5%)	0 (0.0%)	2 (2.3%)
	Not comparable	5 (6.3%)	4 (4.9%)	8 (9.3%)

[a] Two levels change were required for impairment and improvement.

Impairments were observed in eight subjects of which four were in the injection group. In total 2 subjects with impairment also reported AEs associated to vision. Subject 1208 had impairments in all categories of the ophthalmic examination in both treatment periods. These were reported as AEs, accommodation abnormal and vision abnormal, that resolved after seven weeks. The subject had not noticed any deterioration in her eyesight. Two subjects had deteriorations in long distance of the left eye that were considered as not significant by the investigator; subject 1121 during both treatment periods and subject 1072 during open treatment. Subject 1115 had impairments of reading distance of both eyes after week 1 that were probably alcohol induced. After 4 weeks' treatment no significant change was seen. In addition subject 1135 showed no deterioration in the ophthalmic examination but reported an AE, vision abnormal. The AE started after 4 days treatment and resolved after approximately 2 hours. Two subjects in the infusion group had impairments in reading distance. Subject 2001 had impairment of the right eye during both treatment periods that was reported as an AE, accommodation abnormal. The AE started after 7 days treatment and resolved after 13 weeks. Subject 2008 had impairment of the left eye during both treatment periods. The subject had a refraction problem that was present before study start. In the oral group subject 2031 had impairment in long distance of the left eye. The subject had anisometropia in 1999. The investigator suspected cataract and an

incorrect assessment of the results at Visit 1. Subject 1199 had impaired reading distance of both eyes during open treatment that was not clinically significant.

Visual field

Changes in ophthalmic examination, visual field, after 1 week's treatment are shown are shown in the following table and after 4 weeks' treatment in subsequent table.

Table 19 Ophthalmic Examination -Visual field after 1 week's treatment compared with baseline, subjects with values at baseline and after 1 week's treatment (safety population)

Baseline			Yes[a]		No[a]	
After one week's treatment[b]			Yes[a]	No[a]	Yes[a]	No[a]
Head level	Left eye	3-min injection	79	0	0	0
		30-min infusion	81	0	0	0
		oral	84	0	0	0
	Right eye	3-min injection	79	0	0	0
		30-min infusion	81	0	0	0
		oral	85	0	0	0
Eye level	Left eye	3-min injection	79	0	0	0
		30-min infusion	81	0	0	0
		oral	84	0	0	0
	Right eye	3-min injection	79	0	0	0
		30-min infusion	81	0	0	0
		oral	85	0	0	0
Chest level	Left eye	3-min injection	79	0	0	0
		30-min infusion	81	0	0	0
		oral	84	0	0	0
	Right eye	3-min injection	79	0	0	0
		30-min infusion	81	0	0	0
		oral	85	0	0	0

[a] 'Subjects can see examiners hands clearly'.

[b] Esomeprazole 40 mg once daily

Medical Officer comment:

Exhaustive ophthalmic evaluations after administration of i.v. esomeprazole, followed by oral administration of the drug, have not uncovered findings of concern.

Table 20 Ophthalmic Examination -Visual field after 4 weeks' treatment compared with baseline, subjects with values at baseline and after 4 weeks' treatment (safety population)

Baseline			Yes[a]		No[a]	
After four weeks' treatment[b]			Yes[a]	No[a]	Yes[a]	No[a]
Head level	Left eye	3-min injection	78	0	0	0
		30-min infusion	81	0	0	0
		oral	83	0	0	0
	Right eye	3-min injection	78	0	0	0
		30-min infusion	81	0	0	0
		oral	84	0	0	0
Eye level	Left eye	3-min injection	78	0	0	0
		30-min infusion	81	0	0	0
		oral	83	0	0	0
	Right eye	3-min injection	78	0	0	0
		30-min infusion	81	0	0	0
		oral	84	0	0	0
Chest level	Left eye	3-min injection	78	0	0	0
		30-min infusion	81	0	0	0
		oral	83	0	0	0
	Right eye	3-min injection	78	0	0	0
		30-min infusion	81	0	0	0
		oral	84	0	0	0

[a] 'Subjects can see examiners hands clearly'.
[b] Esomeprazole 40 mg once daily.

Discussion of vital signs, ECG, physical findings and other observations related to safety

No changes of clinical importance were found when evaluating vital signs and physical findings, including long and reading distance vision and visual field. Regarding ECG, 34 (14%) ECG measurements were assessed as abnormal at baseline. After comparing the reported changes at baseline with those reported at Visit 8 and at Visit 9, no changes of clinical relevance were found.

In the ophthalmic examination from long and reading distances, the majority of the subjects showed no differences in visual acuity either at week 1 or week 4 compared to baseline. In total there were a larger number of observed improvements than impairments. The changes were equally distributed between the treatment groups. Vision field examination showed no changes in any of the subjects throughout the treatment periods. Overall, the ophthalmic examinations did not indicate any safety concerns regarding visual acuity at long and reading distances, or in the visual field after treatment with i.v. esomeprazole 40 mg.

In clinical practice, the need for treatment with i.v. esomeprazole can be expected to occur at any time point during a PPI treatment period of GERD and is expected to be of short duration in most cases. Although only a switch from i.v. to oral

treatment was studied, the sponsor feels that a switch from oral to i.v. treatment is not likely to reveal any other safety findings than were found in this study. The once daily treatment for 7 days with iv esomeprazole is considered to be sufficient for an adequate safety evaluation of iv esomeprazole.

According to the Sponsor:

- The safety profiles of esomeprazole 40 mg given once daily for 1 week either as an injection, infusion or by oral administration were similar. Neither the AE-pattern nor any of the other safety assessments implied any safety concerns for i.v. administration of esomeprazole.
- The safety profiles of esomeprazole 40 mg given once daily for 1 week either as an injection, infusion or by oral administration and followed by 3 weeks of once daily oral administration of esomeprazole 40 mg were similar.

D. Adequacy of Safety Testing

Essentially the design of this safety study is quite limited as all patients received oral medications for 3 weeks and some for 4 weeks. In order to enroll in the study the patients were required to be able to take oral medicines whereas this i.v. formulation is for patients who for whatever reason are unable to take esomeprazole by mouth.

However, Nexium has been on the market for some time and the PPIs as a class of drugs are considered quite safe. Upon request the Sponsor has submitted their post-marketing safety data from Sweden where Nexium I.V. has been utilized for about a year. In Sweden to date there have been no reportable adverse events with Nexium I.V.

E. Summary of Critical Safety Findings and Limitations of Data

In conclusion, even though the clinical design of study SH-NEP-0006 has distinctive limitations, Nexium I.V. is approvable based on the efficacy for the PK/PD data. The demand for relief of gastroesophageal reflux is extreme as shown by the amount sales. Also, as a group of drugs, this class has proven to be relatively safe.

VIII. Dosing, Regimen, and Administration Issues

The Sponsor has provided data regarding two doses (20 and 40 mg) and two means of giving these doses: injection (in no less than 3 minutes) and infusion (over 10 to 30 minutes). Based on the BAO and MAO data, the 20 mg dose either by 3-min. injection or a 15-min. infusion appears to have similar efficacy to the 20 mg oral dose form.

However, also based on the BAO and MAO data both the 3-min injection and the 15-min infusion of 40 mg i.v. gives slightly less efficacy than the 40 mg oral dosage form, so that with this dose, pharmacodynamic equivalence is not established. Administration of 20 mg and 40 mg over 3-min. or 30-min. infusions give similar PD data.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The small number of patients in the clinical study does not allow for adequate evaluation or PK/PD data.

In oral studies, the AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Similar differences were seen for intravenous administration of esomeprazole. However, dosage adjustment based on gender is not necessary.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

In oral studies, the AUC and Cmax values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state.

Dosage adjustment based on age is not necessary.

C. Evaluation of Pediatric Program

The small number of patients in the clinical study does not allow for adequate evaluation or PK/PD data.

The pharmacokinetics of esomeprazole, whether orally or intravenously administered, have not been studied in patients < 18 years of age.

D. Comments on Data Available or Needed in Other Populations

None

X. Conclusions and Recommendations

A. Conclusions

The Sponsor has submitted thirteen clinical pharmacology studies and one clinical safety study pertaining their application for a new form of Nexium for i.v. injection or infusion. PD and PK were assessed by pentagastrin-stimulated gastric acid output in GERD patients and 24-hour intragastric pH in normal volunteers. Intraesophageal pH data were not submitted. Higher Cmax and AUC values were observed with i.v. administration compared to the oral administration. Two studies using intragastric pH assessments show comparability between the oral and i.v. formulations. However, using maximum acid output (MAO) as the most meaningful and relevant primary efficacy parameter, pharmacodynamic equivalence between the i.v. and the oral formulation was not established in four studies especially for the 40 mg dosage. Also the approved indication for this new formulation is for a short period of time —— 10 days only. The one included clinical safety study, SH-NEP-006, demonstrated that one week of the i.v. formulation followed by three weeks of oral administration of the drug was not associated with serious adverse reactions. It is concluded that the i.v. administration of esomeprazole for —10 days is safe.

B. Recommendations

Based on the long established safety and efficacy of Nexium capsules and on the efficacy presented in this review of the pharmacokinetics and pharmacodynamics of Nexium I.V., this Medical Reviewer recommends that of Nexium I.V. is approvable for adults with GERD and erosive esophagitis. It is indicated for short term use —10 days) Approval should only occur after the C.M.C. issues are resolved and when the label is agreed upon between the Sponsor and the Agency. Clinically at this time, Nexium I.V. is not recommended for de novo use or for maintenance (longer than 10 days). Since, pharmacodynamically, the 40 mg i.v. dose does not appear as efficacious as the oral dose based on the MAO data this information should be incorporated in the label.

XI. References

The ADR Signals Analysis Project (ASAP) Team and Fraunfelder FT. Omeprazole and Visual Disorders: Seeing Alternatives. Pharmacoepidemiol Drug Saf 1996; 5: 27-32.

Chiba N, De Grara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesopghageal reflux disease: a meta-analysis. Gastroenterology. 1997; 112: 1798-810.

Dent J, Jones R, Kahrilas P, Talley NJ. Management of gastro-oesophageal reflux disease in general practice. BMJ 2002;322:344-7.

Dent J, Brun J, Fendrick AM, Fennerty MB, Janssens J, Kathrilas J, et al. An evidence-based appraisal of reflux disease management-- The Genval Workshop report. Gut 1999;44(2 Suppl):S1-S16.

Greenberger, NJ. Update in Gastroenterology. Ann Int Med 1998; 129:309-16.

Holloway RH, Dent J, Narielvala F, Mackinnon AM. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. Gut 1996;649-54.

Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux esophagitis patients: a randomised controlled trial. The Esomeprazole study investigators. Aliment Pharmacol Ther 2000;14(10):1249-58.

Lundell L, Dent J, Bennet RJ, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of esophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-80.

McCabe RD and Young d. Evidence of a H^+K^+ATPase in vascular smoothe muscle cells. Am J Physiol 1992; 311:H1955-H1958.

Metz DC, Pratha V, Martin P, Paul J, Maton PN, Lew E, et al. Oral and intravenous dosage forms of pantoprazole are equivalent in their ability to suppress gastric acid secretion in patients with gastroesophageal reflux disease. Am J Gastroenterol 2000;95(3):626-633.

Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomised controlled trial. Am J Gastroenterol 2001; 96(3):656-665.

Rodriguez LAG, Mannino S, Wallander MA, & Lindblom B. A cohort study of the ocular safety of anti-ulcer drugs. Br J Clin Pharmacol 1996; 42: 213-216.

Schonhofer PS, Werner B. Ocular damage with proton pump inhibitors BMJ 1997; 314: 1805.

B. Individual More Detailed Study Reviews (If performed)

None

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

/s/

Gail Moreschi
6/16/04 06:04:16 PM
MEDICAL OFFICER

Hugo Gallo Torres
6/16/04 06:08:40 PM
MEDICAL OFFICER

03/31/05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 3/29/2005

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: Acting Division Director Approval Comments
NDA 21-689

APPLICANT: **Astra Zeneca**

DRUG: **Nexium® IV** (esomeprazole) for Injection

DIVISION RECOMMENDATION:
I am in agreement with the Division's recommendation that Nexium® IV be approved for the short-term treatment (up to 10 days) of GERD patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with NEXIUM Delayed-Release Capsules is not possible or appropriate.

I. Regulatory History:
This is the second review cycle for this application. Outstanding issues at that time were the resolution of CMC deficiencies and finalization of the package label. This memo will address only these areas. Please refer to my previous memo of 7/9/2004 for review of other areas related to this submission.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:
Chemistry and Manufacturing:
According to the Chemistry review Astra Zeneca's response to the approvable action's list of deficiencies is acceptable. The responses were related to CMC issues regarding compatibility studies with other diluents and IV bags as well as other quires from the Information Request letter dated April 23, 2004.

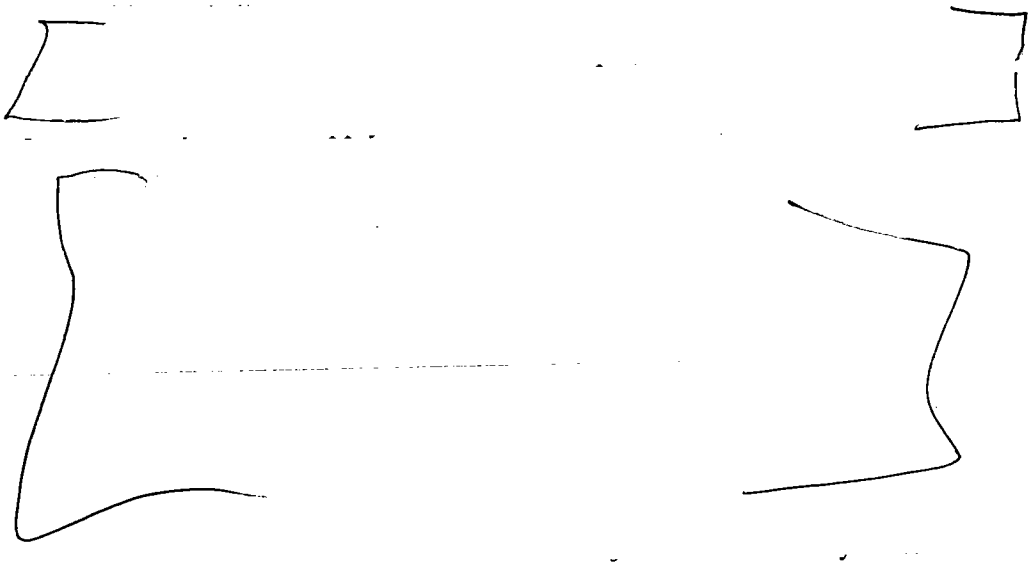
III. Pediatric Use: This is deferred for ages 0-17 years.

IV. Labeling Recommendations:
Labeling recommendations are centered on the safety and efficacy, as well as chemistry and PK/PD areas. Our recommendations were sent to the sponsor and discussed in a telecon with Astra Zeneca on March 24, 2005. Both Astra Zeneca and the Division attendees agreed upon these recommendations.
I wish to address my comments to the indication which does not place any restrictions on the timing of administration, initial or during the course of already

initiated oral therapy, and the indication itself, restriction to Erosive Esophagitis. As I outlined in my previous review, Astra Zeneca performed many PK/PD studies referenced in this submission. Nexium (oral) is approved for Symptomatic GERD and Erosive Esophagitis. The Division of Gastroenterology and Coagulation Drug Products has maintained, in agreement with the literature, that bioequivalence of PPIs (proton pump inhibitors) should be based upon PK as well as PD parameters. For the approval of IV formulations where an oral formulation is already approved, these parameters need further clinical investigation. Thus, some additional clinical experience must be studied, even for an indication where Nexium is already proven to be effective.

There is controversy in the field regarding the "added" activity of administering PPIs orally. Some contend that the oral PPIs might be slightly more active than the IV formulation. For all of the PPIs where an IV formulation is being developed some clinical information regarding symptom relief or healing of esophageal erosion was obtained prior to approval. I feel that this sponsor has addressed this issue with the submission of a relatively large endoscopic study,

Specifically, in the labeling I did not recommend that this product be limited to patients already receiving oral PPIs. Astra Zeneca demonstrated similarity with oral Nexium in this study regarding healing of erosive esophagitis. The statistical review commented on the inadequacy of the study design, however, from a clinical standpoint, the design was appropriate and conducted in the only way that such a study could be performed given the indication. The medical team leader requested more information be gathered based upon the statistical review. He did comment that there were no symptoms of GERD collected in any of the studies.



V. **Phase IV Commitments:** There are none.

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

/s/

Joyce Korvick
3/31/05 11:28:39 AM
MEDICAL OFFICER