CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021689Orig1s014

Trade Name:	NEXIUM I.V.
Generic or Proper Name:	Esomeprazole sodium
Sponsor:	ASTRAZENECA
Approval Date:	March 4, 2014
Indication:	NEXIUM I.V. is a proton pump inhibitor indicated for the treatment of: • Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate. • Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following therapeutic endoscopy in adults

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 021689Orig1s014

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Clinical Review(s)	**X**
Product Quality Review(s)	**X**
Environmental Assessment	**X**
Non-Clinical Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	**X**
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21689/S-014

SUPPLEMENT APPROVAL

AstraZeneca LP
Attention: Judy W. Firor
Director, Global Regulatory Affairs and Patient Safety
1800 Concord Pike, PO Box 8355
Wilmington DE 19803-8355

Dear Ms. Firor:

Please refer to your Supplemental New Drug Application (sNDA) dated May 29, 2008, received May 29, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nexium I.V. (esomeprazole sodium) for Injection.

We acknowledge receipt of your amendments dated June 19, 2008, August 7, 2008, August 21, 2008, August 25, 2008, September 3, 2008, September 4, 2008, September 25, 2008, October 9, 2008, October 22, 2009, September 15, 2010, November 16, 2010, January 10, 2011, January 24, 2011, February 14, 2011, February 21, 2011, March 14, 2011, April 6, 2011, April 19, 2011, May 5, 2011, May 23, 2011, June 1, 2011, October 13, 2011, June 13, 2012, December 14, 2012, February 19, 2013, February 28, 2013, March 12, 2013, March 21, 2013, April 22, 2013, June 20, 2013, June 27, 2013, July 16, 2013, July 25, 2013, August 14, 2013, August 22, 2013, September 4, 2013, September 12, 2013 and March 3, 2014 .

The December 14, 2012, submission constituted a complete response to our June 16, 2011, action letter.

This "Prior Approval" supplemental new drug application provides for the use of Nexium I.V. (esomeprazole sodium) for Injection for risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below (underlined and strike through text) and indicated in the enclosed labeling.

6 ADVERSE REACTIONS

Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers in Adults
The data described below reflect exposure to NEXIUM I.V. for Injection in 375 patients. NEXIUM I.V. for Injection was studied in a placebo-controlled trial. Patients were randomized to receive NEXIUM I.V. for Injection (n=375) or placebo (n=389). The population was 18 to 98 years old; 68% Male, 87% Caucasian, 1% Black, 7% Asian, 4% other, who presented with endoscopically confirmed gastric or duodenal ulcer bleeding. Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for a total treatment duration of 72 hours. After the initial 72-hour period, all patients received oral proton pump inhibitor (PPI) (b) (4) for 27 days.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes with the revisions indicated above approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for the above indication because there are too few children with the disease to study and therefore necessary studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

DONNA J GRIEBEL
03/04/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021689/S-014

COMPLETE RESPONSE

AstraZeneca LP
Attention: Judy W. Firor
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Firor:

Please refer to your Supplemental New Drug Application (sNDA) dated May 29, 2008, received May 29, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nexium® IV (esomeprazole sodium) for Injection.

We acknowledge receipt of your amendments dated June 19, 2008, August 7, 2008, August 21, 2008, August 25, 2008, September 3, 2008, September 4, 2008, September 25, 2008, October 9, 2008, October 22, 2009, September 15, 2010, November 16, 2010, January 10, 2011, Jan 24, 2011, February 14, 2011, February 21, 2011, March 14, 2011, April 6, 2011, April 19, 2011, May 5, 2011, and June 1, 2011 .

The September 15, 2011, submission constituted a complete response to our November 26, 2008, action letter.

We also acknowledge receipt of your amendment dated May 23, 2011, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

This "Prior Approval" efficacy supplemental new drug application proposes the following indication: (b) (4) *risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer.*

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL AND STATISTICAL

The additional data submitted do not provide substantial evidence of efficacy of your product for the proposed indication for the reasons listed below:

1. Trials I-840 and I-841 differ from the efficacy trial, D961DC00001, submitted in the sNDA on May 29, 2008, in several important ways, including the endoscopic treatments administered and the primary endpoints evaluated. Therefore, these trials were not adequately designed to support the proposed indication.

2. When patients from trial I-840 and I-841 are matched to the population enrolled in the original efficacy trial, D961DC00001, based on enrollment criteria, too few patients remain to provide adequate power to show a statistically significant treatment effect. Of the combined total of 607 patients enrolled in the studies, only 52 patients met the enrollment criteria of D961DC00001. The proportion of omeprazole-treated patients in this subgroup who had a rebleeding event within 72 hours was 13.6% (3/22). Although this proportion was lower than that observed in the placebo-treated patients, 23.3% (7/30), the difference was not statistically significant (p=0.49, Fisher's Exact Test).

3. The clinical trial reported by Lau, et al.[1] is comparable in design to D961DC00001 and the trial provides evidence of efficacy of intravenous omeprazole for the proposed indication. However, the study was conducted at a single center in Hong Kong and the population enrolled was ethnically homogeneous. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of *H. pylori* infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which could have contributed to the larger treatment effect observed in the Lau trial. Therefore, the ability to generalize the results of this trial to the U.S. population is limited.

4. There is a substantive difference in the rebleeding rate in the placebo group (20%) of the trial reported by Lau, et al. compared to D961DC00001 (10%). It is not clear why the rebleeding rate in the Lau, et al. trial is double the rate observed in D961DC00001. It may be partially explained by the differences in Asian populations described in #3 above, or by differences in factors such as age and baseline health status, which may impact on the risk of rebleeding. Additionally, operational factors such as differences in endoscopic technique may affect the risk of rebleeding. This inconsistency in rebleeding rate between the trials also raises questions about the ability to generalize the results of this trial to the U.S. population.

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[1] Lau J, Sun J, Lee K, et al, Effect of Intravenous Omeprazole on Recurrent Bleeding after Endoscopic Treatment of Bleeding Peptic Ulcers, N. Engl. J. Med., 2000, Aug 3; 343(5): 310-316

5. There were substantive differences in the efficacy outcomes within important subgroups in the clinical trial reported by Lau, et al. compared to D961DC00001. These inconsistencies raise questions about the reproducibility of the efficacy outcome.

    a. In the subgroup of patients 65 years of age and older, the decrease in proportion of patients with rebleeding within 72 hours in the esomeprazole arm relative to placebo was 2.2% in D961DC00001. In contrast, the decrease in the same subgroup treated with omeprazole relative to placebo in the trial reported by Lau, et al. was 19.7%.

    b. In the subgroup of patients with Forrest Ib classification, there were similar proportions of patients with rebleeding within 72 hours in the esomeprazole and placebo arms in D961DC00001 (a 0.5% difference). In contrast, there was a decrease in the proportion of patients with rebleeding within 72 hours in the omeprazole arm relative to placebo of 10% in the trial reported by Lau, et al.

6. The information from observational studies and literature reviews of intravenous esomeprazole and omeprazole were not considered adequate to constitute primary evidence of the efficacy of the product for the proposed indication.

7. We have reviewed your responses to the deficiencies cited in the November 26, 2008, Complete Response Letter regarding trial D961DC00001. Your responses do not change our conclusion that D961DC00001, as a single adequate and well-controlled trial, does not provide sufficient evidence to support the proposed indication. The following comments are responses to specific issues raised in your resubmission:

    a. Your assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers for D961DC00001 is not persuasive. The Breslow-Day test is not a powerful test for detecting lack of homogeneity. For this reason, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables further limit the usefulness of the test.

    b. A Division of Good Clinical Practice Compliance inspection was performed at site 0102 in the Netherlands because Dr. Ernst J. Kuipers, MD, PhD, the principal investigator at that site, disclosed that he had accepted significant payments from AstraZeneca. The inspection found that the data from this site appear reliable. Nevertheless, as stated in the Complete Response letter, the large magnitude of treatment effect observed at this site, and the impact this single site had on the overall efficacy of the trial, suggest that the efficacy results of DC961DC00001 are not robust.

    c. You contend that the suboptimal pharmacodynamic (PD) effects of esomeprazole on gastric pH observed in the PK/PD studies submitted in the sNDA on May 29, 2008, can be attributed to the fact that the studies were performed in *Helicobacter*

pylori negative healthy subjects, i.e., subjects in whom it would be more difficult to suppress intragastric acidity, and that a pH of 6 would have been more consistently achieved if the population studied had had peptic ulcer disease. We disagree because this position assumes that all patients with peptic ulcer disease have *H. pylori*. Not all patients with peptic ulcer disease are *H. pylori* positive. The populations enrolled in the clinical trials you submitted to this NDA attest to this.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

RECOMMENDATION TO ADDRESS DEFICIENCIES

In order to address the deficiencies that have been identified in this sNDA, the following information should be included in the resubmission:

Conduct at least one additional, adequate, and well-controlled trial to demonstrate the clinical benefit of Nexium® IV for (b) (4) The trial should include some U.S. centers, and should be designed to evaluate a specific population of patients that would be most likely to benefit from treatment with esomeprazole.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

The pharmacokinetic data in patients with hepatic impairment that you provided in the sNDA are not adequate to assess the recommended dose for continuous intravenous infusion of esomeprazole in patients with moderate and severe hepatic impairment.

The following information should be included in the resubmission:

Resubmit the modeling and simulation results of previously collected data to support an estimate of the proper constant infusion rate in patients with moderate and severe hepatic impairment.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

DONNA J GRIEBEL
06/16/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-689/S-014

COMPLETE RESPONSE

AstraZeneca LP
Attention: George Kummeth
Senior Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Kummeth:

Please refer to your supplemental new drug application (sNDA) dated and received on May 29,2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium IV (esomeprazole sodium) for Injection.

We acknowledge receipt of your amendments dated June 19, 2008; August 7, 21, & 25, 2008; September 3, 4, & 25, 2008; and October 9, 2008.

This supplemental new drug application proposes the following new indication:

- (b) (4) *risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer.*

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, we have provided our recommendations to address these issues.

CLINICAL and STATISTICAL

Our review finds that the primary efficacy results for this non-U.S. single study do not provide substantial evidence of efficacy. For a single study to stand alone as substantial evidence of efficacy, it should demonstrate highly statistically significant and clinically meaningful results. Consistency should be demonstrated across subgroups and secondary endpoints. The study should also show internal consistency in demonstrating the treatment effect across study centers. The single study that you have submitted does not meet these criteria for providing substantial evidence for the following reasons:

1. Highly statistically significant results were not demonstrated. Although your protocol specified analysis showed a reduction of 4.4% in the rate of clinically significant

rebleeding within 72 hours after hemostasis compared to placebo (p = .03), that reduction was not highly significant, e.g., p < .001. In addition, the observed outcome was not found to be robust when subjected to the sensitivity analyses listed below:

a. It is appropriate to account for country-to-country variation, so the protocol specified analysis was further stratified by country. This resulted in an insignificant treatment effect (p=0.06), although the absolute reduction in rebleeding remained 4.4%.

b. When the protocol specified analysis was further stratified (retaining stratification by country in the model) using Forrest classification as four separate categories (Forrest Ia, Ib, IIa, and IIb) instead of two (Forrest I and Forrest II), an insignificant treatment effect was observed (p=0.11). The absolute reduction in rebleeding remained 4.4%. We believe the appropriate adjustment for Forrest classification should be by each individual Forrest category because each category has a different risk of rebleeding events. Even if this stratified analysis was conducted without incorporation of country in the model, the p value still shifted to a less persuasive value of p= 0.05.

2. The study lacked internal consistency across study centers. Despite similar patient demographics and disease characteristics, marked variability in the incidence of rebleeding, i.e., the primary endpoint, and treatment effect was observed in different countries and among leading centers. The treatment effect varied widely from -25% to +12% by country and from -31% to +20% in the larger centers that enrolled more than 10 patients. There is no clear explanation for why this occurred, although physician expertise and standards of care may have played a role.

3. The study lacked internal consistency in demonstrating the treatment effect in the important subgroup of patients aged 65 and older. In this subgroup, the proportion of patients that experienced rebleeding in the first 72 hours was 6.2% on the esomeprazole arm and 8.4% on the placebo arm. In contrast, in patients aged less than 65 the proportion of patients that experienced rebleeding in the esomeprazole arm was 5.5%, while on the placebo arm the proportion was 11.9%.

4. The study lacked internal consistency in demonstrating the treatment effect in important secondary efficacy outcomes that were evaluated in the first 72 hours. The proportion of patients who underwent surgery for rebleeding was a prespecified secondary endpoint and the observed outcome for this endpoint was similar between study arms. This analysis was not found to be statistically significant, p = 0.31. The secondary analysis comparing number of blood units transfused in the first 72 hours demonstrated a lower number of units infused on the esomeprazole arm (492) relative to placebo (738), p=0.05, and the secondary analysis that compared the proportion of patients who required endoscopic retreatment in the first 72 hours demonstrated a decreased rate of endoscopic retreatment (4.3%) on the esomeprazole arm relative to placebo (8.2%), p=0.02. Although the secondary analyses of number of blood units transfused and endoscopic retreatment appear

nominally significant, there was no prespecified plan to adjust for multiple comparisons. Taking a conservative approach, these p values are not significant after a Bonferroni adjustment to account for multiple comparisons.

5. One center, Site 0102 in the Netherlands reported the largest treatment effect in all centers that participated in this study, -31% rebleeding events, favoring the esomeprazole arm of the study. The investigator from this site, Dr. Ernest J. Kuipers, MD, Ph.D., reported having accepted significant payments from Astra Zeneca. When we conducted a sensitivity analysis to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, we found that the overall treatment effect observed in the study decreased to -3.73% (95% CI = -7.67, 0.10) and the p value shifted to 0.06.

6. We identified additional study design and conduct concerns that further limit the study's ability to provide persuasive evidence that esomeprazole is effective for the proposed indication. These issues are listed below:

   a. Endoscopic epinephrine injection is currently not an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers. More than a third of the patients in this study were treated with endoscopic epinephrine injection as single therapy. This draws into question the applicability of the outcome observed in this trial to current care of patients with an upper gastrointestinal bleed from a gastric or duodenal ulcer in the United States today.

   b. Although the inclusion criteria excluded patients with more than a single ulcer, a substantial proportion of the randomized patients had multiple ulcers and there was an imbalance between study arms in this prognostic factor that favored the esomeprazole arm. Fewer patients on the esomeprazole arm had multiple ulcers, 13.6%, relative to the placebo arm, 18.5%. This raises concerns regarding the study conduct in this international trial.

   c. Despite randomization, small imbalances in important prognostic factors were observed between the two study arms. The imbalances favored the esomeprazole treatment arm. These prognostic factors included Grade 1a stigmata of risk of rebleeding (esomeprazole=7.5%, placebo=10.3%) and large ulcers (esomeprazole=7.7%, placebo=10.3%).

   d. The lack of an exclusion criterion for intravenous administration of a proton pump inhibitor within 24 hours prior to enrollment is a potential confounding factor for the observed efficacy outcome. Although this was addressed with an amendment during the course of the study, the amendment only excluded patients who had received intravenous doses greater than 40 mg within 24 hours prior to enrollment.

7. There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. (b) (4) [redacted] If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

These deficiencies cannot be addressed adequately through additional analyses of the data in hand. We conclude that further clinical data from at least one additional adequate and well controlled study that provides persuasive and consistent evidence of efficacy will be needed to address all of the deficiencies in your application.

RECOMMENDATION TO ADDRESS DEFICIENCIES

1. Conduct at least one additional, adequate, and well-controlled study to demonstrate the proposed clinical benefit of Nexium IV for (b) (4) [redacted] The study should include some U.S. centers and the study design and analysis plan should address the deficiencies described in this letter above.

2. You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two pharmacokinetic/pharmacodynamic (PK/PD) studies that you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3 study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment.

For the reasons stated above, conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data.

3. Study site 0102 in the Netherlands, which reported the greatest treatment effect in the major randomized, placebo controlled trial that you submitted for our review, will need to be inspected by the Division of Scientific Investigations (DSI) because Dr. Ernst J. Kuipers, MD, PhD, the investigator at that site, has disclosed that he has accepted significant payments from Astra Zeneca. This inspection would be requested as part of our review of any future submission that includes this study as a critical component of establishing the efficacy of Nexium IV for the proposed indication. A recommendation from the DSI inspector that the data from this site can be used for determining the efficacy and safety of Nexium IV will be needed if this study will be used to support a future marketing application. This assessment will be an important component of a future determination of whether this study can stand as one of two adequate and well controlled trials for the proposed indication.

4. Conduct a pharmacokinetic study in a sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.

5. For this application, we note your request for a full waiver for pediatric patients under the age of 18 years for the following reasons:

   - Small number of pediatric patients.
   - Geographically widespread distribution of pediatric patients.

   It is unlikely that a full waiver of pediatric studies will be granted on re-submission. The incidence of H.pylori related peptic ulcer disease in the pediatric population is low; however, peptic ulcers secondary to long term use of steroids, NSAIDs, and chronic renal failure are not uncommon. Pediatric patients are administered intravenous proton pump inhibitors (PPI) prophylactically before starting high dose steroids and for upper gastrointestinal bleeding.

   Therefore, please submit a pediatric plan with your complete response.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Donna Griebel

11/26/2008 05:49:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXIUM I.V. safely and effectively. See full prescribing information for NEXIUM I.V.

NEXIUM® I.V. (esomeprazole sodium) for injection, for intravenous use
Initial US Approval: 2005

----------RECENT MAJOR CHANGES----------

- Indications and Usage, Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults (1.2) 03/2014
- Dosage and Administration, Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults (2.2) 03/2014
- Dosage and Administration, Preparation and Administration Instructions (2.3) 03/2014

----------INDICATIONS AND USAGE----------

NEXIUM I.V. is a proton pump inhibitor indicated for the treatment of:

- Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate. (1 1)
- Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following therapeutic endoscopy in adults (1.2)

----------DOSAGE AND ADMINISTRATION----------

GERD – with Erosive Esophagitis (2.1):

- Adults: Dose is either 20 mg or 40 mg NEXIUM given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes).

- Pediatric: Give the following doses once daily as an intravenous infusion over 10 minutes to 30 minutes (2.1):
  - 1 year to 17 years:
    - Body weight less than 55 kg: 10 mg
    - Body weight 55 kg or greater: 20 mg
  - 1 month to less than 1 year of age: 0.5 mg/kg

- For patients with severe liver impairment (Child Pugh Class C), a maximum dose of 20 mg once daily of NEXIUM should not be exceeded. (2.1, 8.6, 12.3)

Risk Reduction of Rebleeding of Gastric and Duodenal Ulcers in the first 72 hours following therapeutic endoscopy in Adults (2.2):

- 80 mg intravenous infusion given over 30 minutes, followed by a continuous infusion of 8 mg/h over 3 days (72 hours).
- Dose adjustments are needed in patients with liver impairment (2.2, 8.6, 12.3)
  - For patients with bleeding gastric or duodenal ulcers and mild to moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of 6 mg/h should not be exceeded.
  - For patients with severe liver impairment (Child Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded.

----------DOSAGE FORMS AND STRENGTHS----------

NEXIUM I.V. for Injection is supplied as a freeze-dried powder containing 20 mg or 40 mg of esomeprazole per single-use vial. (3)

----------CONTRAINDICATIONS----------

Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (angioedema and anaphylaxis have occurred). (4)

----------WARNINGS AND PRECAUTIONS----------

- Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy. (5.1)
- Atrophic gastritis has been noted with long-term omeprazole therapy. (5.2)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.3)
- Avoid concomitant use of NEXIUM I.V. with clopidogrel. (5.4)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6)
- Avoid concomitant use of NEXIUM with St John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.7, 7.2)
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.8, 12.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥1%) are headache, flatulence, nausea, abdominal pain, injection site reaction, diarrhea, dry mouth, dizziness/vertigo, constipation and pruritus (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- NEXIUM I.V. inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, iron salts, erlotinib, and digoxin). Patients treated with NEXIUM and digoxin may need to be monitored for digoxin toxicity. (7)
- Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. (7)
- NEXIUM I.V. may reduce the plasma levels of atazanavir, nelfinavir, and saquinavir. (7)
- Concomitant treatment with a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. (7)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction (7)
- Clopidogrel: NEXIUM I.V. decreases exposure to the active metabolite of clopidogrel. (7)
- Tacrolimus: NEXIUM may increase serum levels of tacrolimus (7.2)
- Methotrexate: NEXIUM may increase serum levels of methotrexate (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

NEXIUM I.V. for Injection is indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively as an alternative to oral therapy when oral NEXIUM is not possible or appropriate.

1.2 Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults

NEXIUM I.V. for Injection is indicated for risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults.

2 DOSAGE AND ADMINISTRATION

General Information

NEXIUM I.V. for Injection should not be administered concomitantly with any other medications through the same intravenous site and/or tubing. The intravenous line should always be flushed with either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP both prior to and after administration of NEXIUM I.V. for Injection.

The admixture should be stored at room temperature up to 30°C (86°F) and should be administered within the designated time period as listed in Table 1 below. No refrigeration is required.

Table 1 Storage Time for Final (diluted) Product

Diluent	Administer within:
0.9% Sodium Chloride Injection, USP	12 hours
Lactated Ringer's Injection, USP	12 hours
5% Dextrose Injection, USP	6 hours

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

As soon as oral therapy is possible or appropriate, intravenous therapy with NEXIUM I.V. for Injection should be discontinued and the therapy should be continued orally.

2.1 GERD with Erosive Esophagitis

Adult Patients

The recommended adult dose is either 20 mg or 40 mg NEXIUM given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes). Safety and efficacy of NEXIUM I.V. for Injection as a treatment of GERD patients with erosive esophagitis for more than 10 days have not been demonstrated.

Dosage adjustment is not required in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a maximum dose of 20 mg once daily of NEXIUM should not be exceeded [*see Use in Specific Populations (8.6), Clinical Pharmacology, (12.3)*].

Pediatric Patients

The recommended doses for children ages 1 month to 17 years, inclusive, are provided below. Dose should be infused over 10 minutes to 30 minutes.

1 year to 17 years:

Body weight less than 55 kg: 10 mg
Body weight 55 kg or greater: 20 mg

1 month to less than 1 year of age: 0.5 mg/kg

2.2 Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults

Adult dose is 80 mg administered as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/h for a total treatment duration of 72 hours (i.e., includes initial 30-minute dose plus 71.5 hours of continuous infusion). Intravenous therapy is aimed solely at the acute initial management of bleeding gastric or duodenal ulcers and does not constitute full treatment. Intravenous therapy should be followed by oral acid-suppressive therapy.

For patients with liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For patients with mild to moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For patients with severe liver impairment (Child Pugh Class C), a

maximum continuous infusion of 4 mg/h should not be exceeded [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

2.3 Preparation and Administration Instructions

General Information

The reconstituted solution of Nexium I.V. should be stored at room temperature up to 30°C (86°F) and administered within 12 hours after reconstitution. (Administer within 6 hours if 5% Dextrose Injection is used after reconstitution). No refrigeration is required.

Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

Preparation Instructions for Adult Patients

Intravenous Injection (20 mg or 40 mg vial) over no less than 3 minutes

The freeze-dried powder should be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP.

Withdraw 5 mL of the reconstituted solution and administer as an intravenous injection over no less than 3 minutes.

Preparation Instructions for Pediatric Patients

Intravenous Infusion (20 mg or 40 mg) over 10 minutes to 30 minutes

A solution for intravenous infusion is prepared by first reconstituting the contents of one vial* with 5 mL of 0.9% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP and further diluting the resulting solution to a final volume of 50 mL. The resultant concentration after diluting to a final volume of 50 mL is 0.8 mg/mL (for 40 mg vial) and 0.4 mg/mL (for 20 mg vial). The solution (admixture) should be administered as an intravenous infusion over a period of 10 minutes to 30 minutes.

*For patients 1 month to less than 1 year of age, first calculate the dose (0.5 mg/kg) to determine the vial size needed.

Risk Reduction of Re-bleeding of Gastric or Duodenal Ulcers in Adults

Preparation Instructions for Loading dose (80 mg) to be given over 30 minutes

The loading dose of 80 mg is prepared by reconstituting two 40 mg vials. Reconstitute each 40 mg vial with 5 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be further diluted in 100 mL 0.9% Sodium Chloride Injection, USP for intravenous use. Administer over 30 minutes.

Preparation Instructions for Continuous Infusion to be given at 8 mg/hour for 71.5 hours

The continuous infusion is prepared by using two 40 mg vials. Reconstitute each 40 mg vial with 5 mL each of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be further diluted in 100 mL 0.9% Sodium Chloride Injection, USP for intravenous use. Administer at a rate of 8 mg/hour for 71.5 hours.

3 DOSAGE FORMS AND STRENGTHS

NEXIUM I.V. for Injection is supplied as a freeze-dried white to off-white powder containing 20 mg or 40 mg of esomeprazole per single-use vial.

4 CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (angioedema and anaphylaxis have occurred).

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Concomitant Gastric Malignancy

Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy.

5.2 Atrophic Gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

5.3 *Clostridium difficile* Associated Diarrhea

Published observational studies suggest that PPI therapy like NEXIUM may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [*see Adverse Reactions* (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

5.4 Interaction with Clopidogrel

Avoid concomitant use of NEXIUM I.V. with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using NEXIUM I.V. consider alternative anti-platelet therapy. [*see Drug Interactions (7), Clinical Pharmacology (12.3)*]

5.5 Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines. [*see Dosage and Administration (2), Adverse Reactions (6.2)*]

5.6 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically. [*See Adverse Reactions (6.2)*]

5.7 Concomitant use of NEXIUM with St John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St John's Wort or rifampin) can substantially decrease esomeprazole concentrations [*see Drug Interactions (7)*]. Avoid concomitant use of NEXIUM with St John's Wort or rifampin.

5.8 Interactions with Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop esomeprazole treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

5.9 Concomitant use of NEXIUM with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [*see Drug Interactions (7.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience with Intravenous NEXIUM

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The safety of intravenous esomeprazole is based on results from clinical trials conducted in four different populations including patients having symptomatic GERD with or without a history of erosive esophagitis (n=199), patients with erosive esophagitis (n=160), healthy subjects (n=204) and patients with bleeding gastric or duodenal ulcers (n=375).

Symptomatic GERD and Erosive Esophagitis Trials

The data described below reflect exposure to NEXIUM I.V. for Injection in 359 patients. NEXIUM I.V. for Injection was studied only in actively-controlled trials. The population was 18 to 77 years of age; 45% Male, 52% Caucasian, 17% Black, 3% Asian, 28% Other, and had either erosive reflux esophagitis (44%) or GERD (56%). Most patients received doses of either 20 or 40 mg either as an infusion or an injection. Adverse reactions occurring in ≥ 1% of patients treated with intravenous esomeprazole (n=359) in clinical trials are listed below:

Table 2

Adverse reactions occurring at an incidence ≥ 1% in the NEXIUM I.V. group

Adverse Reactions	% of patients Esomeprazole Intravenous (n=359)
Headache	10.9
Flatulence	10.3
Nausea	6.4
Abdominal pain	5.8
Diarrhea	3.9
Mouth dry	3.9
Dizziness/vertigo	2.8
Constipation	2.5
Injection site reaction	1.7
Pruritus	1.1

Intravenous treatment with esomeprazole 20 and 40 mg administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole.

Pediatric

A randomized, open-label, multi-national study to evaluate the pharmacokinetics of repeated intravenous doses of once daily esomeprazole in pediatric patients 1 month to 17 years old, inclusive was performed. The safety results are consistent with the known safety profile of esomeprazole and no unexpected safety signals were identified. [*See Clinical Pharmacology (12.3)*]

Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers in Adults

The data described below reflect exposure to NEXIUM I.V. for Injection in 375 patients. NEXIUM I.V. for Injection was studied in a placebo-controlled trial. Patients were randomized to receive NEXIUM I.V. for Injection (n=375) or placebo (n=389). The population was 18 to 98 years old; 68% Male, 87% Caucasian, 1% Black, 7% Asian, 4% other, who presented with endoscopically confirmed gastric or duodenal ulcer bleeding. Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for a total treatment duration of 72 hours. After the initial 72-hour period, all patients received oral proton pump inhibitor (PPI) for 27 days.

Table 3

Incidence (%) of adverse reactions that occurred in greater than 1% of patients within 72 hours after start of treatment*

	Number(%) of patients	
	Esomeprazole (n=375)	**Placebo (n=389)**
Duodenal ulcer haemorrhage	16 (4.3%)	16 (4.1%)
Injection site reaction[#]	16 (4.3%)	2 (0.5)
Pyrexia	13 (3.5%)	11 (2.8%)
Cough	4 (1.1%)	1 (0.3%)
Dizziness	4 (1.1%)	3 (0.8%)

*Incidence ≥1% in the esomeprazole group and greater than placebo group safety population

[#]Injection site reactions included erythema, swelling, inflammation, pruritus, phlebitis, thrombophlebitis and superficial phlebitis.

With the exception of injection site reactions described above, intravenous treatment with esomeprazole administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NEXIUM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing Reports - There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports occurred rarely and are listed below by body system:

Blood And Lymphatic System Disorders*:* agranulocytosis, pancytopenia; ***Eye Disorders:*** blurred vision; ***Gastrointestinal Disorders:*** pancreatitis; stomatitis; microscopic colitis; ***Hepatobiliary Disorders:*** hepatic failure, hepatitis with or without jaundice; ***Immune System Disorders:*** anaphylactic reaction/shock; ***Infections and Infestations:*** GI candidiasis; ***Metabolism and nutritional disorders:*** hypomagnesemia***; Musculoskeletal And Connective Tissue Disorders:*** muscular weakness, myalgia, bone fracture; ***Nervous System Disorders***: hepatic encephalopathy, taste disturbance; ***Psychiatric Disorders:*** aggression, agitation, depression, hallucination; ***Renal and Urinary Disorders***: interstitial nephritis; ***Reproductive System and Breast Disorders:*** gynecomastia; ***Respiratory, Thoracic and Mediastinal Disorders:*** bronchospasm; ***Skin and Subcutaneous Tissue Disorders:***

alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal).

Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert, **ADVERSE REACTIONS** section.

7 DRUG INTERACTIONS

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of NEXIUM I.V. with clopidogrel. When using NEXIUM I.V., consider use of alternative anti-platelet therapy [*see Clinical Pharmacology (12.3)*].

Omeprazole acts as an inhibitor of CYP 2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26%, respectively. C_{max} and AUC of

one of its active metabolites, 3,4-dihydro-cilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69%, respectively. Co-administration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore, a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required for the recommended doses. However, in patients who may require higher doses, dose adjustment may be considered.

Drugs known to induce CYP2C19 or CYP3A4 (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St John's wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolizers (C_{max} and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with NEXIUM.

Co-administration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37%

and 89% and C_{min} by 39% and 75%, respectively, for nelfinavir and M8. Following multiple doses of atazanavir (400 mg daily) and omeprazole (40 mg daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported with an increase in AUC by 82%, in C_{max} by 75% and in C_{min} by 106% following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, and erlotinib can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Esomeprazole is an enantiomer of omeprazole. Co-administration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

7.1 Interactions with Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors [*see Warnings and Precautions (5.8), Clinical Pharmacology 12.2)*].

7.2 Tacrolimus

Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

7.3 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted [*see Warnings and Precautions (5.9)*].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with NEXIUM in pregnant women. Esomeprazole is the s-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use.

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 57 times and 35 times, respectively, an oral human dose of 40 mg. However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 33.6 times an oral human dose of 40 mg *(see Animal Data)*. Because of the observed effect at high doses of esomeprazole magnesium on developing bone in rat studies, NEXIUM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2 receptor antagonists or other controls.

A population based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995-99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during

pregnancy. The number of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996-2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837, 317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H_2 blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Animal Data

Reproduction studies have been performed with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 57 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole magnesium.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 57 times an oral human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 33 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 16.8 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 33.6 times an oral human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg /kg/day (about 3.4 to 57 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 33.6 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

8.3 Nursing Mothers

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to

discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of NEXIUM I.V. for Injection have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis [*see Clinical Pharmacology, Pharmacokinetics (12.3)*]. However, effectiveness has not been established in patients less than 1 month of age.

1 month to 17 years of age

Use of NEXIUM I.V. for Injection in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis is supported by: a) results observed from a pharmacokinetic (PK) study on NEXIUM I.V. for Injection performed in pediatric patients, b) predictions from a population PK model comparing I.V. PK data between adult and pediatric patients, and c) relationship between exposure and pharmacodynamic results obtained from adult I.V. and pediatric oral data and d) PK results already included in the current approved labeling and from adequate and well-controlled studies that supported the approval of NEXIUM I.V. for Injection for adults.

Neonates 0 to 1 month of age

Following administration of NEXIUM I.V. in neonates the geometric mean (range) for CL was 0.17 L/h/kg (0.04 L/h/kg-0.32 L/h/kg).

The safety and effectiveness of NEXIUM I.V. in neonates have not been established.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 57 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of patients who received oral NEXIUM in clinical trials, 1,459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other

reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

For adult patients with GERD, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). For patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded [*see Dosage and Administration (2), Clinical Pharmacology (12.3)*].

For adult patients with bleeding gastric or duodenal ulcers and liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For adult patients with mild to moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For adult patients with severe liver impairment (Child Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded [*see Dosage and Administration (2.2), Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

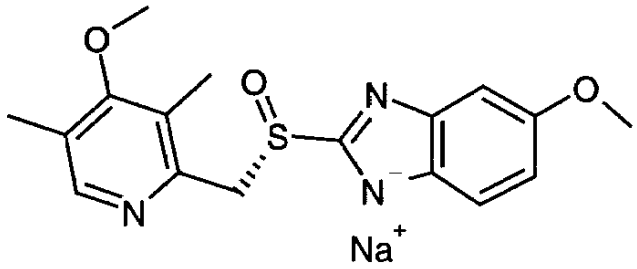
The minimum lethal dose of esomeprazole sodium in rats after bolus administration was 310 mg/kg (about 62 times the human dose on a body surface area basis). The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia and intermittent clonic convulsions.

The symptoms described in connection with deliberate NEXIUM overdose (limited experience of doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and intravenous doses of 308 mg of esomeprazole over 24 hours were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - ADVERSE REACTIONS). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

11 DESCRIPTION

The active ingredient in NEXIUM® I.V. (esomeprazole sodium) for Injection is (*S*)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1 *H*-benzimidazole sodium, a proton pump inhibitor that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is $C_{17}H_{18}N_3O_3SNa$ with molecular weight of 367.4 g/mol (sodium salt) and 345.4 g/mol (parent compound). Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%). The structural formula is:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers of

omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

12.2 Pharmacodynamics

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 subjects were included in the study.

Table 4

Effect of NEXIUM I.V. for Injection on Intragastric pH on Day 5

	Esomeprazole 20 mg (n=22)	Esomeprazole 40 mg (n=38)
% Time Gastric pH>4	49.5	66.2
(95% CI)	41.9-57.2	62.4-70.0

Gastric pH was measured over a 24-hour period

In a study in *H. pylori* negative healthy Caucasian volunteers (n =24), the % time over 24 hours (95 % CI) when intragastric pH was > 6 and > 7 was 52.3 % (40.3 – 64.4) and 4.8 % (1.8 – 7.8), respectively during administration of esomeprazole as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours.

In a study in *H. pylori* positive and *H. pylori* negative healthy Chinese subjects (overall n = 19), the % time over 24 hours (95 % CI) when intragastric pH was > 6 and > 7 was 53 % (45.6 – 60.3) and 15.1 % (9.5 – 20.7) in the overall study population during administration of esomeprazole as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours. When comparing *H. pylori* positive (n =8) *vs.* negative (n =11) subjects, the percentage of time in a 24 h period with

intragastric pH > 6 [59 % vs. 47 %] and with pH > 7 [17 % vs. 11 %] tended to be larger in the *H. pylori* positive subjects.

Serum Gastrin Effects

In oral studies, the effect of NEXIUM on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors.

Enterochromaffin-like (ECL) Cell Effects

There are no data available on the effects of intravenous esomeprazole on ECL cells.

In 24-month carcinogenicity studies of oral omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals [*see Nonclinical Toxicology, (13.1)*]. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients treated orally with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with NEXIUM (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

NEXIUM had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of NEXIUM on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone,

cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

12.3 Pharmacokinetics

Absorption

The pharmacokinetic profile of NEXIUM I.V. for Injection 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. for Injection by constant rate over 30 minutes for five days. The results are shown in the following table:

Table 5

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)

During administration of esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours (for a total of 24 hours) in healthy volunteers (n = 24), esomeprazole PK parameters [geometric mean value (95 % CI)] were as follows: AUC_t 111.1 μmol*h/L (100.5-122.7 μmol*h/L), C_{max} 15.0 μmol/L (13.5-16.6 μmol/L), and steady state plasma concentration (C_{ss}) 3.9 μmol/L (3.5-4.5 μmol/L).

In a Caucasian healthy volunteer study evaluating esomeprazole 80 mg over 30 minutes, followed by 8 mg/h over 23.5 h, systemic esomeprazole exposures were modestly higher (~ 17 %) in the CYP2C19 intermediate metabolizers (IM; n = 6) compared to extensive metabolizers (EM; n = 17) of CYP2C19. Similar PK differences were noted across these genotypes in a Chinese healthy volunteer study that included 7 EMs and 11 IMs. There is very limited PK information for poor metabolizers (PM) from these studies.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. Esomeprazole is completely eliminated from plasma, and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous esomeprazole is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous esomeprazole. During administration of esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours plasma clearance (CL) is approximately 5.9 to 7.2 L/h.

Concomitant Use with Clopidogrel

Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

Specific Populations

Investigation of age, gender, race, renal, and hepatic impairment and metabolizer status has been made previously with oral esomeprazole. The pharmacokinetics of esomeprazole is not expected to be affected differently by intrinsic or extrinsic factors after intravenous administration compared to oral administration. The same recommendations for dose adjustment in special populations are suggested for intravenous esomeprazole as for oral esomeprazole.

Geriatric

In oral studies, the AUC and C_{max} 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

In a randomized, open-label, multi-national, repeated dose study, esomeprazole PK was evaluated following a once-daily 3-minute injection in a total of 50 pediatric patients 0 to 17 years old, inclusive. Esomeprazole plasma AUC values for 20 mg NEXIUM IV were 183% and 60% higher in pediatric patients aged 6 – 11 years and 12 –17 years respectively compared to adults given 20 mg. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 0.5 mg/kg once-daily for pediatric patients 1-11 months of age, 10 mg for pediatric patients 1-17 years with body weight $\leq$55 kg, and 20 mg for pediatric patients 1-17 years with body $\geq$55 kg would achieve comparable steady-state plasma exposures (AUC_{0-24}) to those observed in adult patients administered 20 mg of NEXIUM I.V. once every 24 hours. Further, increasing the infusion duration from 3 minutes to 10 minutes or 30 minutes was predicted to produce steady-state C_{max} values that were comparable to those observed in adult patients at the 40 mg and 20 mg NEXIUM I.V. doses.

Gender

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

Hepatic Impairment

In oral studies, the steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh Class A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver

function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. 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 maximum dose of 20 mg once daily should not be exceeded [*see Dosage and Administration (2), Use in Specific Populations (8.6)*].

There are no pharmacokinetic data available for esomeprazole administered as continuous intravenous administration in patients with liver impairment. The pharmacokinetics of omeprazole 80 mg over 30 minutes, followed by 8 mg/h over 47.5 hours in patients with mild (Child Pugh Class A; n=5), moderate (Child Pugh Class B; n=4) and severe (Child Pugh Class C; n=3) liver impairment were compared to those obtained in 24 male and female healthy volunteers. In patients with mild and moderate liver impairment, omeprazole clearance and steady state plasma concentration was approximately 35% lower and 50% higher, respectively, than in healthy volunteers. In patients with severe liver impairment, the omeprazole clearance was 50% of that in healthy volunteers and the steady state plasma concentration was double that in healthy volunteers.

For adult patients with bleeding gastric or duodenal ulcers and liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For adult patients with mild to moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For adult patients with severe liver impairment (Child Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded [*see Dosage and Administration (2.2), Use in Specific Populations (8.6)*.

Renal Impairment

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

12.4 Microbiology

Effects on Gastrointestinal Microbial Ecology

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton

pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also *Clostridium difficile*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0, and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week oral mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

13.2 Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole [*see Pregnancy, Animal Data (8.1)]*.

Juvenile Animal Study

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg /kg/day (about 17 to 57 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg /kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

14.1 Acid Suppression in Gastroesophageal Reflux Disease (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 Asian, 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 studies. Basal acid output (BAO) and maximal acid output (MAO) were determined 22-24 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 mcg/kg of pentagastrin.

In these studies, after 10 days of once daily administration, the intravenous dosage forms of NEXIUM 20 mg and 40 mg were similar to the corresponding oral dosage forms in their ability to suppress BAO and MAO in these GERD patients (see table below).

There were no major changes in acid suppression when switching between intravenous and oral dosage forms.

Table 6

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)

14.2 Bleeding Gastric or Duodenal Ulcers

In a randomized, double blind, placebo-controlled clinical study, 764 patients were randomized to receive NEXIUM I.V. for Injection (n=375) or placebo (n=389). The population was 18 to 98 years old; 68% Male, 87% Caucasian, 1% Black, 7% Asian, 4% Other, who presented with endoscopically confirmed gastric or duodenal ulcer bleeding. Following endoscopic hemostasis, patients were randomized to either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour for a total of 72 hours or to placebo for 72 hours. After the initial 72-hour period, all patients received oral proton pump inhibitor (PPI) for 27 days. The occurrence of rebleeding within 3 days of randomization was 5.9% in the NEXIUM I.V. treated group compared to 10.3% for the placebo group (treatment difference -4.4%; 95% confidence interval: -8.3%, -0.6%; p=0.03). This treatment difference was similar to that observed at Day 7 and Day 30, during which all patients were receiving an oral PPI.

A randomized, double blind, placebo-controlled single-center study conducted in Hong Kong also demonstrated a reduction compared to placebo in the risk of rebleeding within 72 hours in patients with bleeding gastric or duodenal ulcers who received racemic omeprazole, 50% of which is the S-enantiomer esomeprazole.

16 HOW SUPPLIED/STORAGE AND HANDLING

NEXIUM I.V. for Injection is supplied as a freeze-dried powder containing 20 mg or 40 mg of esomeprazole per single-use vial.

NDC 0186-6020-01 one carton containing 10 vials of NEXIUM I.V. for Injection (each vial contains 20 mg of esomeprazole).

NDC 0186-6040-01 one carton containing 10 vials of NEXIUM I.V. for Injection (each vial contains 40 mg of esomeprazole).

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]. Protect from light. Store in carton until time of use.

Following reconstitution and administration, discard any unused portion of esomeprazole solution.

17 PATIENT COUNSELING INFORMATION

- Advise patients to let their healthcare provider know if they are taking, or begin taking other medications, because NEXIUM can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [*see Drug Interactions (7)*].

- Let patients know that antacids may be used while taking NEXIUM.

- Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [*see Warnings and Precautions (5.3)*].

- Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany

as these may be signs of hypomagnesemia [*see Warnings and Precautions (5.6)*].

NEXIUM is a registered trademark of the AstraZeneca group of companies.

Manufactured for:
AstraZeneca LP
Wilmington, DE 19850

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA # **Supplement #**	21-689 S-014/ Complete Response Submission
Applicant Name	Astra Zeneca LP
Date of Submission	December 14, 2012
PDUFA Goal Date	September 14, 2013 (reflects 3 month extension)
Proprietary Name / **Established (USAN) Name**	Nexium esomeprazole sodium for injection
Dosage Forms / Strength	Lyophilized powder for Injection/ 20 and 40 mg vials
Proposed Indication	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review Second Cycle	Lynne Yao, MD
CDTL Review Third Cycle	Robert Fiorentino, MD
Original Submission Clinical Review	Anil Nayyar, MD/Hugo Gallo-Torres/PhD, MD
Second Cycle Clinical Review	Erica Wynn, MD/Lynne Yao, MD
Third Cycle Clinical Review	Aisha Peterson Johnson, MD xXX/ Robert Fiorentino, MD
Original Statistical Review	Sonia Castilio, PhD/Mike Welch, PhD
Second Cycle Statistical Review	Lisa Kammerman, PhD/ Mike Welch, PhD
Third Cycle Statistical Review	Lisa Kammerman, PhD/ Mike Welch, PhD

Third Cycle Clinical Pharmacology Review (including Pharmacometrics)	Sandhya Apparaju, PhD/Sue-Chi Lee, PhD Kevin Krudys, PhD/Nitin Mehrotra, PhD
Pharmacology/Toxicology	Sushanta Chakder, PhD
PMHS	Carrie Ceresa, Pharm D, MPH/ Jeanine Best, MSN, RN, PNP/Alyson Karesh, MD/Hari Sachs, MD/Lynne Yao, MD
DMEPA	Denise Baugh, PharmD, BCPS/Lubna Merchant, PharmD, MS/Scott Dallas, RPh
OSE	Thang La, PharmD, BCPS/Eileen Wu, PharmDu, MPH
OPDP	Meeta Patel, PharmD
SEALD	Jeanne M. Delasko/Laurie Burke

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
PMHS=Pediatric and Maternal Health Staff
OPDP=Office of Prescription Drug Promotion
SEALD=Study Endpoints and Labeling Development

APPEARS THIS WAY ON ORIGINAL

Division Director Review

1. Introduction

This is the third review cycle for this NDA supplement, which was originally submitted in May 29, 2008. This supplement proposes a new indication, which is associated with a new dose and administration schedule. Nexium® IV (esomeprazole sodium injection) was originally approved in 2005 for short-term treatment (up to 10 days) of GERD in patients with a history of erosive esophagitis, as an alternative to oral therapy when therapy with Nexium Delayed-Release Capsules is not possible or appropriate. The label states that "when oral therapy is possible or appropriate, intravenous therapy with Nexium IV for Injection should be discontinued and the therapy should be continued orally." The approved doses are either 20 or 40 mg once daily by intravenous injection (over no less than 3 minutes) or intravenous infusion (10-30 minutes). The new proposed indication is: "Nexium IV for Injection is indicated for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers". The dose proposed is 80 mg administered as an intravenous infusion over 30 minutes, followed by a continuous infusion of 8 mg/hour given over 3 days, (b) (4) he original supplement submission was supported by a single adequate and well controlled trial. The FDA issued Complete Response letters after each of the prior two review cycles.

The hypothesis that high doses of Nexium IV after therapeutic endoscopy will reduce the risk of rebleed is based on *in vitro* study reports of the impact of acidic pH on clot stability and hemostasis. Green WF, et. al. published a series of *in vitro* studies that evaluated the impact hydrogen ion concentration changes on the soluble and cellular coagulation systems.(Green WR, et al. Gastroenterology, 1978 Jan; 74(1):38-43.) (b) (4) (b) (4) The authors reported that coagulation was "extremely sensitive to relatively minor increases in hydrogen ion concentration. All studies became abnormal at pH 6.8." At pH 6.4, polymerization of fibrinogen was prolonged and platelet aggregation was reduced by >50%. At a pH of 5.4, platelet aggregation and plasma coagulation were nearly completely inhibited, which suggests that the target pH to achieve with Nexium IV should far exceed pH 6.0. Available PD data (gastric pH), summarized in the table below, indicate Nexium IV results in a pH below the target range for a substantial portion of the first 24 hour period after it is initiated. In addition, a "by-subject" responder analysis revealed that <60% of subjects administered the dose proposed for labeling sustained a pH>6 for at least 1 hour in the 24 hour period. The lack of granularity in the pH breakdown in this table in the region between 6 and 7 should be considered, in light of the Green, et al data, which suggest that substantive changes in clotting occur in the range of pH 6.4 to 6.8.

Table 1: Estimates of mean percentage of time with intragastric pH>4, pH>6, pH>7 with IV infusion of esomeprazole at 5 different infusion combinations in healthy subjects;24 hour period by dose level (adapted from Dr. Tien-Mien Chen's Clinical Pharmacology original submission review)

	Esomeprazole Regimen	Estimate
pH>4 (0-24)	40 mg + 8 mg/h	82%
	80 mg + 4 mg/h	80%
	80 mg + 8 mg/h	90%
	120 mg (30 min)+ 8 mg/h	84%
pH>6 (**0-3hr**)	40 mg + 8 mg/h	25%
	80 mg + 4 mg/h	35%
	80 mg + 8 mg/h	46%
	120 mg (30 min)+ 8 mg/h	46%
pH>6 (**0-24h**)	40 mg + 8 mg/h	46%
	80 mg + 4 mg/h	44%
	80 mg + 8 mg/h	**52%**
	120 mg (30 min)+ 8 mg/h	49%
pH>7 (0-24h)	40 mg + 8 mg/h	2%
	80 mg + 4 mg/h	4%
	80 mg + 8 mg/h	5%
	120 mg (30 min)+ 8 mg/h	4%

In a second PK/PD study that evaluated esomeprazole 80 mg + 8 mg/h infusion vs. omeprazole in healthy subjects, again with a 24 hour evaluation period, the proportion of time in which the pH was > 6 was 45% (39, 51). This is similar to the findings of the study summarized in the table above, although numerically lower.

As seen in the following table from my original review, most of the rebleeds in the esomeprazole arm of the single efficacy trial submitted in the original review cycle, D961DC00001 (referred to herein as Study 001), occurred in the first 24 hours. The majority of additional rebleeds on the placebo arm occurred in the subsequent 12 hours beyond 24 hours. In contrast to the 11 additional rebleeds on the placebo arm in that follow-on 12 hour period, there was only 1 additional rebleed in the esomeprazole arm.

Table 2 Proportions of Patients with Rebleeding Events by Time Period in Trial D961DC00001

	Esomeprazole	Placebo
N	375	389
Number of patients with Rebleed in the overall 72 hour period	22 (5.9%)*	40 (10.3%)
Number of patients with Rebleed in the first 24 hours	17 (4.5%)	21 (5.4%)
Number of patients with Rebleed from >24hours to 72 hours.	5 (1.3%)	19 (4.9%)

*percentage of patients in the study arm that experienced rebleed

The first cycle CR letter questioned whether the appropriate dose had been identified, based on these PD findings. The applicant responded in the second cycle submission that these studies were conducted in healthy volunteers and that a greater effect would be anticipated in patients with peptic ulcer disease, citing literature that reported basal gastric pH is higher in patients with H. pylori. A publication by Gillen, et al 1999 (H. pylori infection potentiates the inhibition of gastric acid secretion by omeprazole. Gut. 1999; 468-475), reports a statistically significant difference in median fasting gastric pH between H. pylori positive and negative subjects during omeprazole treatment, respectively: 7.95 (2.7-8.3) vs. 3.75 (1.7-8.5), $p<0.002$. Pre-omeprazole basal fasting pH was similar between groups: 1.6 (1.2-2.9) vs. 1.6 (1.2-7.2). However, the Clinical reviewers in the second cycle were concerned about the generalizability of the H. pylori population to the general peptic ulcer disease population, since not all ulcers are caused by H. pylori. Furthermore, they wondered whether the relative efficacy observed in the Chinese omeprazole study ["the Lau Study"; Lau, et al. 2000; 343(5):310-316] submitted in the second cycle, compared to Study 001, might also be related to a greater PD effect in Chinese patients (pH far exceeding 6), due to lower parietal cell mass in Asians and a possible interaction with H.pylori infections. In the current(third) cycle submission, the applicant attempted to allay these population concerns.

The Clinical reviewer, Dr. Johnson, has addressed each of the second cycle CR issues in her review, issue by issue, and I generally agree with her summary conclusions. The CDTL has recommended approval, noting that the esomeprazole and omeprazole studies submitted for review "suggest….a measureable treatment advantage compared to placebo, across studies and various subgroups." In addition, he was persuaded that additional placebo-controlled trials would be impracticable or unfeasible. I concur. The presentation of this application at a CDER Regulatory Briefing and the panel's discussion was key to my decision to approve this supplemental NDA in this review cycle. My review will focus on key elements of the current submission, input obtained from the Regulatory Briefing, and major efficacy and safety labeling issues.

The approval action of this NDA was delayed as FDA requested safety labeling changes (SLC) for all esomeprazole and omeprazole products, under the Food and Drug Administration Amendments Act (FDAAA). Ultimately, revision of the Nexium IV product label (for the currently marketed product, approved for short term treatment of erosive esophagitis) was approved on February 25, 2014. The full prescribing sections of the label impacted were:

Section 8.1 Pregnancy, Section 8.4 Pediatric Use, and Section 13.2 Animal Toxicology and/or Pharmacology. (See Section 4 Nonclinical Pharmacology/Toxicology of this review, below.)

2. Background

In this section, I have summarized the contents of the Complete Response (CR) letters issued in the previous two review cycles.

First cycle. In the first review cycle, the applicant submitted a single randomized, placebo controlled clinical trial to support the new indication. In addition, two PK/PD studies (24 hours in duration and conducted in healthy volunteers) were submitted as evidence that the dosing regimen achieved gastric pH ≥ 6. The November 26, 2008 CR letter included the following deficiencies:

> "Our review finds that the primary efficacy results for this non-U.S. single study do not provide substantial evidence of efficacy. For a single study to stand alone as substantial evidence of efficacy, it should demonstrate highly statistically significant and clinically meaningful results. Consistency should be demonstrated across subgroups and secondary endpoints. The study should also show internal consistency in demonstrating the treatment effect across study centers. The single study that you have submitted does not meet these criteria for providing substantial evidence for the following reasons:
>
> 1. Highly statistically significant results were not demonstrated. Although your protocol specified analysis showed a reduction of 4.4% in the rate of clinically significant rebleeding within 72 hours after hemostasis compared to placebo (p= .03), that reduction was not highly significant, e.g., p < .001. In addition, the observed outcome was not found to be robust when subjected to the sensitivity analyses listed below:
>   a. It is appropriate to account for country-to-country variation, so the protocol specified analysis was further stratified by country. This resulted in an insignificant treatment effect (p=0.06), although the absolute reduction in rebleeding remained 4.4%.
>   b. When the protocol specified analysis was further stratified (retaining stratification by country in the model) using Forrest classification as four separate categories (Forrest Ia, Ib, IIa, and IIb) instead of two (Forrest I and Forrest II), an insignificant treatment effect was observed (p=0.11). The absolute reduction in rebleeding remained 4.4%. We believe the appropriate adjustment for Forrest classification should be by each individual Forrest category because each category has a different risk of rebleeding events. Even if this stratified analysis was conducted without incorporation of country in the model, the p-value still shifted to a less persuasive value of p= 0.05.
>
> 2. The study lacked internal consistency across study centers. Despite similar patient demographics and disease characteristics, marked variability in the incidence of

rebleeding, i.e., the primary endpoint, and treatment effect was observed in different countries and among leading centers. The treatment effect varied widely from -25% to +12% by country and from -31% to +20% in the larger centers that enrolled more than 10 patients. There is no clear explanation for why this occurred, although physician expertise and standards of care may have played a role.

3. The study lacked internal consistency in demonstrating the treatment effect in the important subgroup of patients aged 65 and older. In this subgroup, the proportion of patients that experienced rebleeding in the first 72 hours was 6.2% on the esomeprazole arm and 8.4% on the placebo arm. In contrast, in patients aged less than 65 the proportion of patients that experienced rebleeding in the esomeprazole arm was 5.5%, while on the placebo arm the proportion was 11.9%.

4. The study lacked internal consistency in demonstrating the treatment effect in important secondary efficacy outcomes that were evaluated in the first 72 hours. The proportion of patients who underwent surgery for rebleeding was a pre-specified secondary endpoint and the observed outcome for this endpoint was similar between study arms. This analysis was not found to be statistically significant, p = 0.31. The secondary analysis comparing number of blood units transfused in the first 72 hours demonstrated a lower number of units infused on the esomeprazole arm (492) relative to placebo (738), p=0.05, and the secondary analysis that compared the proportion of patients who required endoscopic retreatment in the first 72 hours demonstrated a decreased rate of endoscopic retreatment (4.3%) on the esomeprazole arm relative to placebo (8.2%), p=0.02. Although the secondary analyses of number of blood units transfused and endoscopic retreatment appear nominally significant, there was no pre-specified plan to adjust for multiple comparisons. Taking a conservative approach, the p-values are not significant after a Bonferroni adjustment to account for multiple comparisons.

5. One center, Site 0102 in the Netherlands reported the largest treatment effect in all centers that participated in this study, -31% rebleeding events, favoring the esomeprazole arm of the study. The investigator from this site, Dr. Ernest J. Kuipers, MD, Ph.D., reported having accepted significant payments from Astra Zeneca. When we conducted a sensitivity analysis to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, we found that the overall treatment effect observed in the study decreased to -3.73% (95% CI=-7.67, 0.10) and the p-value shifted to 0.06.

6. We identified additional study design and conduct concerns that further limit the study's ability to provide persuasive evidence that esomeprazole is effective for the proposed indication. These issues are listed below:

a. Endoscopic epinephrine injection is currently not an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers. More than a third of the patients in this study were treated with endoscopic epinephrine injection as single therapy. This draws into question the applicability of the outcome observed in this trial to current care of patients with an upper gastrointestinal bleed from a gastric or duodenal ulcer in the United States today.

b. Although the inclusion criteria excluded patients with more than a single ulcer, a substantial proportion of the randomized patients had multiple ulcers and there was an imbalance between study arms in this prognostic factor that favored the esomeprazole arm. Fewer patients on the esomeprazole arm had multiple ulcers, 13.6%, relative to the placebo arm, 18.5%. This raises concerns regarding the study conduct in this international trial.

c. Despite randomization, small imbalances in important prognostic factors were observed between the two study arms. The imbalances favored the esomeprazole treatment arm. These prognostic factors included Grade 1a stigmata of risk of rebleeding (esomeprazole=7.5%, placebo=10.3%) and large ulcers (esomeprazole=7.7%, placebo=10.3%).

d. The lack of an exclusion criterion for intravenous administration of a proton pump inhibitor within 24 hours prior to enrollment is a potential confounding factor for the observed efficacy outcome. Although this was addressed with an amendment during the course of the study, the amendment only excluded patients who had received intravenous doses greater than 40 mg within 24 hours prior to enrollment.

7. There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment. These deficiencies cannot be addressed adequately through additional analyses of the data in hand."

To address the deficiencies, the letter stated "further clinical data from at least one additional adequate and well controlled study that provides persuasive and consistent evidence of efficacy will be needed." Specific recommendations included:

1. Conduct at least one additional, adequate, and well-controlled study to demonstrate the proposed clinical benefit of Nexium IV for (b) (4) The study should include some U.S.

centers and the study design and analysis plan should address the deficiencies described in this letter above.

2. You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two PK/PD studies you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3 study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment. For the reasons stated above, conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data.

3. Study site 0102 in the Netherlands, which reported the greatest treatment effect in the major randomized, placebo controlled trial that you submitted for our review, will need to be inspected by the Division of Scientific Investigations (DSI) because Dr. Ernst J. Kuipers, MD, PhD, the investigator at that site, has disclosed that he has accepted significant payments from Astra Zeneca. This inspection would be requested as part of our review of any future submission that includes this study as a critical component of establishing the efficacy of Nexium IV for the proposed indication. A recommendation from the DSI inspector that the data from this site can be used for determining the efficacy and safety of Nexium IV will be needed if this study will be used to support a future marketing application. This assessment will be an important component of a future determination of whether this study can stand as one of two adequate and well controlled trials for the proposed indication.

4. Conduct a pharmacokinetic study in a sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.

5. Submit a pediatric plan with your complete response.

The applicant met with the Division on June 11, 2009 to discuss a path forward for the application. As stated in the CDTL review, "The Division rejected the applicant's proposal to (b) (4) The Division also stated that the study data from a published study by Lau, et. al., could be

included but would be considered as supportive only because it was a single center trial and was not conducted using esomeprazole. The Division proposed that one path forward would be for the applicant to review and reanalyze the data from previously conducted well-controlled trials using esomeprazole. The applicant agreed to propose and submit a preliminary response to the CR letter for review."

In response to the applicant's July 14, 2009 proposal for information that would be included in a resubmission, the Division sent a December 3, 2009 advice letter, which is summarized in the second cycle CDTL review. The Division indicated its willingness to review the data from previously conducted omeprazole studies as supportive evidence of efficacy.

Second Cycle. The applicant submitted a Complete Response on September 15, 2011. It contained three randomized controlled trials (Study 840, Study 841, and "the Lau Trial") in which intravenous omeprazole was compared to placebo. Another Complete Response letter was issued at the conclusion of the second review cycle, on June 16, 2011. The CR issues were:

> "The additional data submitted do not provide substantial evidence of efficacy of your product for the proposed indication for the reasons listed below:
>
> 1. Trials I-840 and I-841 differ from the efficacy trial, D961DC00001, submitted in the sNDA on May 29, 2008, in several important ways, including the endoscopic treatments administered and the primary endpoints evaluated. Therefore, these trials were not adequately designed to support the proposed indication.
>
> 2. When patients from trial I-840 and I-841 are matched to the population enrolled in the original efficacy trial, D961DC00001, based on enrollment criteria, too few patients remain to provide adequate power to show a statistically significant treatment effect. Of the combined total of 607 patients enrolled in the studies, only 52 patients met the enrollment criteria of D961DC00001. The proportion of omeprazole-treated patients in this subgroup who had a rebleeding event within 72 hours was 13.6% (3/22). Although this proportion was lower than that observed in the placebo-treated patients, 23.3% (7/30), the difference was not statistically significant (p=0.49, Fisher's Exact Test).
>
> 3. The clinical trial reported by Lau, et al. is comparable in design to D961DC00001 and the trial provides evidence of efficacy of intravenous omeprazole for the proposed indication. However, the study was conducted at a single center in Hong Kong and the population enrolled was ethnically homogeneous. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of H. pylori infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which could have contributed to the larger treatment effect observed in the Lau trial. Therefore, the ability to generalize the results of this trial to the U.S. population is limited.

4. There is a substantive difference in the rebleeding rate in the placebo group (20%) of the trial reported by Lau, et al. compared to D961DC00001 (10%). It is not clear why the rebleeding rate in the Lau, et al. trial is double the rate observed in D961DC00001. It may be partially explained by the differences in Asian populations described in #3 above, or by differences in factors such as age and baseline health status, which may impact on the risk of rebleeding. Additionally, operational factors such as differences in endoscopic technique may affect the risk of rebleeding. This inconsistency in rebleeding rate between the trials also raises questions about the ability to generalize the results of this trial to the U.S. population.

5. There were substantive differences in the efficacy outcomes within important subgroups in the clinical trial reported by Lau, et al. compared to D961DC00001. These inconsistencies raise questions about the reproducibility of the efficacy outcome.

    a. In the subgroup of patients 65 years of age and older, the decrease in proportion of patients with rebleeding within 72 hours in the esomeprazole arm relative to placebo was 2.2% in D961DC00001. In contrast, the decrease in the same subgroup treated with omeprazole relative to placebo in the trial reported by Lau, et al. was 19.7%.

    b. In the subgroup of patients with Forrest Ib classification, there were similar proportions of patients with rebleeding within 72 hours in the esomeprazole and placebo arms in D961DC00001 (a 0.5% difference). In contrast, there was a decrease in the proportion of patients with rebleeding within 72 hours in the omeprazole arm relative to placebo of 10% in the trial reported by Lau, et al.

6. The information from observational studies and literature reviews of intravenous esomeprazole and omeprazole were not considered adequate to constitute primary evidence of the efficacy of the product for the proposed indication.

7. We have reviewed your responses to the deficiencies cited in the November 26, 2008, Complete Response Letter regarding trial D961DC00001. Your responses do not change our conclusion that D961DC00001, as a single adequate and well-controlled trial, does not provide sufficient evidence to support the proposed indication. The following comments are responses to specific issues raised in your resubmission:

    a. Your assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers for D961DC00001 is not persuasive. The Breslow-Day test is not a powerful test for detecting lack of homogeneity. For this reason, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables further limit the usefulness of the test.

b. A Division of Good Clinical Practice Compliance inspection was performed at site 0102 in the Netherlands because Dr. Ernst J. Kuipers, MD, PhD, the principal investigator at that site, disclosed that he had accepted significant payments from AstraZeneca. The inspection found that the data from this site appear reliable. Nevertheless, as stated in the Complete Response letter, the large magnitude of treatment effect observed at this site, and the impact this single site had on the overall efficacy of the trial, suggest that the efficacy results of DC961DC00001are not robust.

c. You contend that the suboptimal pharmacodynamic (PD) effects of esomeprazole on gastric pH observed in the PK/PD studies submitted in the sNDA on May 29, 2008, can be attributed to the fact that the studies were performed in Helicobacter pylori negative healthy subjects, i.e., subjects in whom it would be more difficult to suppress intragastric acidity, and that a pH of 6 would have been more consistently achieved if the population studied had had peptic ulcer disease. We disagree because this position assumes that all patients with peptic ulcer disease have H. pylori. Not all patients with peptic ulcer disease are H. pylori positive. The populations enrolled in the clinical trials you submitted to this NDA attest to this.

The applicant requested a formal dispute resolution on January 23, 2012, which was denied because the applicant had not requested a post-action meeting to discuss its concerns. In response to a meeting request, the Division and ODE III leadership met with the applicant on March 22, 2012. The applicant presented a plan to submit PK, PD and clinical data (H.pylori) to address the relevance of the Lau study to the US population. The possibility of presenting the application to an Advisory Committee was discussed. A subsequent meeting June 12, 2012 was held to discuss the applicant's proposed outline of the content of a Cycle 3 Complete response. The following day the applicant requested a six month extension of the one year response time for the complete response, and the Division concurred with the request.

3. CMC

There were no product quality issues cited in the Complete Response letters. The CMC reviewers did not review new data during this final review cycle.

4. Nonclinical Pharmacology/Toxicology

There were no nonclinical issues cited in the Complete Response letters. However, in this review cycle the nonclinical reviewers addressed whether there is nonclinical evidence of cardiovascular safety concerns at the exposure level achieved in humans with this new dosing regimen. I have summarized Dr. Chakder's review findings below. In addition, I have summarized the recent safety labeling changes (SLC) based on animal data that were made to the previously approved Nexium IV label, in response to FDA's request for a SLC for all esomeprazole and omeprazole products.

Cardiovascular safety. Dr. Sushanta Chakder submitted a review this cycle to summarize the nonclinical safety data available to support the higher infusional esomeprazole doses for the new indication. He wrote his review in response to clinical review questions regarding the higher cardiovascular event rate reported in one of the omeprazole studies submitted in support of this application (Study 841). He pointed to intravenous toxicity studies conducted in rats and dogs. To facilitate comparing exposures between the animals and humans, he noted the proposed esomeprazole dose, 80 mg IV infusion over 30 minutes followed by 8 mg/h continuous IV infusion for the next 71.5 hours, is approximately equivalent to a 4.5 mg/kg/24 hr in humans, on the first day of administration.

In rats, intravenous doses of 18 to 36 times the proposed continuous i.v. infusion daily clinical dose (3-6 times the proposed clinical dose, based on BSA), were well tolerated, as defined by no mortality, in two studies. In one study CNS effects, including CNS depression, rigidity, ataxia (at mid and high doses) and convulsions (high dose) were observed. Dr. Chakder informed me that the CNS effects were not durable and convulsions were limited to 1 male and 1 female in the high dose group (mid = 52 mg/kg in females and 86 mg/kg in males; high = 100 mg/kg in females and 160 mg/kg in males). Low dose without effect was 26 mg/kg in males and 48 mg/kg in females, which is 10x the clinical dose (based on the female dose).

In dogs, Dr. Chakder summarized the following nonclinical safety data:

1) Esomeprazole sodium administered by continuous intravenous infusion for 14 or 28 days at doses several fold higher than the proposed daily i.v. infusion dose was well tolerated by dogs.
2) A 2-week continuous IV infusion dog study conducted with dose levels of 120 and 240 mg/kg, was not associated with deaths or treatment-related adverse cardiovascular effects. These doses are about 27 and 54 times the proposed clinical IV dose (14 and 28 times the clinical dose, based on BSA).
3) A 1-month continuous infusion dog study exposed groups to vehicle or esomeprazole sodium at dose levels of 35, 86 and 170 mg/kg/day (10, 250 and 500 μmol/kg/day). Eight deaths occurred across the vehicle control and esomeprazole groups (2, 1, 2 and 3 animals sacrificed pre-terminally from the control, low, mid and high dose groups, respectively). The number of deaths was similar between the vehicle control group and each of the esomeprazole dose levels. No treatment-related effects on QTc parameters were observed. A slight decrease in heart rate was observed in males in Week 4. Thrombus formation in the lung, pleural inflammation, fibrosis and hemorrhage were observed in 0, 1, 1 and 2 males and 1, 1, 3 and 2 females from the control, low, mid and high dose groups, respectively. The 35 mg/kg/day dose was the highest tolerable dose, based on the pulmonary events, which is about 8 times the proposed daily IV clinical dose (4.2 times the clinical dose, based on BSA).

Recently approved Safety Labeling Changes based on animal data. .
The approval action of this NDA was delayed due to a request for safety labeling changes (SLC) for all esomeprazole and omeprazole products, based on new animal data that was considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. The request for SLC was issued by FDA on October 10, 2013. The letter stated "we have become

aware of animal data indicating that the use of esomeprazole in pregnancy may cause fetal harm. Changes in bone morphology and physeal dysplasia were observed in pre- and postnatal developmental toxicity studies in rats." AstraZeneca responded on November 8, 2013. Three Labeling Discussion Extension letters were issued: one on November 27, 2013, one on December 30, 2013, and one on January 30, 2014. Ultimately, revisions of the Nexium IV product label (for the currently marketed product, approved for short term treatment of GERD with erosive esophagitis as an alternative to oral therapy when oral NEXIUM is not possible or appropriate) were approved on February 25, 2014. The full prescribing sections of the label impacted were: Section 8.1 Pregnancy, Section 8.4 Pediatric Use, and Section 13.2 Animal Toxicology and/or Pharmacology. The following labeling changes were made:

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Risk Summary
There are no adequate and well-controlled studies with NEXIUM in pregnant women. Esomeprazole is the s-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 57 times and 35 times, respectively, an oral human dose of 40 mg. However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 33.6 times an oral human dose of 40 mg (*see Animal Data*). Because of the observed effect at high doses of esomeprazole magnesium on developing bone in rat studies, NEXIUM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
Reproduction studies have been performed with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 57 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole magnesium.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 57 times an oral human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 33 times an oral human dose of 40mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg /kg/day (about 16.8 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at

doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 33.6 times an oral human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg /kg/day (about 3.4 to 57 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 33.6 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

8.4 Pediatric Use

Juvenile Animal Data
In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 57 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth [*see Nonclinical Toxicology (13.2)*].

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Reproduction Studies
Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole [*see Pregnancy, Animal Data (8.1)*.

Juvenile Animal Study
A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg /kg/day (about 17 to 57 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg /kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal

day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

5. Clinical Pharmacology

During the second cycle review, the Clinical Pharmacology reviewers determined the following:

1) The applicant had provided adequate information to bridge IV omeprazole and IV Nexium, to permit reliance upon the randomized, placebo controlled omeprazole studies as support for the outcomes observed in the single IV Nexium trial.
2) No further dose finding study is needed in the target population.
3) Although available data suggested esomeprazole Cmax is not impacted by hepatic impairment, the proposed post-loading infusion dose in hepatic impairment was inadequately supported. Modeling and simulation were recommended to "estimate the proper constant infusion rate" for patients with hepatic impairment.

Although the modeling and simulation data submitted in this review cycle to address dosing in hepatic impairment were not found to support the proposed dosing, the reviewers ultimately concluded dosing recommendations for hepatic impairment could be based on available data from an IV omeprazole hepatic impairment study. Esomeprazole and omeprazole PK/PD data established the necessary bridge for this approach. They concluded the Nexium IV infusional dose, after a loading dose of 80 mg infused over 30 minutes, should be 6 mg/h in patients with mild and moderate impairment, and 4 mg/h in severe hepatic impairment.

In this third review cycle, the applicant submitted PK and PD data to address efficacy issues included in the second cycle CR letter related to the generalizability of the efficacy outcomes observed in the Chinese population studied in "the Lau Trial" to the US population. **Items #3 and #4** of the CR letter delineate specific issues that formed the basis for concerns regarding the generalizability. (See Section 2 Background of this review.) In addition, **Item #7(c)** questioned the validity of the applicant's position that the PD effects (and hence treatment impact) of esomeprazole would be expected to be greater in patients than in H. pylori negative healthy volunteers. The Clinical Pharmacology reviewers were critically involved in the review of this information, including:

1) Analyses of impact of CYP2C19 metabolism status (extensive vs. intermediate vs. poor) on PD (pH), since the Asian population has a higher proportion of persons who are CYP2C19 poor metabolizers.
2) Analyses of impact of H.pylori status on PD/PK.

Refer to the Clinical Pharmacology, Clinical and CDTL reviews for the reviewers' excellent summaries of these analyses. Unfortunately, the ability to draw firm conclusions regarding the comparability of the two populations based on the data submitted from a Chinese PK/PD study

and a Caucasian PK/PD study were limited by: 1) both studies were conducted in "healthy" volunteers (non-GI bleeders), and 2) the Caucasian trial did not include H.pylori positive subjects, which limited exploration of the impact of H.pylori status to within Asian subjects, and did not permit impact comparisons between populations.

PD Impact of H. pylori status. Study D961500007, referred to as "Chinese PK/PD Study", was a single dose, randomized crossover study in 20 Chinese healthy volunteers. Nine were H.pylori positive, 7 were extensive metabolizers, 11 were intermediate metabolizers and 2 were poor metabolizers. IV esomeprazole was administered in 5 different regimens, including the regimen proposed for the new indication (80 mg over 30 min, followed by 8 mg/h); however, the treatment period for each regimen was limited to 24 hours. The PD parameters evaluated were percentage of time over 24 hours in which pH exceeded 4, 5, 6, and 7. In addition, percentage time that the pH exceeded 6 in the first 3 hours of dosing was assessed.

Impact of H.pylori status on PD was limited to this intra-study exploration of the Chinese PK/PD data. The following table, reproduced from the third cycle Clinical Pharmacology review, summarizes the PD data by H.pylori status (for the proposed dose). A trend for larger PD outcomes in H.pylori positive Chinese "healthy" volunteers and apparent greater PD variability in the H.pylori negative subjects was noted. The small sample size limits the ability to draw firm conclusions regarding impact of H.pylori status on pH in Chinese healthy subjects. The greatest numerical difference between H.pylori status groups is in "rapidity" of achieving pH>6 within the 24 hour period, as seen in the row "% time when pH>6 over first 3 hours." A higher proportion of H.pylori positive subjects achieve a pH >6 within 3 hours of dose. The trends appear consistent across each of the analyses. There was a numerically higher percentage of time with pH >7 and a higher mean pH in the H.pylori positive patients.

Table 3. Pharmacodynamic Effects of the Proposed Nexium Dosing Regimen in H. pylori positive vs. H. pylori negative Chinese Healthy Subjects

Proposed Regimen E	*H. pylori* Positive (n = 9)	*H. pylori* Negative (n = 11)
% time when pH >4 over 24 h	98.37 ± 0.54	93.69 ± 5.05
% time when pH >6 over 24 h	**59.12 ± 9.56**	**46.7 ± 20.4**
% time when pH> 6 over first 3 h	82.77 ± 5.01	49.4 ± 33.6
% time when pH>7 over 24 h	18.75 ± 9.26	11.14 ± 8.56
Mean pH over 24 h	6.25 ± 0.23	5.84 ± 0.61

Impact of CYP2C19 status. Cross study comparisons of impact of CYP2C19 metabolism status on PK and PD outcomes, between the Chinese and Caucasian healthy volunteer studies, led the reviewers to conclude the two populations (Chinese and Caucasian) were generally comparable, although there was a trend for a higher percentage of time with pH >7 in Chinese subjects. There were some PD differences across gentoypes (EM vs. IM); however, the reviewers noted that PK concentrations "may not explain the PD differences due to general

lack of E-R correlation". Small sample size and high variability limited conclusions. The third boxplot for each population in the two figures below, reproduced from the Clinical Pharmacology review, illustrate the apparent population differences (Asian/ Caucasian) in percentage time pH >7.

Figure 1: Chinese PD study: PD vs. Metabolizer Status

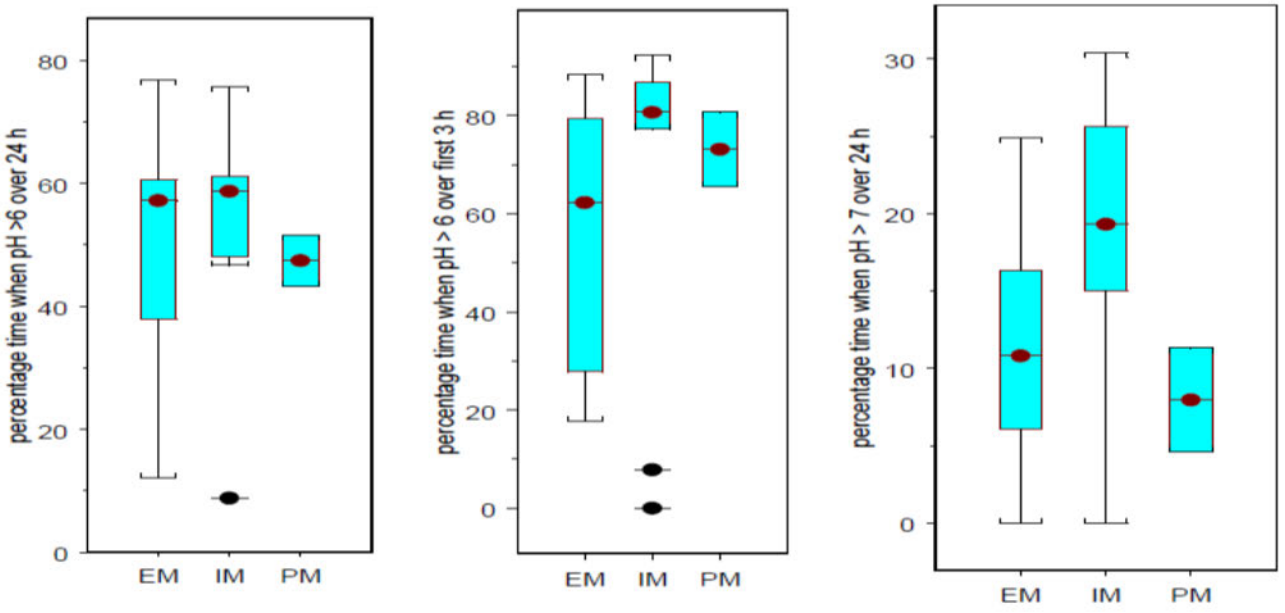
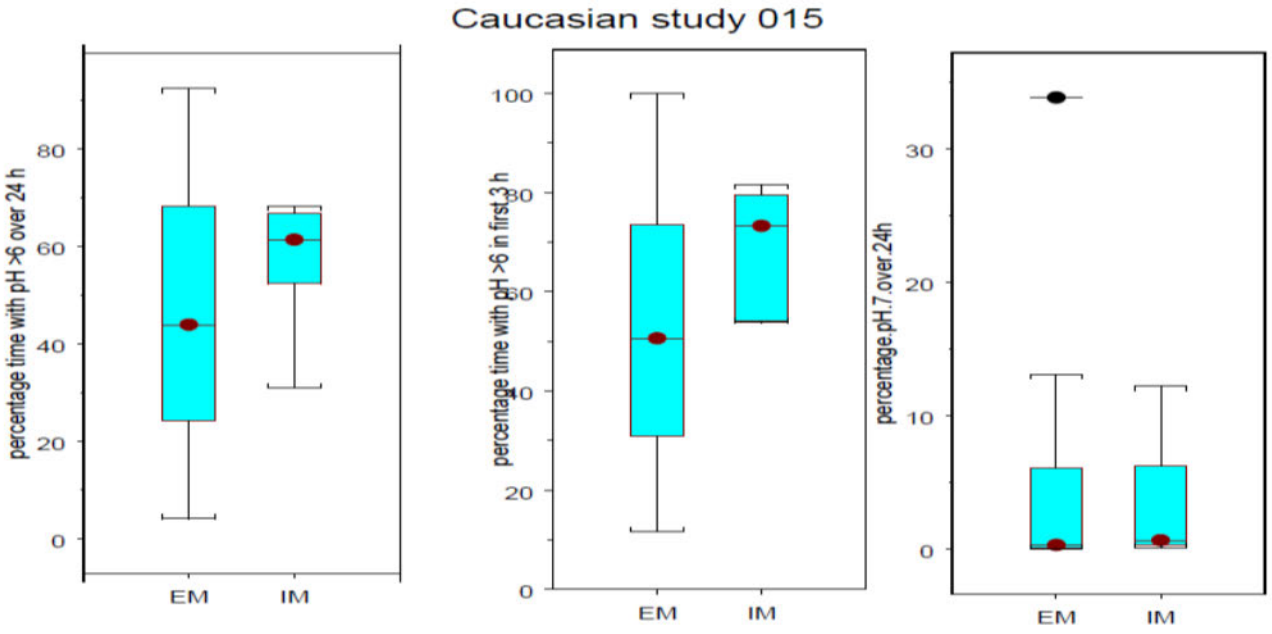


Figure 2: Caucasian PD study: PD vs. Metabolizer Status



Impact of H. pylori status combined with CYP2C19 status. Differences in the PD impact of combining H. pylori status (positive or negative) with CYP2C19 metabolizer status (EM,

IM, or PM) between Caucasian and Chinese populations could not be fully explored because no H. pylori positive healthy volunteers were enrolled in the Caucasian study. When the PD outcomes by metabolizer status in the two studies are examined in the H.pylori negative subset of the Chinese study and the entire population of the Caucasian study, apparent differences between Asians and Caucasians again occur primarily in the analysis of percentage time pH exceeds 7, which is most marked in the intermediate metabolizers (IM). These data are summarized in the table below, reproduced from the Clinical Pharmacology review.

Table 4: PD outcomes by CYP2C19 metabolizer Status and by population (Chinese/Caucasian). Analysis limited to H. pylori negative subjects

CYP2C19 EMs/ *H. pylori* -ve	Chinese (n = 5)	Caucasians (n = 17)
% time when pH >4 over 24 h	93.6 ± 4.00	86.3 ± 10.9
% time when pH >6 over 24 h	44 ± 19.78	45.2 ± 28.5
% time when pH> 6 over first 3 h	42.9 ± 26.2	42.6 ± 24
% time when pH>7 over 24 h	7.48 ± 4.68	4.4 ± 8.5

CYP2C19 IMs/ *H. pylori* -ve	Chinese (n = 5)	Caucasians (n = 6)
% time when pH >4 over 24 h	93.3 ± 6.8	89.6 ± 7.5
% time when pH >6 over 24 h	50.1 ± 25.1	56.9 ± 13.9
% time when pH> 6 over first 3 h	52.7 ± 44.8	53 ± 28.3
% time when pH>7 over 24 h	16.1 ± 10.1	3.4 ± 4.9

Summary. These analyses cannot definitively address the review questions raised in previous review cycles regarding the generalizability of the outcomes observed in the Chinese Lau trial to the US population, for reasons including: 1) the PD studies didn't enroll the patients with upper GI bleed from a gastric or duodenal ulcer, 2) small sample size, 3) no H.pylori positive Caucasians were studied, and 4) dependence on cross study comparisons. Exploration of these two PK/PD studies do suggest that H.pylori negative Chinese "healthy" volunteers may be more likely than Caucasian H.pylori negative healthy volunteers to achieve the higher pH values needed for optimum clot stability (based on published in vitro clot stabilization data), since the Chinese PD study showed a trend toward higher proportion of patients achieving higher pH's, in particular pH>7. In addition, there was a higher proportion of H.pylori positive Chinese subjects who exceeded pH 7 than H.pylori negative subjects, within the Chinese study. Although there were no data available for similar PD analyses in H. pylori positive vs. negative Caucasians, it seems reasonable to expect a similar pattern (differential trend in more favorable effect in H. pylori positive patients) in Caucasians as well.

Exploration of Phase 3 Clinical Trial Outcomes based on PK/PD study findings. Study 001 and the Lau Trial were re-examined during this review cycle from the perspective of the Chinese and Caucasian PK/PD data presented above. The following questions were considered in re-examining the rebleeding data from these trials:

1) Were there imbalances in H.pylori positive/negative between arms within trials and between trials?
2) Was there evidence of more rapid onset of PPI reduction of rebleeding in H.pylori positive patients within Study 001?

3) Was there evidence of a difference in onset of PPI reduction of rebleeding in H.pylori positive patients between the two studies?
4) Was there evidence of a favorable impact of H.pylori status on any risk of rebleed, based on the H.pylori subgroups in the placebo arms of each trial?

There were similar percentages of patients who were H.pylori positive between the trials (74% of Nexium treated patients and 68% of placebo patients in Study 001 vs. 67% of omeprazole treated patients and 54% of placebo patients in the Lau Trial). There was a similar percentage of missing H.pylori status in the two trials (5% in both). A numerically higher proportion of patients were H. pylori positive in the IV PPI arm of both studies; the absolute difference between arms was higher in the Lau Trial than in Study 001 (13% vs. 6%). There was a lower rate of clinical rebleeding in the H. pylori positive patients in the IV PPI arm of both trials, which is consistent with the apparent differential PD effects between H.pylori positive and negative patients observed in the Chinese PD study.

The Caucasian H.pylori negative PD data suggest that the maximum treatment effect does not occur in healthy volunteers until 24 hours into the infusion. In the Chinese "healthy" volunteer PD study, H.pylori positive subjects appeared to achieve pH>6 more rapidly than the negative subjects (twice the number of H. pylori positive subjects achieved pH>6 within 3 hours of initiation of infusion than H.pylori negative). Study 001 (D961DC00001) rebleed data were explored to look for evidence of a more rapid achievement of the desired higher pH in H.pylori positive patients, as manifested by earlier dimunition in rebleeding relative to the H.pylori negative patients. A numerical suggestion of lower rebleed rate for H. pylori positive patients vs. H. pylori negative patients is observed starting at 6 hours in Study 001; however, this pattern and timing were observed in both Nexium and placebo arms. (See Table summarizing Study 001 rebleed data below). The similar pattern between arms suggests that H.pylori positive patients treated with Nexium did not achieve a more rapid onset of desired pH level than the negative patients, at least as manifested by differential rebleed rate between the subgroups. The distribution of rebleeding between H.pylori positive and negative patients in Study 001 is similar between arms (Nexium vs. placebo) until after the first 24 hours of infusion, when percentage of rebleeds appears to plateau in both H.pylori subgroups of the Nexium arm; whereas the rebleeds continue to climb on the placebo arm – most markedly in the H.pylori positive subgroup. These data suggest Nexium IV's onset of PD/treatment effect in Caucasian patients mirrors that of H.pylori negative Caucasian healthy volunteers.

Examination of the distribution of proportion of rebleeding from 24 hours to 72 hours among H. pylori subgroups in the two arms suggests that there is one subgroup for which Nexium IV has the greatest impact relative to placebo, during the 24 hour to 72 hour bracketed period, i.e., the H.pylori positive subgroup. Proportion with rebleeding at 24 hours and 48 hours in the Nexium treated H.pylori positive patients was 3.4% and 4.2%, respectively; while at the same time points, the H. pylori positive placebo arm had 2.4% and 8.3% rebleeding. This contrasts with the proportion rebleeding at 24 and 48 hours in the H. pylori negative subgroups: Nexium = 7.6% and 9.8%, Placebo = 10.1% and 11.8%.

Tables 5 and 6: Proportion of Subjects with a Rebleed at Various Time Points in Study 001 (D961DC00001) and in "the Lau Trial"

D961DC00001 - Proportion of subjects who Re-Bleed within 3, 6, 12, 24, 48 and 72 hours (subgrouped by H. pylori status), ITT population

Re-bleed within (hours)	Esomeprazole n/N(%)		Placebo n/N(%)	
	H. pylori(+)	H. pylori(-)	H. pylori(+)	H. pylori(-)
3	2/264 (0.8%)			3/119 (2.5%)
6	3/264 (1.1%)	2/92 (2.2%)	1/252 (0.4%)	4/119 (3.4%)
12	4/264 (1.5%)	4/92 (4.3%)	4/252 (1.6%)	6/119 (5%)
24	9/264 (3.4%)	7/92 (7.6%)	6/252 (2.4%)	12/119 (10.1%)
48	10/264 (3.8%)	7/92 (7.6%)	18/252 (7.1%)	13/119 (10.9%)
72	11/264 (4.2%)	9/92 (9.8%)	21/252 (8.3%)	14/119 (11.8%)

19 Ezomeprazole subjects have missing H.pylori status, 2 of them rebleed within 72 hours
18 Placebo subjects have missing H.pylori status, 5 of them rebleed within 72 hours

Lau et al - Proportion of subjects who Re-Bleed within 24, 48 and 72 hours (subgrouped by H. pylori status), ITT population

Re-bleed within (hours)	Omeprazole n/N(%)		Placebo n/N(%)	
	H. pylori(+)	H. pylori(-)	H. pylori(+)	H. pylori(-)
24		2/39 (5.1%)	9/64 (14.1%)	7/54 (13%)
48		2/39 (5.1%)	11/64 (17.2%)	9/54 (16.7%)
72	1/78 (1.3%)	3/39 (7.7%)	11/64 (17.2%)	12/54 (22.2%)

3 Omeprazole subjects have missing H. pylori status and 1 of them rebleed within 72 hours
3 Placebo subjects have missing H. pylori status and 1 of them rebleed within 72 hours

The cross study exploration of the influence of ethnicity on rapidity of onset of risk reduction of rebleeding in H.pylori positive patients was hampered by the absence of rebleeding data for time points earlier than 24 hours in the Lau Trial. In contrast to Study 001, where no difference is apparent between esomeprazole and placebo in the H.yplori positive subgroup at 24 hours, it appears that the proportion of H.pylori positive patients with a rebleed on the omeprazole arm of the Lau Trial is dramatically lower than in the H. pylori positive patients on the placebo arm by the first 24 hour analysis.

In contrast to the placebo arm of Study 001, where the H.pylori positive subgroup had a numerically lower rebleed rate than the negative at the earlier time points, in the placebo arm of the Lau trial, there is little difference in rebleed rate between H.pylori positive and negative patients. Similar to Study 001, however, in the proton pump inhibitor (PPI) treatment arm, there was an apparent lower risk of rebleeding in the H. pylori positive patients relative to the PPI treated H. pylori negative patients. If the higher placebo rebleed rate in the Lau trial is attributable to the higher ASA grade patients enrolled in the Lau trial (as discussed in Section

7 Efficacy), the H. pylori subgroup pattern observed in that trial relative to Study 001 might be expected, since other contributing factors could have "over-ridden" the contribution of H.pylori status to rebleeding events in that trial. However, no conclusions can be drawn by these limited data and cross study comparisons.

The further explorations of PK/PD data and the efficacy trial data performed during this review cycle indicate a substantive portion of patients with peptic ulcer bleeds have underlying H. pylori infection, and as noted above, the data suggest that in patients with peptic ulcer bleed, the benefit from Nexium IV may be most apparent in H. pylori positive patients (seen in both The Chinese Lau trial and Study 001). While cross study explorations suggest that the impact of PPI infusion may be expected to be more rapid and pronounced in H.pylori positive relative to H.pylori negative patients in a Chinese population (relative to the population studied in Study 001), no definite conclusions can be drawn. In addition, Study 001 (and the Lau trial) was not designed to determine whether efficacy could only be expected in a particular subgroup.

In summary, I concur with the Clinical Pharmacology review conclusions that the available PK and PD data do not provide strong evidence that an "ethnicity factor" was the basis for differences in clinical outcomes between Study 001 and the Lau trial.

6. Clinical Microbiology

Not applicable, as the product is not intended to be used as an antimicrobial product.

7. Clinical/Statistical-Efficacy

In the first two review cycles, 4 trials (one esomeprazole and 3 omeprazole) were reviewed. The following table summarizes the high level efficacy results of those trials. The data from two of the omeprazole trials (840 and 841) are combined, and the subgroup analysis of those two trials, focusing on patients who had endoscopic therapies utilized in Study 01, is included.

Table 7. Rebleeding Within 72 Hours of Therapeutic Endoscopy

Study	Study Drug*	Placebo	Treatment Difference
01	5.9% (22/376)	10.3% (40/389)	-4.4%
Lau	4.2% (5/120)	20.0% (24/120)	-15.8%
840/841 [combined] All patients with endoscopic therapy	16.7% (17/102)	30.6% (34/111)	-13.9%
Only patients with endoscopic therapy as given in Study 01	13.6% (3/22)	23.3% (7/30)	-9.7%

*esomeprazole in Study 01; omeprazole in Lau study, Study 840, and Study 841
Source: Data reproduced from CDTL, Clinical and Statistical review and Dr. Peterson's presentation at CDER Regulatory Briefing on April 19, 2013

In previous review cycles, the Division's conclusion that substantial evidence of efficacy had not been provided for the proposed indication hinged on the following:

1) The outcome observed in Study 001 (D961DC00001) was not considered adequately robust to serve as a single trial to support approval.
2) The outcome of the Lau Trial was not adequate to support Study 001 because this single center trial enrolled only Chinese patients. The reviewers questioned whether the results were generalizable to the US population due to potential characteristics in Chinese patients that could increase the treatment effect of proton pump inhibitors, such as lower parietal cell mass, CYP2C19 polymorphisms, and H. pylori prevalence. These concerns were reinforced by the larger treatment effect observed in the Lau trial, differences between trials in rebleeding events in the placebo arms, and differences in outcomes between trials within specific population subsets.
3) When the subpopulation of omeprazole trials I-840 and I-841 (non-Chinese trials) that matched the entry criteria for Study 001 was analyzed, the observed outcome was not statistically significant, although it favored omeprazole.

I will discuss this cycle's review conclusions about the adequacy of Study 001 to serve as a single trial to support approval, after first summarizing the current review conclusions regarding the ability of the Lau Trial and Trials 841 and 842 to support Study 001.

The Lau Trial. Items #3, #4, and #5 of the CR letter (Section 2 Background of this review) addressed concerns about the outcome differences between the Lau Trial, which enrolled only Chinese patients, and Study 001. The table below shows the higher placebo rebleed rate observed in the Lau Trial relative to Study 001.

Table 8: Proportion with clinically significant rebleeding within 72 hours in Study001 and Lau Trial

Outcome Variable	Trial by Lau et al		Study001	
	Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)_	Placebo (n = 389)
Pts with clinically significant rebleeding within 72 h, n (%)	**5 (4.2%)**	**24 (20%)**	**22 (5.9%)**	**40 (10.3%)**

With regard to **Item #3**, see Section 5 Clinical Pharmacology for my summary of the analyses of the PK/PD information (including impact of H.pylori status) submitted to address whether meaningful differences exist between Chinese and Caucasian subjects that would be expected to result in a different PPI treatment effect between these populations.

Regarding **Item 4** from the CR letter (difference in placebo rebleed rate between the Lau trial and Study 001), the Statistical reviewer didn't agree with the applicant's approach to identifying explanations for the difference. Her concern focused primarily on the appropriateness of use of Cox Regression Models for the task. She identified the following issues:

1) She didn't agree with the applicant's use of Cox regression models to address the issue. Categorical data analysis models seemed better suited because the primary endpoint of interest was a categorical endpoint (rebleeding within 72 h = yes/no).
2) The applicant's Cox regression models treated all events as occurring at distinct times, even though the "distinct time" of the event was only known in Study 001. In the Lau Trial, "precision" of time of rebleed was limited to whether it occurred on Day 1, 2 or 3 of the trial.
3) There was a low ratio of rebleeding events to number of independent variables (6:1). "…higher ratios are necessary to ensure stable estimates of regression model parameters."
4) Multi-colinearity, which could affect estimates, was not assessed.
5) The applicant didn't limit the analyses to the data from placebo control subjects.

The Statistical reviewer conducted her own exploratory analysis, limited to the placebo control patients in the two trials, since the greatest discrepancy in rebleeding between trials was confined to the placebo arms and this particular "discrepancy" in results between studies was subject of the CR letter (**Item 4**). She found that rebleeding (by Day 3) in the placebo arm subjects appeared related to: 1) whether a patient was hospitalized at sign of GI bleeding (3.5% rate in those hospitalized vs 14% in those not hospitalized), 2) Forrest Class (Rebleeding: Ia=22% , Ib=7%, IIa 14%, IIb = 22%), and 3) ASA Grade (Rebleeding: 1=9%, II = 12%, III or IV = 20%). She used logistic regression models to explore the relationships between these variables and rebleeding by Day 3 and found a consistent relationship between the variables and rebleeding across the two studies.

When the specific variables associated with the subcategories with highest rebleed rate (e.g., Ia and IIb for Forrest Class) were examined for relative distribution between the placebo arms between trials, there was a similar distribution between studies, with the following exceptions:

1) There was a higher proportion of placebo patients who were categorized Forrest IIb in the Lau trial than in Study 001 (18% vs. 10%)
2) There was a higher proportion of placebo patients who were categorized ASA Grade III or IV in the Lau trial (44% vs 13%)
3) There was a higher proportion of placebo patients who were not hospitalized at sign of GI bleeding in Study 001. (This variable specifically referred to whether a patient was in the hospital for another problem when they manifested peptic ulcer bleeding as a new additional problem.)

The greatest difference between the trials in these variables appears to be in the ASA Grade of the subjects. The applicant pointed to the enrollment of a "more severely ill" population in the Lau Trial as an explanation for the discrepancy in outcome between the placebo arms of the two trials. The Statistical reviewer's exploratory analysis appears to support this. See also Section 5 Clinical Pharmacology of my review, where I speculate that ASA status may have "over-ridden" the contribution of H.pylori status to risk of rebleeding in the Lau trial, as evidenced by the lack of difference in rebleeding events within the Lau placebo arm between the H.pylori negative and positive subgroups, in contrast to the differences observed between H. pylori subgroups within the placebo arm of Study 001. Ultimately, the Statistical reviewer concluded that these cross-study analyses are exploratory only and cannot establish whether the Lau trial results are generalizable to a broader population.

The second cycle CR letter's **Item 5** referred to concerns about differences in efficacy between the Lau Trial and Study 01 in patients aged ≥65 years and in the Forrest Ib subgroup. The third cycle CDTL, Dr. Fiorentino, cautioned about the limitations of cross study comparisons and noted that the direction of the trend in benefit was consistent between the two trials in patients ≥65 years.

Table 9: Rebleeding Event Rates By Age Subgroup by Trial

Outcome Variable		Trial by Lau et al		Trial D961DC00001	
		Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)_	Placebo (n = 389)
	Age subgroup				
Patients with clinically significant rebleeding within 72 hours, n (%)					
	≥ 65 years	5/76 6.6%	21/80 26.3%	6.2%	8.4%
	< 65 years	0/44	3/40 7.5%	5.5%	11.9%

It is difficult to describe the cross study comparisons of outcomes (difference between treatment and placebo) observed in the Forrest Ib patients as similar (0.5% vs. 10%, Study 01 vs. Lau, respectively) in directional trend. However, I concur with the CDTL's conclusion that these cross study subgroup exploratory analyses comparisons are not adequate to establish that the drug is ineffective in a subgroup.

Additional exploratory analyses of comparability of the Lau Trial and Study 001. In his review, the CDTL presented some additional analyses that were utilized to further explore the comparability of qualitative aspects of the rebleeding outcomes observed in Study 001 and the Lau Trial (summarized in Tables 13 and 14 of the CDTL review). The CDTL acknowledged that these summary data didn't allow for identification of meaningful differences between trials. These cross study comparisons were hampered by differences in scope of data evaluated: data limited to Days 1-3 in Study 001 vs. encompassing Days 1-30 for the Lau Trial. In addition, some of the defining components of the enumerated "diagnostic subcriteria" do not match between trials. For example, "melena" is a component of two subcriteria in the Lau Trial, but limited to one criterion in Study 001(entirely unique to Study 001).

There appeared to be similarity between the two trials in characterization of the rebleeds, based on rates and distribution between study arms, at least in terms of the 3 subcriteria that were most consistent in definitions utilized in the two trials [Study 001/Lau: 1) blood in stomach at endoscopy/fresh blood at endoscopy; 2) active bleeding from peptic ulcer at endoscopy/spurter or ooze at endoscopy; 3) vomiting significant amounts of fresh blood, both trials]. The only numerical "outlier" was a higher placebo "spurter or ooze" in the Lau trial on the placebo arm (10.9%) compared to "active bleeding" in the placebo arm of Study 001 (6.4%).

The reviewers also requested that the applicant further characterize the rebleed events in the first 30 days, using the identified diagnostic criteria data in both trials, based on number of criteria present within individual patients. Some differences between trials were noted. Examination of the distribution over the range of having only one of the criteria vs. all 6 criteria, reveals that there were patients in Study 001 who met 4-6 diagnostic criteria vs. no patients in the Lau Trial who met 4-6 criteria. In addition, there were 15 patients in the Lau Trial who had only one of the diagnostic criteria vs. no patients in Study 001 who met only one criterion. However, in light of the existence of some missing data regarding these descriptor subcategories, it is possible that the number of single criterion rebleeders in the Lau trial merely reflects missing data.

The applicant was also asked to characterize the rebleeds in Study 001 regarding site of bleeding: duodenal vs. gastric. The tables summarizing these data, which are presented in the CDTL review, show that the within-arm rebleed rate was nearly identical between ulcer sites – gastric vs. duodenal. The treatment effect for esomeprazole appeared identical regardless of ulcer site. Endoscopy report data indicated that there were patients who had multiple ulcers identified at baseline endoscopy, although the other ulcers were not identified as a source of bleeding. The applicant was asked to provide the number of patients whose rebleed event occurred in a site (gastric/duodenal) that differed from baseline. In response, the applicant stated that no patient bled from a new site; however, as shown in Table 17 of the CDTL review, since not all re-bleeds were documented with endoscopy, that cannot be definitively established. The information provided in Tables 16 and 17 of the CDTL review allow derivation of the distribution of endoscopically undocumented rebleeds by baseline site of bleeding (duodenum vs. gastric). This information is summarized in the table below.

Table 10: Distribution of non-endoscopically documented rebleeds, based on baseline site

Duodenum = Baseline site of bleeding		
	No. Rebleed without endoscopic documentation/Total number of Rebleeds	% undocumented by endoscopy
Esomeprazole	3/14	22%
Placebo	9/25	36%
Gastric = Baseline site of bleeding		
	No. Rebleed without endoscopy/Total number of Rebleeds	% undocumented by endoscopy
Esomeprazole	5/8	62%
Placebo	2/15	19%

The distribution of nonendoscopically documented rebleeding by baseline site of bleed appears similar between baseline gastric and duodenal sites. The numerically higher proportion of undocumented rebleeds in the baseline gastric site of the esomeprazole arm is not interpretable in light of the small numbers in this cell. In the first 72 hours on study, based on the Study 001 protocol, these non-endoscopically documented bleeds must have manifested with at least two clinical B signs or C to be counted as a clinically significant rebleed event. The protocol criteria are summarized in the table below, reproduced from the first cycle Clinical Review.

Table 4: Diagnosis criteria for clinically significant rebleeding

Rebleeding diagnosed by:	Criteria for diagnosis
"A" Endoscopy – initiated by clinical signs of bleeding defined as: one of B1 or B2 or B3 and Endoscopic verification, i.e., one of A1 or A2. It is the result of the endoscopy that defines if there is a rebleeding or not	A1 Blood in the stomach (this criterion was not used during the first 6 hours after primary endoscopic hemostasis) A2 A verified active bleeding from a peptic ulcer (Forrest class Ia, Ib)
"B" A true clinically based definition included at least 2 of B1 and/or B2 and/or B3	B1 Vomiting of fresh blood or fresh blood in a gastric tube or hemetochezia or melena after a normal stool. B2 Decrease in Hb>20 g/L (or Hct>6%) during 24 Hours or an increase in Hb<10 g/L (or Hct<3%) despite ≥2 units of blood has been transfused during 24 hours B3 Unstable circulation systolic BP ≤90 mmHg or pulse ≥110/min (after have had a stable circulation)
C Hematemesis	C Vomiting significant amounts (>200 mL) of fresh blood as estimated by the investigator

(Above Table is taken from Table 4 of Clinical Study Protocol for Study D961DC00001)

In summary, multiple items of the CR letter pointed to apparent inconsistencies between the outcomes in the Lau Trial and Study 001. There was concern that the inconsistencies might be secondary to differences in ethnicities enrolled in the trials. In this review cycle, the reviewers have carefully re-evaluated the inconsistencies identified by the previous review teams and have considered them within the context of available data regarding PK/PD effects of the proton pump inhibitors in Chinese vs. Non-Chinese healthy volunteers and in H.pylori negative and positive Chinese healthy volunteers. The Clinical reviewers in this cycle observed that there was general consistency in direction of treatment effect between the two efficacy trials and that the relatively high placebo rebleed rate in the Lau Trial seemed reasonable to attribute to the high ASA status eligible for enrollment in the Lau Trial. The reviewers didn't consider the individual subgroup analyses pointed to in the previous CR letter grounds for concluding that the overall primary outcome of Study 001 was not reliable. In light of the CDER Regulatory Briefing discussion on this topic, presented later in this Section, I have concurred with the conclusions of the third cycle Clinical Review team.

Studies 840 and 841. Second cycle Complete Response letter **Items #1 and #2** address issues related to Studies 840 and 841(omeprazole trials). The Statistical Reviewer in the current review cycle ultimately deferred to the Clinical reviewers to determine whether the applicant's selection of a larger subgroup for efficacy analysis from Trials 840 and 841 is relevant. The smaller subgroup (N=52) identified by FDA for analysis was selected by matching patients between Trials 840/841 and Study 001 based on eligibility criteria. The applicant's proposed larger subset, N=137, matched subjects on the same treatment modalities, with or without additional endoscopic treatment. The analysis of the treatment difference observed in this larger subgroup, stratifying by type of endoscopic treatment, yielded a nominal p value that was <0.05. The Statistical Reviewer pointed out the relatively consistent numerical pattern favoring omeprazole across various analyses, which is shown in Table 11 below (reproduced from the Statistical review). The Clinical reviewer also pointed to the consistent trend in treatment effect across these subgroup analyses, including all patients with endoscopic treatment (N=213), the applicant's proposed larger population (N=137) and the FDA's matched population (N=52). She considered this consistent trend as supportive evidence of efficacy for Nexium IV for the proposed indication. She also specifically stated in her review that even if the difference in the smaller subgroup considered most relevant to the FDA was not statistically significant, the trend favoring omeprazole "is important and provides supportive evidence for the efficacy of Nexium IV for the proposed indication."

Table 11. Rebleeding rates within 72 h: Studies 840 and 841, by type of endoscopic treatment.

	Treatment Group		
Endoscopic treatment	Omeprazole	Placebo	Treatment Difference
Any type of endoscopic treatment (n=213)	16.7% (17/102)	30.6% (34/111)	-13.9%
Endoscopic treatment differed from endoscopic treatment used in D961C00001 (n=76)	23.8% (10/42)	38.2% (13/34)	-14.4%
Same endoscopic treatment used in D961C00001, plus additional endoscopic treatment (n=137)	11.7% (7/60)	23.3% (21/77)	-15.6%
Same endoscopic treatment used in D961C00001 (n=52)	13.6% (3/22)	23.3% (7/30)	-9.7%

Source: Adapted from Dr. Peterson's presentation, CDER Regulatory Briefing on April 19, 2013

Studies 840 and 841 were presented at the CDER Regulatory Briefing. Members of the panel also pointed to similarities in the treatment differences across analyses, and stated it was not surprising that the difference was not statistically significant in the subgroup considered most relevant to FDA reviewers, in light of the markedly reduced sample size. While I agree that, of course, it is not surprising that the small number of patients in the subgroup of interest to FDA is not significant, and that the trends across analyses consistently favor omeprazole, I do not consider the findings of these exploratory analyses of the combined data from 840/841, to constitute substantive support of the Nexium trial, Study 001. These trials were designed with endpoints that were vague and differed from Study 001. There was no pre-specified plan to combine specific subsets of patients for analysis, as submitted in this NDA. While, the trends

observed in these exploratory analyses contribute to a sense of confidence in the treatment effect observed in Study 001, I don't recommend inclusion of these data in the product label.

Study 001: Adequacy as a Single Trial and the CDER Regulatory Briefing. In the second cycle CR letter**, Item 7** reiterated that Study 001, as a single adequate and well-controlled trial, does not provide sufficient evidence to support the proposed indication. **Item 7** included specific issues identified in the second cycle, including the applicant's use of Breslow-Day test to support homogeneity of the treatment effect across study centers and an issue regarding removal of one of the study sites (Site 012) from the primary analysis.

In her current review, the Statistical reviewer has stated that she "generally agrees with the Applicant's response that the Breslow-Day test was inconclusive regarding the presence or absence of heterogeneity of treatment effect….." With regard to the influence of Site 0012, the Statistical reviewer concluded that the Clinical reviewers must decide whether the contents of the current NDA submission combined with the results of the single adequate and well controlled trial that investigated Nexium IV are sufficient to support the proposed indication. The Clinical Reviewer noted that the second cycle inspection of Site 012 had determined that the data from that site were reliable. The CDTL states in his review, "The fact that ……post hoc analyses removing one or more sites from the primary analysis result in a different p-value, do not in themselves suggest that the overall results or conclusions are invalid."

When the Division presented the Cycles 1 and 2 review issues concerning the adequacy of Study 001 at a CDER Regulatory Briefing, the reviewers explained that the interest in the exploratory analyses and associated p value shifts (including the analysis removing Site 012) was driven by the fact that Study 001 was a single trial submitted for a new indication. The prior approvals of esomeprazole for other indications were not regarded as evidence that could be reasonably relied upon to support the new proposed indication, due to the unique nature of the new indication… (b) (4) (which differs from improving symptoms of GERD or healing of esophagitis). Although the panelists acknowledged why the Division conducted these analyses, they supported the CDTL's conclusion that changes in p values in post hoc analyses do <u>not</u> indicate the results of the prospectively defined analysis are invalid.

The Clinical reviewer summarized the April 19, 2013 CDER Regulatory Briefing in Section 9.4 of her review. The specific purpose of the meeting was to discuss the adequacy of evidence to support approval of Nexium IV for the proposed indication. The Division pointed out that intravenous proton pump inhibition has become the standard of care in the setting of upper gastrointestinal bleeding, and that for this reason the applicant stated that it could not conduct a placebo controlled trial, or a trial with an H2 blocker as a control arm. With regard to efficacy, the panel was asked, "Do the data presented (Study 01, the Lau et al. study, Studies 840 and 841, and PK/PD studies) represent substantial evidence of efficacy for the proposed indication (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers")? Some members of the panel answered, "yes." Others were less convinced, as they were not certain that the omeprazole data, in particular the Lau Trial, provided adequate support, in light of remaining questions regarding population differences; however, this group was generally

supportive of reliance on the single trial, Study 001, despite the lack of a highly persuasive p value. They were persuaded that the trial could not be repeated, due to practice guidelines recommending proton pump inhibitors in this setting. They pointed to the FDA Guidance to Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, as support for this approach. In particular, this Guidance states:

> "Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well controlled efficacy study to support approval - generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, *and a confirmatory study would have been difficult to conduct on ethical grounds*.(emphasis added)……
>
> Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome *and confirmation of the result in a second trial would be practically or ethically impossible*. (emphasis added)"

Summary. I concur with the reviewers that a decrease in rebleeding events was observed across the esomeprazole and omeprazole trials submitted in support of this application, which provides some confidence that if the single esomeprazole trial could be repeated, the treatment impact would be reproduced. I think the data package submitted in this NDA, taken together, would make it practically or ethically impossible to repeat the study. Based on this, and consistent with the majority recommendation of the CDER Regulatory Briefing panel, I have concluded that the efficacy data submitted are adequate to support approval of this supplemental NDA. I concur with the reviewers that the efficacy data presented in Section 14 Clinical studies of the product label should be limited to the data from Study 001, and that this section should acknowledge support provided by the Lau trial, without presenting specific data from the Lau Trial. I also concur with the reviewers' decision (b) (4) (b) (4) the primary endpoint was re-bleeding, which was defined by major evidence of bleeding. (b) (4) (b) (4).

8. Safety

No safety issues were cited in the previous CR letters. The Clinical reviewer in this 3rd cycle concluded that there are no new safety signals from the clinical trials submitted in support of this application. The safety data from Studies 840 and 841 were re-scrutinized during this review cycle as they were terminated early due to an imbalance in mortality observed in Study 841. This imbalance (11 deaths in the omeprazole arm vs. 1 in the placebo arm) was presented to the Regulatory Briefing panel, along with the mortality data from the other trials evaluated in this application. A similar imbalance in mortality was not observed in those trials.

Table12. Death by Day 30 (Study 01, Study Lau), Death by Day 21 (Studies 840/841)

Study Drug	Study 01	Study Lau	Study 840	Study 841
Esomeprazole/Omeprazole	0.8 (3/375)	4.2% (5/120)	6.2% (8/130)	7.4% (11/148)
Placebo	1.5% (6/389)	10.0% (12/120)	5.9% (8/135)	0.6% (1/162)

Source: Clinical Review, Table 25, page 36/43, Aisha Peterson, dated 07/15/2013.

The causes of deaths in Study 841 included GI hemorrhage (single death in each arm). Among the remaining 10 deaths, myocardial infarction was reported in 5. Congestive heart failure/heart failure was reported in 2. Cerebral infarction/stroke was reported in 2. Pulmonary embolism was reported in 1. Study 841 was conducted in Sweden and Norway and eligibility criteria required age ≥60 years for study entry. Patients only received therapeutic endoscopic intervention (sclerotherapy, heater probe, etc) if their bleed was categorized Forrest Ia (spurting). The mean age was 74 years, which is over a decade older than the mean age of the patients who entered Study 001 and the Lau Trial. The authors of the publication in which the Study 841 was reported (Hasselgren, et al. Scand J Gastroenterol. 1997;32:328-333) discussed the imbalance in mortality and couldn't identify a definitive explanation for it.They noted that mortality rates associated with peptic ulcer bleeds reported in the literature differ depending on the length of follow up from presentation with an acute bleed, and concluded that the mortality in the placebo arm of Study 841 was "unexpectedly low." They also pointed to the higher proportion of patients in the omeprazole group that presented with a hemoglobin <9.0g and a lower proportion of patients in the omeprazole arm who had a history of peptic ulcer (literature reports had observed a lower mortality risk in patients with a history of previous ulcer). They ultimately stated the observation could have been due to chance.

The Regulatory Briefing panel discussed these data, in addition to summary information presented by the Division regarding its history of evaluating questions regarding cardiovascular risk associated with proton pump inhibitors. These safety reviews have been triggered by observations of numeric imbalances of cardiovascular events in two proton pump inhibitor applications, both presented to previous CDER Regulatory Briefings. In response to these review observations, the Division had requested that commercial sponsors of proton pump inhibitors provide comprehensive, summary cardiovascular data from controlled trials to the Division for review. Based on the Division's review of these data, the Division concluded there was not a cardiovascular signal for PPIs that necessitated a dedicated study to characterize the risk. The panelists concluded that the data in the current Nexium IV NDA do

not present a cardiovascular safety concern that should preclude approval or prompt further study.

The Clinical reviewer concluded in her review that the available data from these studies suggest that the mortality findings in Study 841 were most likely due to chance. The CDTL noted in his review that a biological basis for any association between omeprazole and cardiovascular deaths is unknown. I concur with the recommendations of the CDER Regulatory Briefing panel that the apparent cardiovascular mortality imbalance observed in one of the trials submitted for review does not constitute a safety signal that should preclude approval of this supplemental NDA. In addition, I do not believe that it constitutes a signal that should prompt requiring a post-marketing dedicated cardiovascular safety trial.

The Clinical reviewer also evaluated the applicant's search of its global patient safety database for reports associated with use of Nexium IV for "stress ulcer" or gastrointestinal hemorrhage, and/or where the daily dose of intravenous esomeprazole was the same or exceeded the proposed dose for the current proposed indication. This search was updated to include May 1, 2010 to August 31, 2012. She did not identify any new safety concerns. Three events resulted in death. Review of the narratives found in her review indicates that one death was attributed to aspiration and the other two appeared to be related to anaphylaxis. In both cases, there was a concomitant medication that was also suspect, including a beta-lactam in one of the patients.

In conclusion, the safety data were evaluated and carefully considered. No safety issue precludes the approval of the Nexium IV for the proposed indication. See Section 4 Nonclinical Pharmacology/Toxicology (above) regarding a recent Safety Labeling Change (SLC) made to all esomeprazole and omeprazole labels based on animal data. The label for the currently marketed Nexium IV product was revised and approved in response to the FDA's request for SLC prior to taking action on this NDA supplement for a new indication.

9. Advisory Committee Meeting

There was no advisory committee meeting for this supplemental application.

10. Pediatrics

Refer to my first and second cycle reviews. In the last review cycle, the PMHS reviewer recommended a full waiver for the proposed indication. The PMHS reviewer stated that if the applicant were to seek a broader indication such as (b) (4) pediatric studies may be feasible. The Pediatric Review Committee concurred with granting the full waiver.

11. Other Relevant Regulatory Issues

No additional financial disclosures were submitted in this third cycle. The financial disclosure review in the initial review cycle identified one investigator, Dr. Ernst J. Kuipers, who reported receiving significant financial payments. He was principal investigator at Site 0102 (Netherlands) in Study 001. The largest treatment effect in all participating centers was observed at this site, -31% rebleeding events. A sensitivity analysis was conducted to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, and the overall treatment effect observed in the study decreased to -3.73% (95% CI = -7.67, 0.10). However, a DSI inspection of Site 0102 identified no significant deficiencies and a Form FDA 483 was not issued. The study data from Site 102 were considered reliable. See further discussion in Section 2 Background and Section 7 Clinical/Statistical-Efficacy of this review.

12. Labeling

The CDTL has summarized the major labeling changes that were prompted by review of this application. As pointed out in the CDTL review, the applicant proposed (b) (4) [redacted]. For this reason, the applicant's proposed language was removed. The Dosage and Administration section will state, "Intravenous therapy is aimed solely at the acute initial management of bleeding gastric or duodenal ulcers and does not constitute full treatment. Intravenous therapy should be followed by oral acid-suppressive therapy." (There are oral proton pump inhibitors that are approved for healing of gastric/duodenal ulcers, i.e. omeprazole, rabeprazole, and lansoprazole.) The Clinical Studies section will describe the treatment on study, post completion of the 3-day intravenous infusion, as "After the initial 72 hour period, all patients received oral proton pump inhibitor for 27 days."

The OPDP reviewer's label review recommendations were considered and addressed. Although the reviewer recommended specific revisions to Section 14 Clinical Studies description of the Lau trial (referred to in the label as "A randomized, double blind, placebo-controlled single-center study conducted in Hong Kong"), not all the recommended changes were made. The Division did not agree that the factually accurate description of omeprazole as "50% of which is the S-enantiomer esomeprazole" overstated the efficacy of Nexium IV. In addition, the Division did not agree with including the specific efficacy results from the Lau trial.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment - I concur with the reviewers and the recommendations of the CDER Regulatory Briefing panel that the applicant has provided sufficient evidence in this application to establish that Nexium IV, administered in the proposed dose of 80 mg intravenous loading dose over 30 minute infusion, followed by 8 mg/hour for 3 days, is effective for risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults. Although the p-value from the single phase 3 study of esomeprazole submitted to support the proposed indication was not highly statistically persuasive, the trial was a relatively large, multicenter trial, and the applicant submitted data from intravenous omeprazole trials, which demonstrated similar impact on rebleeding. The consistent improvement in rebleeding events in this serious condition observed across these trials would make it very difficult, if not impossible and unethical, to repeat the esomeprazole study to assure the reproducibility of the outcome observed in that trial. The imbalance in mortality observed in patients treated with omeprazole in one of the trials submitted for review was carefully considered in the decision to approve. I concur with the reviewers and the CDER Regulatory Briefing panel that this imbalance in one of the trials does not constitute a safety signal that should preclude approval. I have also concluded that it does not constitute a safety signal that justifies a post marketing safety required study or REMS.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None

- Recommendation for other Postmarketing Requirements and Commitments - None

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/s/

DONNA J GRIEBEL
03/04/2014

Summary Review for Regulatory Action

Date	June 16, 2011
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	21-689 S-014/ Complete Response Submission
Applicant Name	Astra Zeneca LP
Date of Submission	September 15, 2010
PDUFA Goal Date	June 16, 2011
Proprietary Name / **Established (USAN) Name**	Nexium esomeprazole sodium for injection
Dosage Forms / Strength	Lyophilized powder for Injection/ 20 and 40 mg vials
Proposed Indication	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Original Medical Officer Review	Anil Nayyar, MD/Hugo Gallo-Torres/PhD, MD
Complete Response Medical Officer Review	Erica Wynn, MD/Lynne Yao, MD
Original Statistical Review	Sonia Castilio, PhD/Mike Welch, PhD
Complete Response Statistical Review	Lisa Kammerman, PhD/ Mike Welch, PhD
Microbiology Review	Bryan Riley, PhD/ Stephen Langille, PhD
Clinical Pharmacology Review	Dilara Jappar, PhD/Sue-Chi Lee, PhD
DSI	John Lee, MD
PMHS	Amy Taylor, MD/Hari Sachs, MD/Lisa Mathis, MD
OSE	Julia Ju, PhD/Patty Green, PhD/Ester Zhou, MD PhD/Diane K Wysowki, PhD/Solomon Iyasu, MD, MPH

OND=Office of New Drugs
DSI=Division of Scientific Investigations
PMHS = Pediatric and Maternal Health Staff
OSE=Office of Surveillance and Epidemiology

Division Director Review

1. Introduction

Nexium® IV (esomeprazole sodium injection) was approved in 2005 for short-term treatment (up to 10 days) of GERD in patients with a history of erosive esophagitis, as an alternative to oral therapy when therapy with Nexium Delayed-Release Capsules is not possible or appropriate. The label states that "when oral therapy is possible or appropriate, intravenous therapy with Nexium IV for Injection should be discontinued and the therapy should be continued orally." The approved doses for this product are either 20 or 40 mg once daily by intravenous injection (over no less than 3 minutes) or intravenous infusion (10-30 minutes). No new dosage format/presentation is proposed in this new application to accommodate the higher dose and the infusional administration schedule.

In an NDA supplement, (sNDA 21-689/S014), submitted May 29, 2008, the applicant, AstraZeneca, proposed a new indication, for which there is a new dose and administration schedule. The new indication is "Nexium IV for Injection is indicated for (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers". The dose proposed in the label for this indication is 80 mg administered as an intravenous infusion over 30 minutes, followed by a continuous infusion of 8 mg/hour given over 3 days, (b) (4)

The applicant submitted a single randomized, placebo controlled clinical trial in the sNDA to support the new indication. In addition, two PK/PD studies, 24 hours in duration and conducted in healthy volunteers, were submitted to provide evidence that the dosing regimen achieved the pharmacodynamic goal of raising gastric pH to at least 6. A Complete Response (CR) letter was issued on November 26, 2008. The deficiencies cited in the CR letter were:

> "Our review finds that the primary efficacy results for this non-U.S. single study do not provide substantial evidence of efficacy. For a single study to stand alone as substantial evidence of efficacy, it should demonstrate highly statistically significant and clinically meaningful results. Consistency should be demonstrated across subgroups and secondary endpoints. The study should also show internal consistency in demonstrating the treatment effect across study centers. The single study that you have submitted does not meet these criteria for providing substantial evidence for the following reasons:
>
> 1. Highly statistically significant results were not demonstrated. Although your protocol specified analysis showed a reduction of 4.4% in the rate of clinically significant rebleeding within 72 hours after hemostasis compared to placebo ($p = .03$), that reduction was not highly significant, e.g., $p < .001$. In addition, the observed outcome was not found to be robust when subjected to the sensitivity analyses listed below:

a. It is appropriate to account for country-to-country variation, so the protocol specified analysis was further stratified by country. This resulted in an insignificant treatment effect (p=0.06), although the absolute reduction in rebleeding remained 4.4%.
b. When the protocol specified analysis was further stratified (retaining stratification by country in the model) using Forrest classification as four separate categories (Forrest Ia, Ib, IIa, and IIb) instead of two (Forrest I and Forrest II), an insignificant treatment effect was observed (p=0.11). The absolute reduction in rebleeding remained 4.4%. We believe the appropriate adjustment for Forrest classification should be by each individual Forrest category because each category has a different risk of rebleeding events. Even if this stratified analysis was conducted without incorporation of country in the model, the p-value still shifted to a less persuasive value of p= 0.05.

2. The study lacked internal consistency across study centers. Despite similar patient demographics and disease characteristics, marked variability in the incidence of rebleeding, i.e., the primary endpoint, and treatment effect was observed in different countries and among leading centers. The treatment effect varied widely from -25% to +12% by country and from -31% to +20% in the larger centers that enrolled more than 10 patients. There is no clear explanation for why this occurred, although physician expertise and standards of care may have played a role.

3. The study lacked internal consistency in demonstrating the treatment effect in the important subgroup of patients aged 65 and older. In this subgroup, the proportion of patients that experienced rebleeding in the first 72 hours was 6.2% on the esomeprazole arm and 8.4% on the placebo arm. In contrast, in patients aged less than 65 the proportion of patients that experienced rebleeding in the esomeprazole arm was 5.5%, while on the placebo arm the proportion was 11.9%.

4. The study lacked internal consistency in demonstrating the treatment effect in important secondary efficacy outcomes that were evaluated in the first 72 hours. The proportion of patients who underwent surgery for rebleeding was a prespecified secondary endpoint and the observed outcome for this endpoint was similar between study arms. This analysis was not found to be statistically significant, p = 0.31. The secondary analysis comparing number of blood units transfused in the first 72 hours demonstrated a lower number of units infused on the esomeprazole arm (492) relative to placebo (738), p=0.05, and the secondary analysis that compared the proportion of patients who required endoscopic retreatment in the first 72 hours demonstrated a decreased rate of endoscopic retreatment (4.3%) on the esomeprazole arm relative to placebo (8.2%), p=0.02. Although the secondary analyses of number of blood units transfused and endoscopic retreatment appear nominally significant, there was no prespecified plan to adjust for multiple comparisons. Taking a conservative

approach, these p-values are not significant after a Bonferroni adjustment to account for multiple comparisons.

5. One center, Site 0102 in the Netherlands reported the largest treatment effect in all centers that participated in this study, -31% rebleeding events, favoring the esomeprazole arm of the study. The investigator from this site, Dr. Ernest J. Kuipers, MD, Ph.D., reported having accepted significant payments from Astra Zeneca. When we conducted a sensitivity analysis to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, we found that the overall treatment effect observed in the study decreased to -3.73% (95% CI=-7.67, 0.10) and the p-value shifted to 0.06.

6. We identified additional study design and conduct concerns that further limit the study's ability to provide persuasive evidence that esomeprazole is effective for the proposed indication. These issues are listed below:

   a. Endoscopic epinephrine injection is currently not an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers. More than a third of the patients in this study were treated with endoscopic epinephrine injection as single therapy. This draws into question the applicability of the outcome observed in this trial to current care of patients with an upper gastrointestinal bleed from a gastric or duodenal ulcer in the United States today.

   b. Although the inclusion criteria excluded patients with more than a single ulcer, a substantial proportion of the randomized patients had multiple ulcers and there was an imbalance between study arms in this prognostic factor that favored the esomeprazole arm. Fewer patients on the esomeprazole arm had multiple ulcers, 13.6%, relative to the placebo arm, 18.5%. This raises concerns regarding the study conduct in this international trial.

   c. Despite randomization, small imbalances in important prognostic factors were observed between the two study arms. The imbalances favored the esomeprazole treatment arm. These prognostic factors included Grade 1a stigmata of risk of rebleeding (esomeprazole=7.5%, placebo=10.3%) and large ulcers (esomeprazole=7.7%, placebo=10.3%).

   d. The lack of an exclusion criterion for intravenous administration of a proton pump inhibitor within 24 hours prior to enrollment is a potential confounding factor for the observed efficacy outcome. Although this was addressed with an amendment during the course of the study, the amendment only excluded patients who had received intravenous doses greater than 40 mg within 24 hours prior to enrollment.

7. There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment. These deficiencies cannot be addressed adequately through additional analyses of the data in hand."

In order to address the deficiencies, the letter stated that "further clinical data from at least one additional adequate and well controlled study that provides persuasive and consistent evidence of efficacy will be needed." Specific recommendations in the letter included:

1. Conduct at least one additional, adequate, and well-controlled study to demonstrate the proposed clinical benefit of Nexium IV for (b) (4) The study should include some U.S. centers and the study design and analysis plan should address the deficiencies described in this letter above.

2. You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two pharmacokinetic/pharmacodynamic (PK/PD) studies that you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3 study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment. For the reasons stated above, conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data.

3. Study site 0102 in the Netherlands, which reported the greatest treatment effect in the major randomized, placebo controlled trial that you submitted for our review, will need to be inspected by the Division of Scientific Investigations

(DSI) because Dr. Ernst J. Kuipers, MD, PhD, the investigator at that site, has disclosed that he has accepted significant payments from Astra Zeneca. This inspection would be requested as part of our review of any future submission that includes this study as a critical component of establishing the efficacy of Nexium IV for the proposed indication. A recommendation from the DSI inspector that the data from this site can be used for determining the efficacy and safety of Nexium IV will be needed if this study will be used to support a future marketing application. This assessment will be an important component of a future determination of whether this study can stand as one of two adequate and well controlled trials for the proposed indication.

4. Conduct a pharmacokinetic study in a sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.

5. Submit a pediatric plan with your complete response.

The applicant met with the Division on June 11, 2009 to discuss a path forward for the application. As stated in the CDTL review, "The Division rejected the applicant's proposal to (b) (4) The Division also stated that the study data from a published study by Lau, et. al., could be included but would be considered as supportive only because it was a single center trial and was not conducted using esomeprazole. The Division proposed that one path forward would be for the applicant to review and reanalyze the data from previously conducted well-controlled trials using esomeprazole. The applicant agreed to propose and submit a preliminary response to the CR letter for FDA review."

In response to the applicant's July 14, 2009 proposal regarding the information that would be included in a resubmission, the Division sent an advice letter on December 3, 2009. The CDTL summarized the information in that advice letter in her review. The Division indicated its willingness to review the data from previously conducted omeprazole studies as supportive evidence of efficacy.

This review will focus on the elements that led the Clinical/Statistical reviewers to conclude that the evidence provided in this complete response did not, in combination with the originally reviewed randomized, controlled esomeprazole trial provide substantial evidence of efficacy of esomeprazole for the proposed indication.

2. Background

The hypothesis that Nexium IV administered as a "loading dose" that is higher than the approved intravenous dose, coupled with a follow on continuous infusion, will decrease the risk of rebleed from a gastric or duodenal ulcer is linked to what is known about the impact of acidic pH on clot stability and hemostasis. Green WF, et. al. published a series of *in vitro* studies that evaluated the impact of changes in hydrogen ion concentration on the soluble and cellular coagulation systems.(Green WR, et al. Gastroenterology. 1978 Jan; 74(1):38-43.)

The authors reported that coagulation was "extremely sensitive to relatively minor increases in hydrogen ion concentration. All studies became abnormal at pH 6.8." At pH 6.4, polymerization of fibrinogen was prolonged and platelet aggregation was reduced by >50%. At a pH of 5.4 platelet aggregation and plasma coagulation were nearly completely inhibited. Patchett SE, et al. conducted in vitro studies of the impact of gastric juice (from patients and healthy volunteers) on formation of fibrin clots. They showed that gastric juice markedly increased fibrinolysis (Patchett SE, et al. Gut. 1989 Dec; 30(12):1704-7), which was attributed to acid dependent proteases. Pepsinogen is activated to pepsin in gastric acid.

(b) (4)

The applicant conducted a dose finding study, 24 hours in duration, in healthy volunteers to identify a dose that achieved maintaining pH>6 for a sustained period of time. The dose selected was evaluated in the setting of the single phase 3 trial submitted in the original sNDA. The proportion of time the pH exceeded 6 over 24 hours is summarized in the table below, which demonstrates that the pH is <u>below</u> the target range for a substantial portion of the 24 hour period at the dose selected for the single trial submitted in the first review cycle.

Table 1: Estimates of mean percentage of time with intragastric pH>4, pH>6, pH>7 with intravenous infusion of esomeprazole at 5 different infusion combinations in healthy subjects, during the 24 hour period by dose level (adapted from Dr. Tien-Mien Chen's Clinical Pharmacology review from original submission)

	Esomeprazole Regimen	Estimate
pH>4 (0-24)	40 mg + 8 mg/h	82%
	80 mg + 4 mg/h	80%
	80 mg + 8 mg/h	90%
	120 mg (30 min)+ 8 mg/h	84%
pH>6 (**0-3hr**)	40 mg + 8 mg/h	25%
	80 mg + 4 mg/h	35%
	80 mg + 8 mg/h	46%
	120 mg (30 min)+ 8 mg/h	46%
pH>6 (**0-24h**)	40 mg + 8 mg/h	46%
	80 mg + 4 mg/h	44%
	80 mg + 8 mg/h	**52%**
	120 mg (30 min)+ 8 mg/h	49%
pH>7 (0-24h)	40 mg + 8 mg/h	2%
	80 mg + 4 mg/h	4%
	80 mg + 8 mg/h	5%
	120 mg (30 min)+ 8 mg/h	4%

Another way of looking at these data is to evaluate the proportion of subjects that achieved a pH of >6, instead of the proportion of time spent at a pH >6. The proportion of subjects administered the 80 mg IV loading + infusion of 8 mg/hr who sustained a pH>6 for at least 1 hour in the 24 hour period was 58%. This compared to 64% at the 120 mg level, 50% at the 80 mg + 4 mg infusion and only 26% at the 40 mg + 8 mg infusion dose. With this by-patient responder analysis, the 120 mg dose level is numerically higher in achieving a pH>6 than the dose selected to take into phase 3 evaluation. The percentage time at a pH greater than 6 was similar for the two dose levels for the overall 24 hour period, however.

In a second PK/PD study which evaluated esomeprazole 80 mg + 8 mg/h infusion vs. omeprazole in healthy subjects, again with an evaluation period limited to 24 hours, the proportion of time in which the pH was > 6 was 45% (39, 51). This is similar to the findings of the study summarized in the table above, although numerically lower for the proportion of time pH exceeds 6.

The reviewers in the original review cycle raised questions about whether the appropriate dose had been identified for the proposed indication, in light of the limited time pH exceeded 6. This issue was cited in the CR letter. As stated in the Clinical Pharmacology review, the Clinical review and the CDTL review of this resubmission, the applicant has stated that the dose is appropriate. The applicant noted that the pharmacodynamic studies were conducted in healthy volunteers. The applicant proposes that a greater effect would be anticipated in patients with peptic ulcer disease because there is evidence in the literature that the basal gastric pH is higher in patients with H. pylori. The applicant cited literature to support that proton pump inhibitors have a greater impact on gastric pH in patients with H. pylori. The literature includes a publication by Gillen, et al 1999 (H. pylori infection potentiates the inhibition of gastric acid secretion by omeprazole. Gut. 1999; 468-475), in which the authors report a statistically significant difference in median basal fasting gastric pH between H. pylori positive subjects during omeprazole treatment than in H. pylori negative subjects, respectively: 7.95 (2.7-8.3) vs. 3.75 (1.7-8.5), $p<0.002$. The pre-omeprazole basal fasting pH was similar between the groups: 1.6 (1.2-2.9) vs. 1.6 (1.2-7.2). I concur with the Clinical reviewer's concerns about the generalizability of the cited data from the H. pylori population to the general peptic ulcer disease population. Not all ulcers are caused by H. pylori.

3. CMC

This supplement proposes the use of the existing approved drug product. There were no product quality issues cited in the Complete Response letter. The Product Quality Microbiology Reviewers entered a review of the proposed product labeling during this review cycle. They noted that the labeling provides "for extended room temperature holding periods for the drug product admixtures. However, no microbiology stability data was provided to support the holding conditions. Growth of microorganisms inadvertently introduced in to the admixture during dilution of the drug product could potentially harm the patient." They stated that "microbiological data should be provided to demonstrate that the reconstituted product solution will not support microbial growth during the proposed storage periods." A risk assessment summarizing studies that show adventitious microbial contamination does not

grow under the proposed storage conditions was needed. An information request was sent to the applicant during this review cycle. The Microbiology reviewer evaluated the information submitted in response and determined that product labeling was supported by data. An addendum review was entered that documented that there were no remaining CMC issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

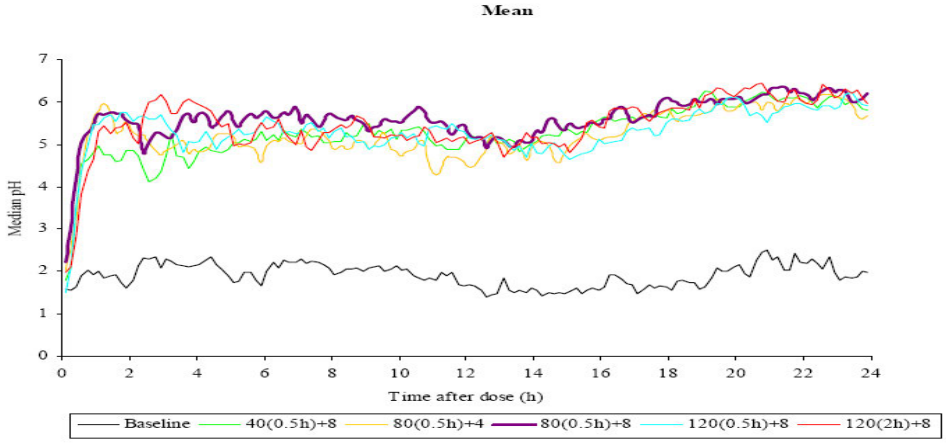
There were no nonclinical issues cited in the Complete Response letter.

5. Clinical Pharmacology

There were two Clinical Pharmacology issues in the CR letter: 1) the Agency questioned whether the dose evaluated in the single efficacy trial was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two PK/PD studies submitted for review, and 2) there was inadequate information to permit proper dosing in patients with hepatic impairment. The applicant submitted responses to these two issues. In addition, because efficacy data from omeprazole trials were submitted in this CR response to support the efficacy of esomeprazole for the proposed indication, it was important to establish the bridge between esomeprazole and omeprazole. The applicant submitted PK/PD data as a foundation for use of the omeprazole efficacy data.

The Clinical Pharmacology reviewers determined that the applicant had provided information that supported that no further dose finding study is needed in the target population. The Clinical Pharmacology reviewers found the literature that demonstrated that H. pylori positive patients can be expected to have a more pronounced impact of PPI (omeprazole) on gastric pH persuasive. However, I do not find that this literature supports that there will be a similar effect in the general population of patients with upper gastrointestinal ulcer bleeding secondary to causes other than H. pylori. In addition, the gastric pH data presented by Gillen, et. al. refer to fasting basal pH, not pH measurements over a 24 hours period. The Clinical Pharmacology reviewers re-examined the PK/PD dose finding data from healthy volunteers and noted that higher doses do not increase the PD effect. It is unknown whether a higher infusion rate (>8 mg/hour) would change the PD results. However, as shown in the figure below, the data suggest that the pH reaches the pH 6 level at 24 hours, so the current dose regimen might be achieving more sustained periods at a pH >6 after 24 hours. In the initial 24 hours, it is possible that the presence of blood in the stomach might alter gastric pH (increasing it) in the target population, even if that population does not have H. pylori.

Figure 1. Median Intragastric pH Profiles at Baseline and during administration of Esomeprazole to Healthy Subjects, Treatments A-E (D9615C00015)



The following table from my original review points out that most of the rebleeds in the esomeprazole arm in the single esomeprazole efficacy trial submitted in the original review cycle, D961DC00001, occurred in the first 24 hours.

Table 2 Proportions of Patients with Rebleeding Events by Time Period in Trial D961DC00001

	Esomeprazole	Placebo
N	375	389
Number of patients with Rebleed in the overall 72 hour period	22 (5.9%)*	40 (10.3%)
Number of patients with Rebleed in the first 24 hours	17 (4.5%)	21 (5.4%)
Number of patients with Rebleed from >24hours to 72 hours.	5 (1.3%)	19 (4.9%)

*percentage of patients in the study arm that experienced rebleed

The majority of additional rebleeds on the placebo arm occurred in the subsequent 12 hours beyond 24 hours. There were 11 additional rebleeds on the placebo arm in that follow-on 12 hours. In contrast there was only 1 additional rebleed in the subsequent 12 hours beyond the first 24 hour period on the esomeprazole arm. These efficacy data and the PK/PD data were what prompted the suggestion that additional dose exploration for the first 24 hour period might result in identification of a more effective dose.

To address the hepatic impairment issue in the CR letter, the applicant submitted information on: 1) an oral esomeprazole study that was conducted in patients with hepatic impairment, and 2) an intravenous omeprazole study conducted in patients with hepatic impairment. The Clinical Pharmacology reviewer noted that in the oral esomeprazole study, in which the esomeprazole dose was 40 mg, the Cmax "was not influenced by the severity of liver impairment." However, she noted that patients with severe hepatic impairment had AUCs 2-3 fold higher than subjects with normal hepatic function. The intravenous omeprazole study evaluated an 80 mg dose of omeprazole infused over 30 minutes, followed by a 24 hour

infusion of 8 mg /hour (similar dosing regimen used in the single esomeprazole efficacy trial). In this intravenous study, the omeprazole mean AUC increased with liver severity: 1.46 fold in mild impairment, 1.74 fold in moderate impairment, and 2 fold higher in severe impairment (relative to normal controls).

After evaluating these data, the Clinical Pharmacology reviewer stated (b) (4) She concurred with the proposal to utilize the same loading dose as recommended for patients without hepatic impairment, since the available data suggest that Cmax is not impacted by hepatic impairment. (b) (4) The applicant proposed (b) (4) 4 mg/hour in patients with severe hepatic impairment. The Clinical Pharmacology reviewers recommended that the applicant should conduct modeling and simulation to "estimate the proper constant infusion rate in moderate and sever hepatic impairment patients." I concur.

With regard to establishing a bridge between esomeprazole and omeprazole to support reliance on the submitted intravenous omeprazole clinical trials, the Clinical Pharmacology reviewers examined the following information:

1) A PK/PD (intragastric pH) comparison of esomeprazole 80 mg intravenous infusion over 30 minutes, followed by an 8 mg/hour continuous infusion, to omeprazole dosed similarly, in Study D961DC00004.
2) Two studies that compared PK/PD of a lower dose (40 mg) of esomeprazole and omeprazole administered over a 30 minute infusion.
3) Comparative PK between esomeprazole and omeprazole after oral and intravenous administration.

The Clinical Pharmacology reviewer noted that differences between the two products were dependent on route of administration, with the greatest difference observed with oral administration. The AUC and Cmax of esomeprazole were approximately 14% higher than omeprazole when the products were administered by a "loading" 80 mg intravenous infusion followed by a continuous infusion of 8 mg/hour. These data are summarized in the figure and table below, which are reproduced from the Clinical Pharmacology review.

Figure 2. Mean plasma concentrations following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects (N=39)

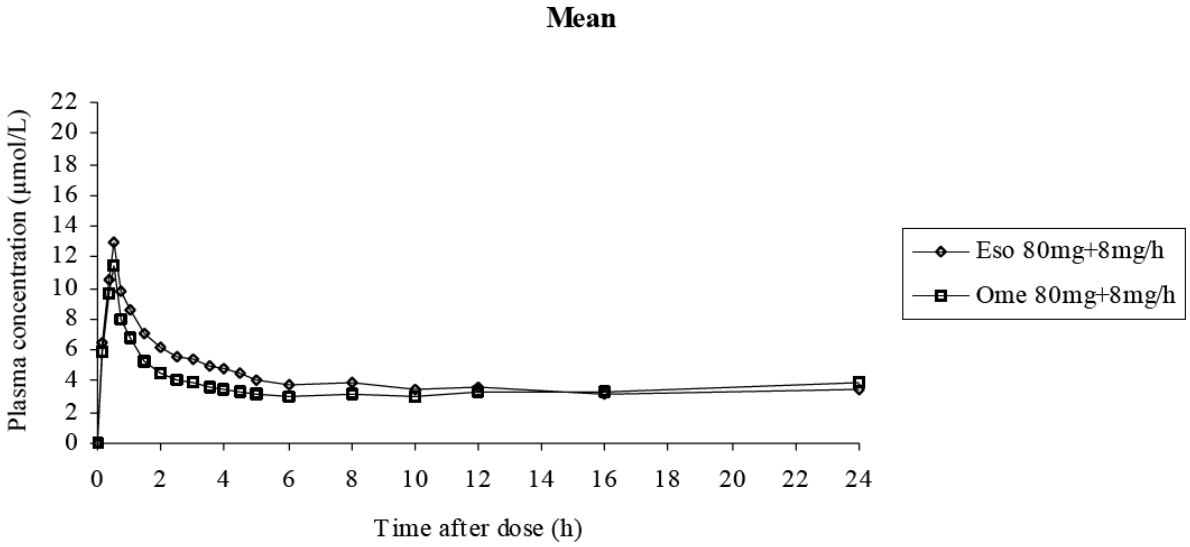


Table 3. Estimated geometric means and 95% CIs for Cmax (µmol/L), AUC) (µmol*h/L), Css (µmol/L) and CL (L/h) following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects

Variable	Treatment	N	Estimate	95% CI	
				Lower	Upper
C_{max}	Esomeprazole	39	12.82	11.92	13.78
	Omeprazole	39	11.28	10.49	12.13
AUC_t	Esomeprazole	38	95.47	86.03	105.94
	Omeprazole	38	83.97	75.67	93.19
C_{ss}*	Esomeprazole	39	3.23	2.93	3.57
CL*	Esomeprazole	39	7.17	6.49	7.91

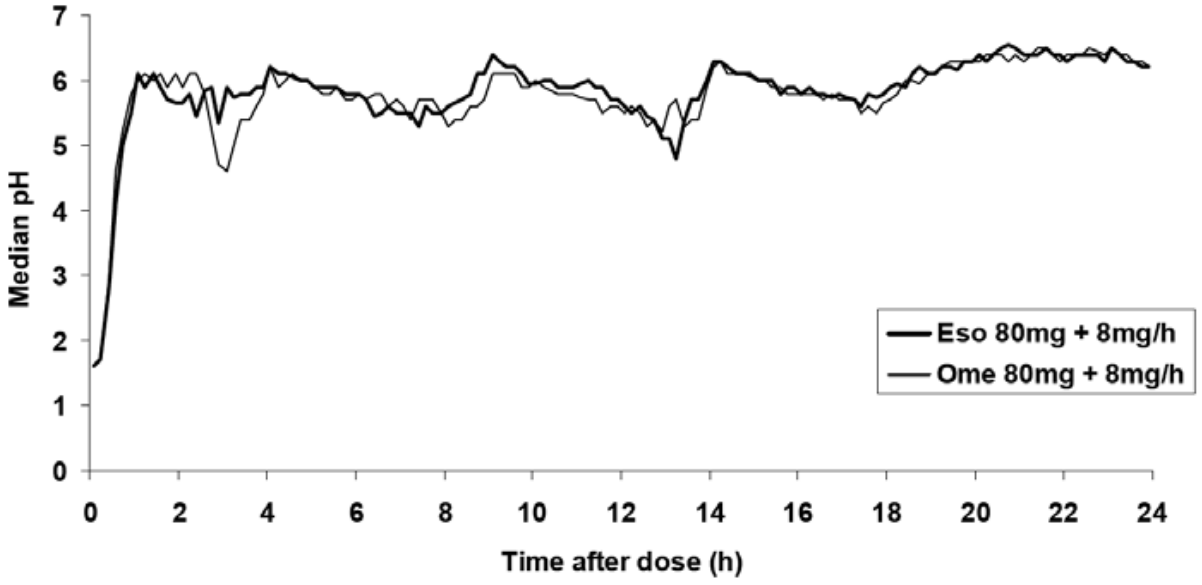
* C_{ss} and CL could not be calculated for omeprazole

The studies of a lower dose, 30 mg infusion, revealed that the esomeprazole AUC was 36%-43% higher than omeprazole and the esomeprazole Cmax was 12-18% higher. After oral dosing, the AUC of esomeprazole was approximately 70% higher than omeprazole and the Cmax was 25-30% higher. Because the exposures for esomeprazole were similar, but somewhat higher than omeprazole, the reviewers concluded that there was an adequate bridge supporting evaluation of favorable omeprazole efficacy data in this sNDA when it was administered at the same doses.

Comparative PD data between an esomeprazole 80 mg intravenous infusion followed by 8 mg/hr and omeprazole administered in the same regimen reveal a similar PD effect in healthy

subjects. The data are summarized in the figure below, which is reproduced from the Clinical Pharmacology review. These data further support the bridge.

Figure 3 Median intragastric pH profile following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects (N=39)



In summary, I concur with the Clinical Pharmacology review conclusions that the applicant should conduct modeling to support the proposed doses in the product label for patients with moderate and severe hepatic impairment. I concur that a new dose finding trial is difficult to support (but not on the grounds that H. pylori patients have a greater pH response to PPIs). I concur that the applicant has provided adequate data to support a bridge between the omeprazole efficacy trials in patients with upper gastrointestinal bleeding ulcers and the single esomeprazole efficacy trial, as long as the same dose and administration schedule was studied.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this complete response submission or the initial submission because esomeprazole is not intended as an antimicrobial product.

7. Clinical/Statistical-Efficacy

In addition to the original single esomeprazole efficacy trial (D961DC0001) that was originally submitted to the sNDA, the applicant included 3 major omeprazole trials in this complete response to support the efficacy observed in the esomeprazole trial (Trial I-840, Trial I-841, and the trial reported in a publication by Lau, et al). The major features of those trials are summarized in the Tables below, which are reproduced from the Clinical Review.

Table 4: Clinical studies included in the applicant's complete response submission

Trial Name	Trial Type	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population
D961DC0001 (TRIAL 01)	Safety and Efficacy	Multicenter International Prospective Randomized Double-blind, Parallel Group, Placebo-controlled	Esomeprazole (a bolus 80mg over 30 min followed by a continuous infusion of 8mg/hr for 71.5 hours) or Placebo Follow-up treatment after IV Esomeprazole with Oral Esomeprazole 40mg once daily for 27 days	767 Randomized 764 Treated	Patients who had undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer classified as Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment modalities varied.)
Lau, et. al.	Safety and Efficacy	Single Center (Hong Kong) Randomized Double-blind, Parallel Group Placebo-controlled	Omeprazole (a bolus intravenous injection of 80mg over 30 min followed by a continuous 8mg/hr infusion for 71.5 hours) or Placebo Follow-up therapy after IV Omeprazole infusion with oral 20mg Omeprazole once daily for 8 weeks	320 Planned 240 Randomized	Hospitalized Patients who had undergone successful endoscopic treatment of a bleeding peptic ulcer. Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment was injection epinephrine followed by thermocoagulation)
Trial I-840 (study stopped prematurely due to safety monitoring)	Safety and Efficacy	Multicenter International Double Blind Parallel Group Placebo Control	Omeprazole 80mg given intravenously as a bolus dose over 30 minutes followed by 8mg/hr for 71.5 hours or Placebo Follow-up therapy after IV Omeprazole infusion with oral 20mg Omeprazole once daily for 21 days. (Oral therapy started at 48hours)	350 Planned 274 Randomized	Hemodynamically unstable outpatients and inpatients with PUB endoscopically classified as Forrest Ia, Ib, IIa, or IIb. (Endoscopic treatments varied. Pre-entry endoscopic treatment only in patients classified as Forrest Ia or IIa)
Trial I-841	Safety and Efficacy	Multicenter International Randomized Double-Blind Parallel Group Placebo-Controlled	Omeprazole 80mg given intravenously as a bolus over 30 minutes followed by continuous infusion of 8mg/hr for 3 to 5 days. (If there were signs of bleeding during day 2 or 3 the infusion was given for 120 hours) Follow-up therapy after IV Omeprazole with Omeprazole 20mg daily for 21 days	400 Planned 333 Randomized	Patients ≥ 60 years old with endoscopic signs of peptic ulcer bleeding and clinical symptoms of upper gastrointestinal bleeding. (Forrest Ia, Ib, IIa, IIb) (Endoscopic treatments varied. Pre-entry endoscopic intervention was only to be used in patients with bleeding classified as Forrest Ia)

Table 5 Comparisons of Trials Submitted (The Lau trial, I-840, I-841, and trial D961DC00001)

	Lau, et. al. 2000	I-840	I-841	D961DC00001
Definition of endpoint criterion	Fresh hematemesis Hypotension: Systolic Blood Pressure<90 Tachycardia PR>110 and Melena Drop in hemoglobin by 20g/l in 24 hours and melena	Moderate: • Hematemesis • Significant amount of coffee grounds or red blood in the nasogastric tube • Hemoglobin falling 16g/l or more • Neither tachycardia or hypertension Severe: • Voluminous hematemesis, red blood in the nasogastric tube or in stools • Unstable circulation or rapid transfusions required to prevent it.	Hemodynamic ally unstable and/or Hb fall>10g/l over 12 hours Fresh Blood (macroscopic in the nasogastric tube or fresh hematemesis) Blood transfusion was necessary to maintain the hemoglobin level.	Blood in the stomach or a verified active bleeding from a peptic ulcer (Forrest class Ia, Ib) **Or** At least 2 of the following: • Vomiting of fresh blood or fresh blood in a gastric tube or hematochezia or melena after a normal stool • Decrease in hemoglobin >20g/l or (hematocrit >6%) despite ≥ 2 units of blood has been transfused during 24 hours • Unstable circulation systolic blood pressure ≤90mm Hg or pulse≥110/min (after having had a stable circulation) **Or** Hematemesis (vomiting of significant amount of (>200ml) of fresh blood)
Therapeutic endoscopic procedures	Injection therapy (epinephrine) followed by captive thermocoagulation with heater probe	Preferably injection technique but thermal coagulation or electrocoagulation allowed	E.g.: sclerotherapy, heater probe	Injection therapy (epinephrine) and/or one of the following: coagulation with heater probe, electrocautery, hemoclips.
Drug and dosing	Placebo or Omeprazole (a bolus I.V. injection of 80mg followed by a continuous infusion of 8mg/hr for 72 hours)	Placebo or Omeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)	Placebo or Omeprazole (a bolus infusion of 80mg over 30mg followed by a continuous infusion of 8mg/hr for 71.5 hours). If signs of rebleeding occurred within 48 hours the continuous infusion was given for 120 hours	Placebo or Esomeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)
Oral Follow-Up Treatment After I.V. treatment	Omeprazole (20mg once daily for 8 weeks)	After 48 hr I.V. therapy, all patients received Omeprazole (20mg once daily until F/U visit Day21)	Omeprazole (20mg once daily until follow-up visit, day 21)	Esomeprazole (40mg once daily for 27 days)
Inclusion criteria Age (years)	≥ 16 years	>18 years	>60 years	≥18 years

	Lau, et. al. 2000	I-840	I-841	D961DC00001
Signs of Gastrointestinal Bleeding	Within 24 hours after admission endoscopy performed	Within 12 hours prior to endoscopy	Within 48 hours prior to admission	Within 24 hours prior to endoscopy
Forrest Classification of Bleeding Ulcers	Ia, Ib, IIa, or IIb	Ia, Ib, IIa, or IIb	Ia, Ib, IIa, or IIb	Ia, Ib, IIa, or IIb
Successful endoscopic hemostasis	Yes	Only Forrest Ia, IIa	Only Forrest Ia	Yes

Sources: Table 9 "Comparisons of the study by Lau et al (Lau et al 2000), studies I-840, I-841 and D961DC00001)" Applicants Supporting Document page 32.

Study Synopsis Trials I-840 and I-841.

The Clinical reviewer evaluated the entry criteria, patient demographics and endoscopic treatments administered in the 3 major omeprazole trials, and determined that differences in the populations studied, endoscopic treatments administered, and definitions of the primary endpoint precluded substantive comparisons between the esomeprazole trial and Trials I-840 and I-841. The Clinical reviewer and Statistical reviewer conducted exploratory analyses of these trials by examining the patients enrolled and identifying patients who received an endoscopic treatment allowed in the esomeprazole trial D961DC00001. Fifty-two such patients were identified: 22 treated with placebo and 30 with omeprazole. No statistically significant difference in proportion of patients with rebleeding events within 72 hours was observed between groups in this exploratory analysis.

The trial reported in a publication by Lau, et. al , heretofore referred to as "the Lau trial", was similar enough to D961DC00001 that the Clinical and Statistical reviewers determined that this trial merited careful review. There were immediate concerns about this trial because it was a single center trial, conducted in Hong Kong. The population studied was exclusively Asian. D961DC00001 was a multicenter, international trial. However, the enrollment criteria regarding Forrest Class and endoscopic intervention were generally consistent between the two trials. The dose and administration schedule for omeprazole was the same as utilized for esomeprazole in trial D961DC00001. Although the primary endpoints differed, the primary endpoint of D961DC00001 was a prespecified secondary endpoint in the Lau trial. The clinical definition of rebleeding was not identical between the trials. In the Lau trial, all rebleeds that were suspected clinically were confirmed with endoscopy. In trial D961DC00001, rebleeding could be diagnosed by clinical criteria alone.

The demographics for the populations enrolled in the two trials are summarized in the table below, which is reproduced from the Clinical Review. Patients in the Lau trial were somewhat older, and there was a higher proportion of patients who presented in hemodynamic shock. Known positive H. pylori status was similar between the two trials. There were more patients with unknown or "trace" H. pylori status in D961DC00001.

Table 6 Comparison Baseline Characteristics trial D96DC00001 and Lau Trial

Characteristic	Lau Trial		Trial D961DC00001	
	Omeprazole (N = 120)	Placebo (N = 120)	Esomeprazole (N = 375)	Placebo (N = 389)
Gender, n (%)				
Male	80 (66.7%)	80 (66.7%)	254 (67.7%)	268 (68.9%)
Female	40 (33.3%)	40 (33.3%)	121 (32.3%)	121 (31.1%)
Age, years				
Mean (SD)	64 (17.2)	67 (15.9)	62.1 (17.1)	60.2 (17.6)
Min – Max	18 – 99	22 - 95	18 – 95	18 – 98
Patients per age category, n (%)				
< 65 years	44 (36.7%)	40 (33.3%)	182 (48.5%)	210 (54.0%)
≥ 65 years	76 (63.3%)	80 (66.7%)	193 (51.5%)	179 (46.0%)
Shock at Presentation, n (%)				
No	104 (86.7%)	106 (88.3%)	356 (94.9%)	370 (95.1%)
Yes	16 (13.3%)	14 (11.7%)	19 (5.1%)	19 (4.9%)
H. pylori status, n (%)				
Negative	42 (35.0%)	56 (46.7%)	92 (24.5%)	119 (30.6%)
Positive	78 (65.0%)	64 (53.3%)	246 (65.6%)	226 (58.1%)
Trace			18 (4.8%)	26 (6.7%)
Missing			19 (5.1%)	18 (4.6%)
Forrest Class, n (%)				
Ia	14 (11.7%)	9 (7.7%)	28 (7.5%)	40 (10.3%)
Ib	50 (41.7%)	49 (40.8%)	166 (44.3%)	163 (41.9%)
IIa	38 (31.7%)	36 (30.0%)	136 (36.3%)	151 (38.8%)
IIb	18 (15.0%)	26 (21.7%)	42 (11.2%)	34 (8.7%)
Missing	0	0	3 (0.8%)	1 (0.3%)
Ulcer location, n (%)				
Gastric	53 (44.2%)	48 (40.0%)	157 (41.9%)	155 (39.8%)
Duodenal	67 (55.8%)	72 (60.0%)	216 (57.6%)	233 (59.9%)
Missing	0	0	2 (0.5%)	1 (0.3%)
Hemoglobin, g/L				
Mean (SD)	94.5 (27.2)	95 (25.7)	97.7 (24.9)	97.4 (25.9)
Hospitalized at time of UGI bleeding prior to enrollment, n(%)				
Not hospitalized	98 (81.7%)	97 (80.8%)	338 (90.1%)	354 (91.0%)
Hospitalized	22 (18.3%)	23 (19.2%)	37 (9.9%)	35 (9.0%)
Previous history of gastric or duodenal ulcer, n (%)	38 (31.7%)	45 (37.5%)	112 (29.9%)	118 (30.3%)
Previous ulcer bleeding, n (%)	36 (30.0%)	36 (30%)	---	--
Previous complications related to gastric or duodenal ulcer, n (%)	---	---	44 (11.7%)	41 (10.5%)
Medication use prior to enrollment, n(%)				
NSAIDs	39 (32.5%)	40 (33.3%)	151 (40.3%)	157 (40.4%)
Acetylsalicylic acid (dose unknown)	23 (19.2%)	18 (15.0%)	103 (27.5%)	103 (26.5%)
Warfarin	5 (4.2%)	5 (4.2%)	9 (2.4%)	13 (3.3%)

The efficacy results in the two trials are summarized in the table below, which is reproduced from the Clinical Review.

Table 7: Proportion of patients with clinically significant rebleeding within 72 hours and 30 days, Trial D961DC00001 and the Lau Trial

Outcome Variable	Trial by Lau et al		Trial D961DC00001	
	Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)_	Placebo (n = 389)
Patients with clinically significant rebleeding within 72 hours, n (%)	**5 (4.2%)**	**24 (20%)**	**22 (5.9%)**	**40 (10.3%)**
Patients with clinically significant rebleeding within 30 days	8 (6.7%)	27 (22.5%)	29 (7.7%)	53 (13.6%)

The incremental difference between omeprazole and placebo in proportion of patients who had clinically significant bleeding within 72 hours is much greater in the Lau trial than the difference between esomeprazole and placebo observed in D961DC00001. The difference in the Lau trial was statistically significant, both for the primary endpoint (30 days) and the secondary endpoint (72 hours). Although the outcome in the Lau trial seemed persuasive on its face, the reviewers expressed concern about the apparent greater treatment effect observed in this single center trial conducted in an exclusively Asian population. They questioned the generalizability of the observation to non-Asian populations. They noted that studies have demonstrated that Asian populations have a lower parietal cell mass, a higher prevalence of H. pylori infection and a higher prevalence of cytochrome 2C19 genetic polymorphism. The lower parietal cell mass and the higher prevalence of H. pylori infection could result in a greater treatment effect observed in an exclusively Asian population. The summary table above indicates that the proportion of patients who were H. pylori positive in the two trials was similar, however, there were more patients with unknown status in D961DC00001. The Clinical Pharmacology review presents data on impact of poor metabolizer phenotype on omeprazole AUC and Cmax (both increase).

The Clinical reviewers also noted the higher rate of events in the placebo arm of the Lau trial relative to the placebo arm of D961DC00001. They considered the possibility that greater patient age and the higher proportion of patients in hemodynamic shock at study entry in the Lau study created a high risk study population, leading to a higher placebo event rate. In the original review of D961DC00001, however, the Clinical reviewer noted that in the sub-population of patients greater than 65 years of age, the apparent treatment effect of esomeprazole was not as great as in the younger patients in the study.

Ultimately, the Clinical reviewers concluded that the data from the Lau trial do not adequately support the effect of intravenous esomeprazole for the reduction of risk of rebleeding of endoscopically treated peptic ulcers. I concur. The Lau trial was a single center trial that enrolled an ethnically homogeneous population. The magnitude of the treatment effect in the two trials differs, and the basis for the differences is not clear. A publication by Ghassemi KA, et. al. (Gastric Acid Inhibition in the Treatment of Peptic Ulcer Hemorrhage. Current Gastroenterology Reports 2009, 11:462-469) also observed this discrepancy and noted that historically studies of treatment for peptic ulcer bleeding in Asian populations have had discrepant results compared to studies that enrolled more diverse populations. The authors attributed the difference to factors such as lower mean age of Asian patients, smaller parietal

cell mass in Asian patients, higher prevalence of slow PPI metabolizers, and H. pylori prevalence in Asians.

The same authors considered whether the relative small absolute difference in percentage of events in 72 hours between the esomeprazole arm and placebo in D961DC00001 supported standardized treatment of patients with this regimen. They ultimately concluded that is was justified in light of a cost effectiveness analysis, and noted that a subgroup analysis of 30-day rebleeding rates suggested that Forrest Ib patients do not require high-dose intravenous PPI therapy because they have a lower rate of rebleeding. The latter conclusion was based on the fact that the observed rate of rebleed in 72 hours in the Forrest Ib subgroup was 5% in both the placebo and esomeprazole arms. (b) (4) Interestingly, in exploratory efficacy analyses by Forrest Class, the difference between omeprazole and placebo in the Forrest Ib subclass in the Lau trial was nominally significant (2% vs. 16%, p=0.02), favoring omeprazole. This subgroup analysis encompassed rebleeding over 30 days. In the Lau study, the proportions of rebleeding events in the first 72 hours in the Ib subgroup were 2% (omeprazole) and 12% (placebo).

An additional apparent inconsistency in efficacy within a subgroup between the two trials was observed in the ≥65 years of age subgroup. In the original review of D961DC00001, the Clinical reviewer was concerned that the treatment effect in patients ≥65 did not appear as great as in patients younger than 65 years of age. The Clinical reviewer of this complete response submission compared the subgroup efficacy analyses by age between the two trials and observed the magnitude of effect differed between trials. It was much greater in the Lau trial in the subgroup of older patients. This is summarized in the table below.

Table 8: Rebleeding Event Rates By Age Subgroup by Trial

Outcome Variable		Trial by Lau et al		Trial D961DC00001	
		Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)	Placebo (n = 389)
	Age subgroup				
Patients with clinically significant rebleeding within 72 hours, n (%)					
	≥ 65 years	5/76 6.6%	21/80 26.3%	6.2%	8.4%
	< 65 years	0/44	3/40 7.5%	5.5%	11.9%
Patients with clinically significant rebleeding within 30 days					
	≥ 65 years	6/76 7.9%	24/80 (30%)	___	___
	<65 years	2/44 4.6%	3/40 7.5%	___	___

I concur with the CDTL that these differences between the trials increase concern that we have limited ability to generalize the results of the single center Lau trial to a more heterogeneous U.S. population.

The reviewers state that the applicant acknowledged the level of significance in the single study did not reach the level of significance needed for a single study to support efficacy in its complete response submission. However, the applicant challenged some of the elements of the deficiencies listed in the CR letter. The Statistical reviewer summarized the applicant's specific disagreements, and evaluated the arguments that they put forth. The applicant maintained that the results of the single trial are consistent across subgroups, secondary endpoints and study centers. The Statistical reviewer agreed with some of the applicant's points, and disagreed with others.

Because a single study was submitted to support the proposed indication in the initial sNDA, the original FDA Statistical reviewer conducted a series of sensitivity analyses to assess the robustness of the study results. The following, taken from my original review, summarizes some of the major exploratory analyses that the FDA reviewers conducted during the original review cycle:

1) To address the concern that the Forrest Class I vs. II stratification, which was in the prespecified analysis, had been changed after closing the study, the reviewers conducted an analysis utilizing the original planned analysis, incorporating pooled Forrest Class I and II. This analysis yielded efficacy results similar to those presented by the applicant in this NDA utilizing the modified Statistical Analysis plan, p=0.027. (The p value shifted minimally from 0.026.)

2) To address the issue of collapsing the four Forrest categories into two stratification categories, the reviewers adjusted the primary efficacy analysis utilizing all four classification categories in the model. This analysis also incorporated the applicant's prespecified stratification factor of type of endoscopic treatment. The results of this exploratory analysis yielded a nonsignificant p-value of 0.169. The treatment effect remained -4.4% for proportion of treatment effect esomeprazole minus placebo.

3) Regarding the concerns about the variation in standard of care across countries and centers, the reviewers explored the following:
    a. Dropping all patients treated with only epinephrine injection from the analysis, since this stand alone treatment is no longer considered sufficient therapy in the U.S. This reduced the population by 143 in the esomeprazole arm and by 142 in the placebo arm. The overall treatment effect remained -4.5% (esomeprazole minus placebo), but the p-value shifted to 0.067. This shift, however, might be anticipated with dropping approximately a third of the patients from the ITT analysis.
    b. Dropping the center from the Netherlands, Site 0102, which had the largest treatment effect in favor of esomeprazole, 30.9%, from the analysis. The number of patients randomized at this site was 53 of the total 764 ITT population. Dropping this site from the analysis resulted in a slightly

diminished overall treatment effect, -3.73% ((5% CI= -7.67, 0.10) (esomeprazole minus placebo), and a shift in the p-value to 0.06.

c. Adding country as a stratification factor to explore the treatment effect by country. (The reviewers could not do a similar analysis by center because only a limited number of centers had randomized >12 subjects.) When country was added as a stratification factor to the model that incorporated the applicant's original prespecified analysis stratification factors of endoscopic treatment (single vs. combination) and pooled Forrest Class (I vs. II), the p-value shifted to non-significant, p=0.058. The treatment effect remained -4.4% for proportion of treatment effect esomeprazole minus placebo. If the model incorporated adjustment for the Forrest class by individual classification – Ia, Ib, IIa, IIb – and country, the p-value shifted to 0.327.

4) The reviewers evaluated subgroup analyses to examine the trial for consistency of the observed outcome among important subgroups. The treatment effect for esomeprazole was most pronounced in younger patients, less than age 65 (6% rebleed vs. 12% rebleed). In patients over the age of 65 (total N = 372), the rebleed rate was 6% on the esomeprazole arm and 8% on the placebo arm.

The FDA's exploratory analyses included an investigation of the contribution of country to the overall results of this single trial (which didn't enroll patients at sites within the US). Adjustment by country was explored because analyses adjusting by study center could not be performed due to low enrollment at many sites. The CR letter stated "It is appropriate to account for country-to-country variation, so the protocol specified analysis was further stratified by country. This resulted in an insignificant treatment effect (p=0.06), although the absolute reduction in rebleeding remained 4.4%."

In the Complete Response, the applicant asserted that the Breslow-Day test supports the homogeneity of the treatment effect across study centers. The Statistical reviewer did not agree: "Because the Breslow-Day test is not a very powerful test for detecting lack of homogeneity, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables in the original study further limits the usefulness of the test. Additionally, the test assesses the consistency of odds ratios, whereas the estimate of interest was the difference between two treatment groups." The Statistical reviewer noted that the applicant expressed concerns about the FDA's use of the Mantel-Haenszel test, stratified by country. The applicant stated that 29/64 2X2 tables would have to be excluded in this analysis due to absence of observations in table cells. The Statistical reviewer examined the FDA analysis from the original review and found that no tables were excluded from the analysis because the original reviewer utilized a PROC FREQ SAS procedure to implement the Mantel-Haenszel test, which adds a value of 0.5 to cells with no observations. In addition, the Mantel-Haenszel analysis was not limited to the country stratification.

The CR letter cited concerns about variability in treatment effect across centers and concerns about Center 0102, located in the Netherlands, which had a very large treatment effect favoring esomeprazole. The table below, reproduced from the Statistical reviewer's addendum review, summarizes the observed treatment effect in each center.

Table A.1
Study D961DC00001: Treatment Effect and 95% Confidence Interval by Center (ITT Population)

Center Number	n_{Nexium} / $n_{Placebo}$	Esomeprazole – Placebo (%)	95% C.I.
11	1 / 3	**66.67**	
12	6 / 6	-16.67	
23	3 / 3	**16.67**	
41	3 / 4	-25.00	
76	7 / 5	**14.29**	
82	3 / 4	-25.00	
84	3 / 3	-33.33	
98	7 / 8	-25.00	
99	5 / 5	-20.00	
105	5 / 5	**20.00**	
106	1 / 2	**100.00**	
110	1 / 2	-50.00	
121	1 / 2	-100.00	
122	5 / 7	-8.57	
133	1 / 1	-100.00	
138	7 / 6	-16.67	
143	2 / 1	**50.00**	
144	3 / 4	-50.00	
160	2 / 4	**25.00**	
163	3 / 2	**33.33**	
174	2 / 2	-50.00	
175	3 / 5	-20.00	
176	4 / 4	**50.00**	
177	7 / 11	**14.29**	
180	7 / 3	-19.04	
183	7 / 6	**14.29**	
186	3 / 3	-33.00	
201	5 / 3	**20.00**	
215	8 / 8	-12.50	
21 (Denmark)	13 / 16	-6.25	(-30.23, 18.60)
53 (France)	13 / 13	0.0	(-26.17, 26.17)
78 (Germany)	10 / 10	-20.00	(-56.67, 19.04)
101 (Hong Kong)	25 / 25	-4.00	(-22.22, 13.51)
102 (the Netherlands)	**11 / 10**	**-30.91**	**(-66.10, 7.99)**
127 (Romania)	12 / 12	-8.33	(-38.48, 18.85)
145 (Russia)	12 / 16	-12.50	(-38.48, 14.43)
149 (South Africa)	14 / 15	7.62	(-20.12, 35.97)
184 (Turkey)	12 / 13	-7.69	(-37.57, 18.91)

Source: Statistical Reviewer's Listing

The applicant maintained that the data from site 0102 were high quality and that the large treatment effect could have resulted from recruitment of higher risk patients at this site. The Statistical reviewer remained concerned about the robustness of this single study, however, in light of the fact that if the 21 subjects enrolled at the site are removed from the analysis, the p-value shifts to >0.05. [The overall treatment effect observed in the study decreased to -3.73% (95% CI=-7.67,0.10) and p-value shifted to 0.06.] This concern is based on the fact that 21 is a relatively small fraction of the total of 767 patients in the entire study, and yet the p-value is impacted by their removal. Interestingly, the Hong Kong site in D961DC00001 enrolled double the number of patients enrolled in the Netherlands, and the treatment effect was much smaller, even smaller than that observed in the Lau trial discussed earlier in this review.

The CR letter cited inconsistencies in treatment effect among subgroups. The Statistical reviewer stated in her addendum review that she agreed with the applicant that the results did not appear to vary substantially among subgroups defined by race, age, and gender. She placed the following quote from the original sNDA statistical review from 11/13/2008 in her addendum review to show the subgroup data she examined to support her conclusion:

> Table A.2 presents descriptive results by race, age and gender. In the larger subgroups numerical differences favor esomeprazole over placebo. The rate of clinically significant rebleeding within 72 hours is less in the esomeprazole group compared to the placebo group for the following subgroups:
>
> - Caucasian (5.5% for esomeprozole vs. 10.8% for placebo)
> - Oriental (3.7% for esomeprozole vs. 7.4% for placebo)
> - less than 65 years of age (5.5% for esomeprozole vs. 11.9% for placebo)
> - at least 65 years of age (6.2% for esomeprozole vs. 8.4% for placebo)
> - males (5.9% for esomeprozole vs. 10.4% for placebo)
> - females (5.8% for esomeprozole vs. 9.9% for placebo)

The reviewers from the original review were concerned that there might be differences in efficacy between older and younger age groups based on the fact that the rate of rebleed was halved in the <65 years of age group, but was reduced by approximately 25% in the older age group. Nearly half of the patients enrolled in this trial were ≥ 65. Although this subgroup analysis does not constitute robust evidence of difference of treatment effect, the observation was included in the CR letter as one of many points that created concerns about relying on a single trial, particularly without a highly persuasive p value. As noted in the discussion of the Lau trial results, the treatment effect in the older age group in that trial appeared greater than that in the younger age group, and differed from the analysis in D961DC00001. Nearly 2/3 of patients in the Lau trial were ≥ 65 years of age.

Ultimately, the Statistical reviewer has concluded that the applicant's responses "do not dispel concerns regarding the level of statistical significance, and issues with the distribution of the treatment effect across study center and country." She stated, however, that the review question now, after submission and review of the omeprazole trials, is not whether the data from the esomeprazole trial is adequate to stand alone as substantial evidence of efficacy to support approval of the proposed indication, but "whether the original study can be considered one of two studies to support the efficacy of esomeprazole, where the other studies are the omeprazole studies contained in the resubmission." She concluded that the Lau omeprazole study results " appeared persuasive, the issue is whether the results can be generalized to the United States. Thus, the approval of the desired indication seems to rest on the original study."

8. Safety

Safety data sets for omeprazole studies I-840 and I-841and the esomeprazole Study D961DC00001 (from the original sNDA submission) were submitted in this complete response. For the Lau trial (omeprazole), case report forms were submitted. Postmarketing safety information for esomeprazole was also submitted. The Clinical reviewer did not review the safety data sets from study I-840 and I-841. However, the Clinical reviewers noted that mortality was higher in the omeprazole arm of I-841. The Clinical reviewer evaluated the safety data from the Lau trial and the postmarketing safety data.

Because the case report forms for the Lau study did not identify the patient's treatment group assignment, interpretation of association with treatment was impossible. An information request was sent late in the review cycle for this information, and it will be reviewed with the next cycle. There were five patients in the omeprazole group who died within 30 days after the initial endoscopy, none due to recurrent bleeding. Twelve patients in the placebo group died within 30 days of the initial endoscopy. Four died after surgery (gastrectomy for recurrent bleeding in 3 and excision of a perforated ulcer in 1). Two placebo patients, deemed unfit for surgery, died from recurrent bleeding. The remaining six died from complications related to concurrent illnesses.

The submitted postmarketing safety data included 41 case reports describing 45 serious adverse events (SAEs) and 20 non-serious adverse events, which were identified in the applicant's most recent periodic safety update report. In ten of the case reports, the indication for use was gastrointestinal bleeding. Two of the reports were from clinical trials where esomeprazole had been given either as a concomitant drug or the indication was for use in pediatric patients. Three deaths were reported; one case of agranulocytosis, hematoma, and acute hepatitis. Doses were provided in 35 case reports, and ranged from 20mg to 200mg daily. When recorded, the time from initiation of the intravenous esomeprazole therapy to the onset of the adverse event ranged from 0 days to 61 days.

I concur with the CDTL's conclusions that the safety data within this submission were limited and revealed no new safety signal.

9. Advisory Committee Meeting

There was no advisory committee meeting for this supplemental application.

10. Pediatrics

The applicant requested a waiver of pediatric studies because "studies are impossible or highly impractical because the number of patients is so small and geographically dispersed." The Clinical reviewers of the initial submission did not agree and requested that a pediatric program be developed for this indication. The application was not discussed at PeRC during that review cycle because it is not going to be approved.

In the resubmission, the applicant again requested a full waiver. Pediatric and Maternal Health Staff (PMHS) was consulted to evaluate the feasibility of pediatric studies for the proposed indication; (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. The applicant provided peptic ulcer incidence rates in children from Germany and Sweden (4.3/100,000 and 0.5/100,000 respectively) and stated that only a fraction of these patients would have bleeding. The applicant also provided data from a claims data base as a basis for projecting the number of pediatric patients with bleeding peptic ulcer in the U.S. The PMHS reviewer concluded that studies in pediatric patients who undergo therapeutic endoscopy for acute bleeding gastric or duodenal ulcers are impossible or highly impracticable because the number of patients is so

small or the patients are geographically dispersed. She recommended that a full waiver for the proposed indication. The PMHS reviewer stated that if the applicant were to seek a broader indication such as (b) (4) pediatric studies may be feasible. The Pediatric Review Committee concurred with granting the full waiver.

The potential for a Written Request for pediatric studies was discussed; however, esomeprazole was granted pediatric exclusivity on May 1, 2009. The CDTL noted in her review that "Since esomeprazole is an enantiomer of omeprazole, the exclusivity granted to esomeprazole at that time was considered a second period of exclusivity for the moiety. Therefore, esomeprazole is not eligible for any further periods of exclusivity."

11. Other Relevant Regulatory Issues

No additional financial disclosures were submitted with the complete response. The financial disclosure review in the initial review cycle identified that one investigator, Dr. Ernst J. Kuipers, reported receiving significant financial payments and was a principal investigator at a site in the original pivotal trial, site 0102 in the Netherlands. The largest treatment effect in all centers that participated in this study was observed at this site, -31% rebleeding events, favoring the esomeprazole arm of the study. A sensitivity analysis was conducted to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, and the overall treatment effect observed in the study decreased to -3.73% (95% CI = -7.67, 0.10). The p-value shifted to 0.06.

A DSI consult was obtained to inspect site 0102. The DSI consult concluded that no significant deficiencies were observed and a Form FDA 483 was not issued. The study data from Site 102 appear reliable with respect to the study protocol as written and submitted in the NDA.

12. Labeling

This supplement will not be approved at this time. There were no labeling negotiations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Complete Response
- Risk Benefit Assessment – I concur with the Clinical and Statistical reviewers that the applicant has not provided sufficient evidence in this application to establish that Nexium IV, administered in the proposed dose of 80 mg intravenous loading dose over 30 minute infusion, followed by 8 mg/hour for 3 days, is effective in (b)(4) The p-value from the single phase 3 study submitted in the first review cycle was not highly statistically persuasive and was not found to be robust in multiple sensitivity

analyses. The sensitivity analyses selected were meaningful as they addressed potential confounders in the conduct of the trial and its analysis. The applicant's responses to the elements of the deficiencies identified in trial D961DC00001 in the CR letter did not change the reviewers' position that the trial was not adequate to stand alone as a single trial that provides substantial evidence of efficacy.

I concur with the reviewers that the data from the submitted omeprazole studies are not sufficient to support approval of Nexium IV for the proposed indication. The omeprazole data from the Lau trial are clinically and statistically persuasive; however, it is not clear that the data from this study are generalizable to the U.S. population because this study was performed at a single site in Hong Kong. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of *H. pylori* infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which may potentially lead to a larger treatment effect.[1] In addition, there were inconsistencies in magnitude in the observed treatment effect between the Lau trial and D961DC00001, both overall and within specific subgroups. Therefore, the data presented by the applicant in this resubmission do not adequately establish the effectiveness of intravenous esomeprazole for the reduction of risk of rebleeding of endoscopically treated peptic ulcers.

I concur with the reviewers that the applicant should conduct at least one additional phase 3 trial to replicate the findings of the study submitted in this supplement.

The following description of this NDA supplement's deficiencies and how they may be addressed will be conveyed in the Complete Response letter:

CLINICAL AND STATISTICAL

The additional data submitted do not provide substantial evidence of efficacy of your product for the proposed indication for the reasons listed below:

1. Trials I-840 and I-841 differ from the efficacy trial, D961DC00001, submitted in the sNDA on May 29, 2008, in several important ways, including the endoscopic treatments administered and the primary endpoints evaluated. Therefore, these trials were not adequately designed to support the proposed indication.

2. When patients from trial I-840 and I-841 are matched to the population enrolled in the original efficacy trial, D961DC00001, based on enrollment criteria, too few patients remain to provide adequate power to show a statistically significant treatment effect. Of the combined total of 607 patients enrolled in the studies, only 52 patients met the

[1] Leontiadis GI, Sharma VK, Howden CW; Systematic review and meta-analysis: enhanced efficacy of proton-pump inhibitor therapy for peptic ulcer bleeding in Asia—a post hoc analysis from the Cochrane Collaboration.; *Alimen. Pharmacol. and Therap;* .2005; 21:1055-1061.

enrollment criteria of D961DC00001. The proportion of omeprazole-treated patients in this subgroup who had a rebleeding event within 72 hours was 13.6% (3/22). Although this proportion was lower than that observed in the placebo-treated patients, 23.3% (7/30), the difference was not statistically significant (p=0.49, Fisher's Exact Test).

3. The clinical trial reported by Lau, et al.[2] is comparable in design to D961DC00001 and the trial provides evidence of efficacy of intravenous omeprazole for the proposed indication. However, the study was conducted at a single center in Hong Kong and the population enrolled was ethnically homogeneous. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of *H. pylori* infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which could have contributed to the larger treatment effect observed in the Lau trial. Therefore, the ability to generalize the results of this trial to the U.S. population is limited.

4. There is a substantive difference in the rebleeding rate in the placebo group (20%) of the trial reported by Lau, et al. compared to D961DC00001 (10%). It is not clear why the rebleeding rate in the Lau, et al. trial is double the rate observed in D961DC00001. It may be partially explained by the differences in Asian populations described in #3 above, or by differences in factors such as age and baseline health status, which may impact on the risk of rebleeding. Additionally, operational factors such as differences in endoscopic technique may affect the risk of rebleeding. This inconsistency in rebleeding rates between the trials also raises questions about the ability to generalize the results of this trial to the U.S. population.

5. There were substantive differences in the efficacy outcomes within important subgroups in the clinical trial reported by Lau, et al. compared to D961DC00001. These inconsistencies raise questions about the reproducibility of the efficacy outcome.

    a. In the subgroup of patients 65 years of age and older, the decrease in proportion of patients with rebleeding within 72 hours in the esomeprazole arm relative to placebo was 2.2% in D961DC00001. In contrast, the decrease in the same subgroup treated with omeprazole relative to placebo in the trial reported by Lau, et al. was 19.7%.

    b. In the subgroup of patients with Forrest Ib classification, there were similar proportions of patients with rebleeding within 72 hours in the esomeprazole and placebo arms in D961DC00001 (a 0.5% difference). In contrast, there was a decrease in the proportion of patients with rebleeding within 72 hours in the omeprazole arm relative to placebo of 10% in the trial reported by Lau, et al.

6. The information from observational studies and literature reviews of intravenous esomeprazole and omeprazole were not considered adequate to constitute primary evidence of the efficacy of the product for the proposed indication.

[2] Lau J, Sun J, Lee K, et al, Effect of Intravenous Omeprazole on Recurrent Bleeding after Endoscopic Treatment of Bleeding Peptic Ulcers, N. Engl. J. Med., 2000, Aug 3; 343(5): 310-316

7. We have reviewed your responses to the deficiencies cited in the November 26, 2008, Complete Response Letter regarding trial D961DC00001. Your responses do not change our conclusion that D961DC00001, as a single adequate and well-controlled trial, does not provide sufficient evidence to support the your proposed indication. The following comments are responses to specific issues raised in your resubmission:

    a. Your assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers for D961DC00001 is not persuasive. The Breslow-Day test is not a powerful test for detecting lack of homogeneity. For this reason, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables further limit the usefulness of the test.

    b. A Division of Good Clinical Practice Compliance inspection was performed at site 0102 in the Netherlands because Dr. Ernst J. Kuipers, MD, PhD, the principal investigator at that site, disclosed that he had accepted significant payments from AstraZeneca. The inspection found that the data from this site appear reliable. Nevertheless, as stated in the Complete Response letter, the large magnitude of treatment effect observed at this site, and the impact this single site had on the overall efficacy of the trial, suggest that the efficacy results of DC961DC00001 are not robust.

    c. You contend that the suboptimal pharmacodynamic (PD) effects of esomeprazole on gastric pH observed in the PK/PD studies submitted in the sNDA on May 29, 2008, can be attributed to the fact that the studies were performed in *Helicobacter pylori* negative healthy subjects, i.e., subjects in whom it would be more difficult to suppress intragastric acidity, and that a pH of 6 would have been more consistently achieved if the population studied had had peptic ulcer disease. We disagree because this position assumes that all patients with peptic ulcer disease have H. pylori. Not all patients with peptic ulcer disease are H. pylori positive. The populations enrolled in the clinical trials you submitted to this NDA attest to this.

In order to address the deficiencies that have been identified in this sNDA, the following information should be included in the resubmission:

Conduct at least one additional, adequate, and well-controlled trial to demonstrate the clinical benefit of Nexium® IV (b) (4) The trial should include some U.S. centers, and should be designed to evaluate a specific population of patients that would be most likely to benefit from treatment with esomeprazole.

Additional Comments:

The pharmacokinetic data in patients with hepatic impairment that you provided in the sNDA are not adequate to assess the recommended dose for continuous intravenous infusion of esomeprazole in patients with moderate and severe hepatic impairment.

The following information should be included in the resubmission:

Resubmit the modeling and simulation results of previously collected data to support an estimate of the proper constant infusion rate in patients with moderate and severe hepatic impairment

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/s/

DONNA J GRIEBEL
06/16/2011

Summary Review for Regulatory Action

Date	November 26, 2008
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	21-689 S-014
Applicant Name	Astra Zeneca
Date of Submission	May 29, 2008
PDUFA Goal Date	November 28, 2008
Proprietary Name / **Established (USAN) Name**	Nexium esomeprazole sodium for injection
Dosage Forms / Strength	Intravenous
Proposed Indication	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Anil Nayyar, MD/Hugo Gallo-Torres/PhD, MD
Statistical Review	Sonia Castilio, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD/David Joseph, PhD
CMC Review/OBP Review	David Lewis, PhD/Hasmukh Patel, PhD
Microbiology Review/Email November 25, 2008	James L. McVey, PhD/ David Hussong, PhD
Clinical Pharmacology Review	Tien-Mien Chen, PhD/Sue-Chi Lee, PhD
OPS/IO/PARS	Raanan A. Bloom, PhD

OND=Office of New Drugs

APPEARS THIS WAY ON ORIGINAL

Division Director Review

1. Introduction

Nexium® IV (esomeprazole sodium injection) was approved in 2005 for short-term treatment (up to 10 days) of GERD in patients with a history of erosive esophagitis, as an alternative to oral therapy when therapy with Nexium Delayed-Release Capsules is not possible or appropriate. The label states that "when oral therapy is possible or appropriate, intravenous therapy with Nexium IV for Injection should be discontinued and the therapy should be continued orally." The approved doses for this product are either 20 or 40 mg once daily by intravenous injection (over no less than 3 minutes) or intravenous infusion (10-30 minutes). No new dosage format/presentation is proposed in this new application to accommodate the higher dose and the infusional administration schedule. Nexium IV is currently supplied as 20mg and 40 mg vials.

In this NDA supplement, the applicant, AstraZeneca, proposes a new indication, for which there is a new dose and administration schedule. The new indication is "Nexium IV for Injection is indicated (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers". The dose proposed in the label for this indication is 80 mg administered as an intravenous infusion over 30 minutes, followed by a continuous infusion of 8 mg/hour given over 3 days, (b) (4) (b) (4) (b) (4) The oral formulation indications include: 1) healing of erosive esophagitis, maintenance of healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease, reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers based on age or history of gastric ulcers, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

The applicant submitted a single randomized, placebo controlled clinical trial to support this new indication. In addition, two PK/PD studies, 24 hours in duration, both conducted in healthy volunteers, were submitted to provide evidence that the dosing regimen achieved the pharmacodynamic goal of raising gastric pH to at least 6. This review will focus on the elements that led the clinical/statistical reviewers to conclude that the evidence provided in this single randomized, controlled trial coupled with the PK/PD data, is not adequately robust to support approval at this time.

2. Background

As stated above, the intravenous Nexium IV product was approved in 2005. The development plan for the indication proposed in the current supplement was the subject of correspondence between the FDA and the applicant. Responses to meeting questions were accepted in lieu of

a meeting on February 9, 2004. The review division concurred to a placebo controlled trial in the first 72 hours after endoscopic intervention, but recommended that pharmacodynamic data be collected on Days 1, 4 and 8.

The hypothesis that the higher dose of Nexium IV coupled with a continuous infusion would decrease the risk of rebleed is linked to what is known about the impact of acidic pH on clot stability and hemostasis. Green WF, et. al. published a series of in vitro studies that evaluated the impact of changes in hydrogen ion concentration on the soluble and cellular coagulation systems.(Green WR, et al. Gastroenterology. 1978 Jan; 74(1):38-43.) At pH 6.4, polymerization of fibrinogen was prolonged and platelet aggregation was reduced by >50%. At a pH of 5.4 platelet aggregation and plasma coagulation were nearly completely inhibited. Patchett SE, et al. conducted in vitro studies of the impact of gastric juice (from patients and healthy volunteers) on formation of fibrin clots. They showed that gastric juice markedly increased fibrinolysis (Patchett SE, et al. Gut. 1989 Dec; 30(12):1704-7), which was attributed to acid dependent proteases. Pepsinogen is activated to pepsin in gastric acid.

(b) (4)

The applicant conducted a dose finding study, 24 hours in duration, to identify the optimal dose for achieving the pharmacodynamic goal of maintaining pH>6. That dose was then evaluated in the setting of a phase 3 trial that enrolled a population of patients who presented with an upper gastrointestinal bleed from either a gastric or peptic ulcer. The study utilized a 72 hour intravenous treatment, followed then by oral daily dosing for the remainder of a 30 day period. The primary clinical benefit endpoint was reduction in rebleeding during the 3 day period of intravenous esomeprazole infusion. In the Clinical Pharmacology/Biopharmaceutics section of this review I will summarize the PK/PD data and the observed potential for the dose and administration schedule to achieve the PD goal of increasing the pH to >6. In the Clinical/Statistical section of this review I will examine the efficacy outcome reported in the single randomized, placebo controlled efficacy study submitted to support marketing approval for this new indication, and how that outcome correlates with the pharmacodynamic effects described in the PK/PD studies.

A single efficacy study was submitted to support approval of this supplemental NDA. The major focus of the clinical/statistical review was whether this single study provides adequately robust evidence of effectiveness to support the approval of Nexium IV for the proposed new indication –

(b) (4)

– as a stand alone trial.

3. CMC/Device

This supplement proposes the use of the existing approved drug product, The only CMC issue was the Environmental Assessment, due to the increased dose and potential increased use of this product. The supplement was reviewed for Environmental Assessment and the

recommendation was "FONSI" (Finding of No Significant Impact), by Raanan Bloom, PhD, from HFD-003.

I concur with the CMC reviewer that this supplement is approvable from a CMC standpoint.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The current Nexium IV product label's Clinical Pharmacology section reports pharmacokinetic data for the intravenous 20 mg and 40 mg doses in healthy volunteers who were administered Nexium IV daily x 5 days. The pharmacokinetic parameters are for the fifth day of dosing, and reveal some accumulation in the AUC with increasing dose. While the C_{max} increases in a dose proportional fashion, the AUC more than doubles with doubling of the dose. A similar phenomenon was observed previously in evaluation of the pharmacokinetics of the oral Nexium doses of 20 and 40 mg over 5 days of administration – a dose proportional increase in C_{max} between the two doses, but a tripling of AUC between the 20 and 40 mg dose levels, with a slight increase in the $t_{1/2}$ at the 40 mg dose level relative to 20 mg.

Pharmacokinetics of Nexium After **IV** Dosing for 5 Days

	Nexium IV 20 mg	Nexium 40 mg
AUC(micromole*h/L)	5.1	16.2
	(4.0-6.6)	(14.5, 18.2)
C_{max} (micromole/L)	3.9	7.5
	(3.2,4.7)	(6.9,8.1)
$T_{1/2}$ (hour)	1.1	1.4
	(0.9, 1.2)	(1.3, 1.5)

The pharmacodynamic (PD) effects of Nexium dosed IV daily x 5 days were reported in the Clinical Pharmacology review of the initial NDA for Nexium IV – NDA 21-689. The PD effects were reported as percentage of time with pH>4. The following table is a reproduction with modification of Table 4 Estimates of geometric means of the percentage time pH >4 after IV and oral administration of 40 mg multiple doses of esomeprazole from the Clinical Pharmacology review:

Pharmacodyamic Effects of Esomeprazole 40mg IV and PO: Percentage Time pH >4

Study Day	Treatment	Estimate	95% CI
Day 1	40 mg **IV**	**42%**	(35,48)
	40 mg PO	37%	(30,44)
Day 5	40 mg **IV**	**66%**	(62,70)
	40 mg PO	64%	(60,67)

The table above shows an increase in the pharmacodynamic effect over time with both the oral and intravenous products.

PK (Table 3 Estimates of geometric means of the primary PK parameters after IV and oral administration of 40 mg multiple doses of esomeprazole) is reproduced from the Clinical Pharmacology review of the initial review of NDA 21-689 for Nexium IV. The table shows that the AUC increases from Day 1 to Day 5, while the C_{max} remains fairly stable. The $t_{1/2}$ increases slightly and clearance decreases.

Estimates of geometric means PK parameters after multiple doses of IV and oral esomeprazole

		Treatment	Estimate	95% CI
AUC	Day 1	40 mg IV	9.9	(8.2,11.9)
	Day 5	40 mg IV	16.2	(14.5, 18.1)
C_{max}	Day 1	40 mg IV	6.8	(6.0, 7.6)
	Day 5	40 mg IV	7.5	(6.9, 8.1)
$T_{1/2}$	Day 1	40 mg IV	1.1	(0.9, 1.2)
	Day 5	40 mg IV	1.4	(1.3,1.5)
Clearance	Day 1	40 mg IV	11.7	(10.0, 13.7)
	Day 5	40 mg IV	7.1	(6.4, 8.0)

In a study of longer duration, the PK/PD of intravenous esomeprazole 40 mg dosing (30 minute infusion) x 10 days was evaluated. Again the AUC was noted to increase, $t_{1/2}$ increased and clearance decreased when the values at Day 10 were compared to Day 1. The percentage of time that the pH was >4 increased from a mean of 33% on Day 1 to 56% on Day 10.

The pharmacodynamic impact of the oral 20 and 40 mg dose levels administered over a 5 day period on intragastric pH is presented in the Nexium oral product label. The table below is taken (and modified) from the Delayed Release capsule and oral suspension label. Please note that these pharmacodynamic data were obtained after 5 days of dosing, and the reference pH is 4.

Effect of **Oral** Nexium on Intragastric pH on **Day 5**

	Nexium 20 mg oral	Nexium 40 mg oral
Percent Time Gastric **pH >4** (hours)	**53%**	**70%**
Coefficient of variation	37%	26%
Median 24 hour pH	**4.1**	**4.9**
Coefficient of variation	27%	16%

In the review of the oral Nexium NDA, NDA 21-153, which is publicly available, the clinical pharmacology reviewer noted that when the oral Nexium doses of 5, 10 and 20 mg were evaluated to examine the correlation of AUC with percentage of inhibition of pentagastrin-stimulated acid secretion, the antisecretory effect was dose dependent across those doses. An

increased effect upon repeated daily doses was noted. A lower AUC was needed for maximal inhibition of acid secretion on day 5 relative to Day 1. These data are summarized in the table below, which is reproduced and modified from Table 1 Summary of the mean primary PK and PD parameters for each treatment form the Clinical Pharmacology review, which is publicly available on the CDER website, from NDA 21-153 esomeprazole (page 34 of that review).

PK/PD of Ascending Doses of **Oral** Esomeprazole Over Five Days

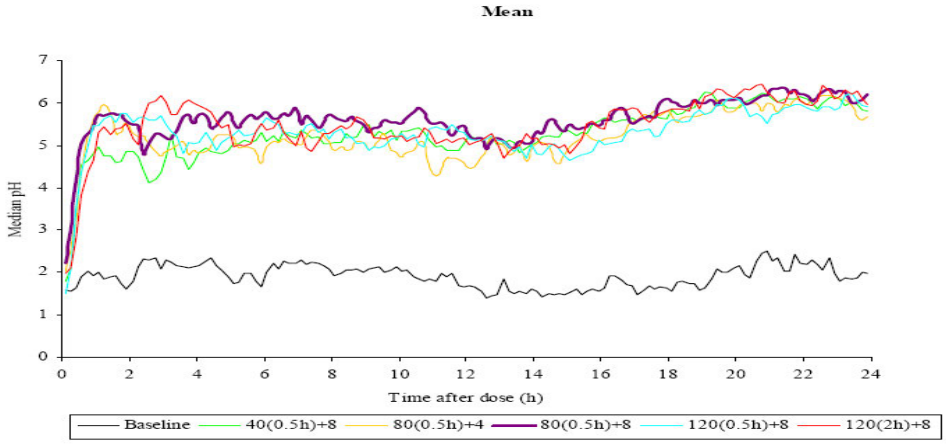
Dose	Day	AUC (micromole·h/L)	% Inhibition of pentagastrin stimulated acid secretion
5 mg	Day 1	0.3	15%
	Day 5	0.3	28%
10 mg	Day 1	0.7	29%
	Day 5	1.0	62%
20 mg	Day 1	1.5	46%
	Day 5	3.1	90%

In the current NDA supplement, the studies conducted to evaluate the pharmacokinetics and pharmacodynamic effects of the proposed new dose regimen, with increase of the initial 30 minute infusion dose to 80 mg, and the addition of an 8 mg/hour infusion, were limited to 24 hours duration. The PK/PD studies included an esomeprazole dose finding study in healthy subjects and a study that evaluated the esomeprazole dose identified in the latter study vs. omeprazole.

In the dose finding study, the initial intravenous loading doses evaluated were 40 mg, 80 mg, and 120 mg. The infusional dose levels for the remainder of the 72 hour period were 8 mg/hr in each combination, with the exception of one group, a combination of 80 mg loading dose followed by a 4 mg/hour infusion. The AUC_{0-24} and C_{max} at the selected dose administration schedule, 80 mg loading dose + 8 mg/hr maintenance infusion, were 110 (+/- 23) micromole-h/L and 14 (+/-3) micromole/L, respectively, which is substantially higher than the C_{max} and AUC observed after five days of single intravenous infusions of 40 mg Nexium, as reported in the product label. In the second PK/PD study, which compared the selected dose to omeprazole, the observed esomeprazole AUC_{0-24} and C_{max} were slightly lower – 99 micromole-h/L (+/- 26) and 13 micromole/L (+/-3).

The PD effects observed in the first 24 hours evaluated are presented in Dr. Tien-Mien Chen's clinical pharmacology review. The following figure is reproduced from his review. This figure summarizes the median intragastric pH profiles for the healthy subjects treated in the 24 hour dose finding study described above. Note that the curves do not consistently reach a pH of 6 until late in the 24 hours, and do not achieve a pH of 7.

Figure 1. Median Intragastric pH Profiles at Baseline and during administration of Esomeprazole to Healthy Subjects, Treatments A-E (D9615C00015)



The 80 mg loading dose followed by an 8 mg/hour infusion resulted in a higher percentage of time that the intragastric pH was >6 (52%), compared to the 40 mg dose level (44%) and the 80 mg + 4 mg/hour infusion dose levels (46%). This was true in the first 3 hours after starting treatment as well – the selected dose (80 mg loading followed by 8 mg/hour infusion) was associated with a higher percentage of time spent at a pH > 6 – 46% vs. 25% for the 40 mg dose level and 35% for the 80 mg + 4 mg/hour dose. The higher dose levels didn't result in further improvement over the 80 mg loading dose level (120 mg loading followed by 8 mg/hour). These outcomes are summarized in the table below.

Table: Estimates of mean percentage of time with intragastric pH>4, pH>6, pH>7 with intravenous infusion of esomeprazole at 5 different infusion combinations in healthy subjects, during the 24 hour period by dose level (adapted from Dr. Tien-Mien Chen's review)

	Esomeprazole Regimen	Estimate
pH>4 (0-24)	40 mg + 8 mg/h	82%
	80 mg + 4 mg/h	80%
	80 mg + 8 mg/h	90%
	120 mg (30 min)+ 8 mg/h	84%
pH>6 (**0-3hr**)	40 mg + 8 mg/h	25%
	80 mg + 4 mg/h	35%
	80 mg + 8 mg/h	46%
	120 mg (30 min)+ 8 mg/h	46%
pH>6 (**0-24h**)	40 mg + 8 mg/h	46%
	80 mg + 4 mg/h	44%
	80 mg + 8 mg/h	52%
	120 mg (30 min)+ 8 mg/h	49%
pH>7 (0-24h)	40 mg + 8 mg/h	2%
	80 mg + 4 mg/h	4%
	80 mg + 8 mg/h	5%
	120 mg (30 min)+ 8 mg/h	4%

The mean percentage of time spent over a pH of 4 in the first 24 hours was also reported – 90% - at the 80 mg + 8 mg/hour dose selected for study in the subsequent phase 3 trial. This compares favorably to the Day 5 data for the percentage of time spent at a pH>4 (70%) for the Nexium oral dose of 40 mg daily.

Another way of looking at these data is to evaluate the proportion of subjects that achieved a pH of >6, instead of the proportion of time spent at a pH >6. The proportion of subjects administered the 80 mg IV loading + infusion of 8 mg/hr who sustained a pH>6 for at least 1 hour in the 24 hour period was 58%. This compared to 64% at the 120 mg level, 50% at the 80 mg + 4 mg infusion and only 26% at the 40 mg + 8 mg infusion dose. With this by-patient responder analysis, the 120 mg dose level is numerically higher in achieving the targeted pH level than the dose selected to take into phase 3 evaluation. The percentage time at a pH greater than 6 was similar for the two dose levels for the overall 24 hour period, however. The figure presented earlier in this section does suggest that the 120 mg dose level may have more success achieving the targeted PD effect earlier in a 24 hour period. However, the percentage of time spent at a pH >6 in the first 3 hours of treatment is actually numerically lower in the 120 loading dose group than in the dose level selected for phase 3 study.

In the second PK/PD study which evaluated esomeprazole 80 mg + 8 mg/h infusion vs. omeprazole in healthy subjects, again with an evaluation period limited to 24 hours, the proportion of time in which the pH was >4 was 88% (85, 92) for esomeprazole and the

proportion of time it was > 6 was 45% (39, 51). This is similar to the findings of the study summarized in the table above, although numerically lower for the proportion of time at a pH that exceeds 6.

(b) (4)

The healthy subject data presented as by patient responder, i.e. proportion of subjects who achieved a pH>6 for at least one hour, suggests that there may be an incremental increase of the number of individuals who achieve the target range with a further incremental dose increase above the dose studied in the phase 3 trial. The figure presented at the beginning of this section suggests that there is a trend upward at the end of the 24 hours toward sustaining pH closer to the target pH. Unfortunately, no measurements beyond the first 24 hours were obtained. Despite the substantial proportion of time spent at a pH ≤6 documented in the 24 hour PD studies at the dose level selected for the phase 3 trial, there was a reduction of rebleed events in the major phase 3 study. Most of the events of rebleeding in the study occurred in the first 3 days on treatment. In fact, the majority of the rebleeding events that occurred on the esomeprazole arm occurred in the first 24 hours on treatment, as compared to the placebo arm, in which about half of the rebleed events occurred in the first 24 hours. These data are presented in the Clinical/Statistical section of this review.

The clinical pharmacology reviewers noted that although the PK/PD studies were limited to 24 hours of exposure to Nexium, the PK/PD for the dose regimen had been adequately characterized. They did express concerns that the studies were only performed in healthy volunteers, and not the target population. They state in their review that it is impossible to correlate the PD in healthy subjects with the clinical endpoint of prevention of rebleeding.

The clinical pharmacology reviewers expressed concern that patients with moderate or severe hepatic impairment were excluded, so PK data from this population were not available for this new dose regimen. I concur with their recommendation that the applicant should conduct a hepatic impairment study with the new dose regimen, or revise the label placing restriction on the use in patients with hepatic impairment.

6. Clinical Microbiology

The microbiology reviewer examined the endotoxin limits for this product and, taking into consideration the maximum allowed endotoxin permitted by these limits, calculated the maximum endotoxin exposure a patient would experience taking the new and higher dose proposed in this application. He noted that the product's limit for endotoxin content is (b) (4) EU/mg. At the new dose (80 mg over 30 minutes, followed by 8 mg/hour for 71.5 hours), the maximum exposure to a patient in any 1 hour would be (b) (4) EU. That exposure level is about half the generally accepted patient exposure limit. The reviewer calculated that the product, given the maximum generally accepted patient exposure limit and the total dose administered in this schedule, would even be safe with a higher endotoxin limit, (b) (4) EU/mg. The applicant's test sensitivity for detecting endotoxin is (b) (4) EU.

This information was conveyed to Chantal Phillips and me via email dated November 25, 2008.

7. Clinical/Statistical-Efficacy

The single randomized, placebo controlled study submitted to support marketing approval of Nexium IV for this new indication randomized 767 patients in 91centers in 16 countries around the world. There were no North American sites. The highest enrollment occurred in Russia, 111/767 enrolled patients. The next highest accruing countries were Sweden (101), Denmark (71), France (58), Germany and Netherlands (53 each), followed by Romania and Hong Kong (50 each). The placebo controlled portion of this study was limited to the first 72 hours post endoscopic intervention. After 72 hours, the intravenous infusion of esomeprazole or placebo was discontinued and oral therapy with esomeprazole 40 mg x 1 daily was initiated for the remaining 27 days of the 30 day study period.

To be eligible patients' source of gastrointestinal bleeding had to be from a single gastric or duodenal site that met the criteria of Forrest Classification Ia (arterial bleed), Ib (ooze), IIa (non-bleeding visible vessel), or IIb(adherent clot). Patients could not have multiple lesions and had to have undergone intervention with injection and/or one of the following: heater probe, electrocautery, or hemoclips. Approximately midway through the study, on June 21, 2006 when 382 of 767 patients had been randomized, the protocol was amended to exclude patients who had received intravenous proton pump inhibitor within 24 hours of study entry. The final demographic distribution revealed that approximately 2/3 were male, nearly 90% had presented with melena, and approximately 60% had duodenal ulcers. Although eligibility criteria stated that patients should have only a single ulcer, 14% on the esomeprazole arm had multiple ulcers vs. 19% on the placebo arm. Data were missing for this descriptor in 8% of randomized esomeprazole patients and 6% of placebo patients.

Laine and Peterson reported in a review article published in the New England Journal of Medicine in 1994 (September 15, 1994. Volume 331; No. 11: 717-727) a summary of the prognosis for rebleeding associated with the Forrest classification categories eligible for this study. This publication reported that 55% (17-100) of actively bleeding ulcers rebleed, that ulcers associated with a visible vessel (Forrest II) are associated with a 43% (0-81) risk of rebleeding, and those with adherent clot (Forrest IIb) a 22% (14-36) risk of rebleeding. These risk levels were based on review of multiple publications and the associated range of risk of rebleed for each level is large.

The primary endpoint of the study was the proportion of patients who experienced clinically significant rebleeding in the first 72 hours after endoscopic treatment. The clinical reviewers concurred with the applicant's definition of significant rebleeding. The study was powered based on the assumption that 15% of the patients on placebo would rebleed and 7% would rebleed on the esomeprazole arm (90% power to show this difference). Literature indicates that rebleeding occurs in 15-20% of endoscopically treated ulcers. (Lau, et al. NEJM. August 3 2000, Vol 343. No 5: 310-316.) The applicant prospectively planned to evaluate the primary endpoint utilizing the Mantel-Haenszel test, stratified for the type of endoscopic treatment

received at baseline. Two pre-specified interim analyses were performed during the conduct of the trial, when approximately 33% and 67% of the patients had completed the study, and the final test of the primary endpoint was adjusted for the two interim looks, utilizing a p value of 0.0489. In the original protocol two prognostic factors were planned for incorporation in the final analysis – Forrest class (I vs. II) and endoscopic treatment (single vs. combination). The plan to adjust for Forrest classification was dropped by the applicant when "after a blinded review of the data" they found no difference in rebleed rates between Forrest class I (pooled a and b) and II (pooled a and b). The statistical analysis plan was changed after completion of the study, in a document dated December 17, 2007, to limit the stratification to endoscopic treatment. The study completed on December 14, 2007.

The FDA clinical and statistical reviewers were concerned by the changes to the analysis plan after completion of the study. The clinical reviewer was further concerned that stratification by Forrest classification had not been appropriately applied in the "blinded review of the data". This was because the applicant utilized a pooled grouping of I (Ia + Ib) vs. II (IIa+IIb). Dr. Nayyar pointed out that it is more appropriate to evaluate each of the subcategories as individual factors, since each of the subcategories have different individual prognoses. The table below shows that there were small imbalances between study arms in each of the Forrest Class categories. Most of the patients in this study had either an oozing lesion or an exposed vessel. The small differences in the worst category, active bleeding, favored the esomeprazole arm, and the small differences in the best prognostic category in this study, adherent clot, also favored the esomeprazole arm.

Proportion of Patients in Each Forrest Class (Table adapted from Dr. Sonia Castilio's Biostatistics review Table 3.2)

Forrest Class	Esomeprazole	Placebo
Ia (actively bleeding)	7.5%	10.3%
Ib (oozing)	44.2%	41.9%
IIa (exposed vessel)	36.3%	38.8%
IIb (adherent clot)	11.2%	8.7%

Dr. Nayyar was also concerned by multiple international sites that participated in the study, and the lack of US study sites. He worried that the standard of care, technical expertise, and consistency in application of the endoscopic intervention would vary greatly across centers and countries, which could result in widely variant outcomes among the centers. He also worried that the standard of care and technical expertise at many of the centers would not be consistent with the standards of practice in the U.S. His concerns were reinforced when he and the biostatistical reviewer examined the treatment outcomes by center and observed that there were widely divergent outcomes among the centers. Over half of the centers, 59%, observed either no treatment effect or the effect couldn't be estimated. All 8 of the French centers, which enrolled 58 of the total 767 randomized in this study, and 3 of the UK centers, which only enrolled 5 patients, observed no treatment effect. The reviewers examined the reported treatment effect in centers that enrolled at least 20 subjects, excluding centers that reported no treatment effect, and found that the highest treatment effect center was site 0102 in the Netherlands. This center demonstrated a treatment effect of 30.9% - favoring esomeprazole.

Of note, the investigator at this center was the only investigator in this study who reported accepting "significant payments" from the applicant. These were "honoraria for work on the study". He was a member of the Steering Committee.

The overall efficacy finding for the primary endpoint in this study - proportion of rebleeding in the first 72 hours after endoscopic intervention - is summarized in the table below, which is adapted from Table 3.3 in Sonia Castilio's Biostatistics review:

	Esomeprazole	Placebo	Treatment Effect Esomeprazole minus Placebo (with 95% CI)
N	375	389	
% Rebleed (n)	5.9% (22)	10.3% (40)	-4.4% (CI = -8.3%, -0.6%)
p-value			0.0256

Although the absolute treatment difference was small, the proportion of patients on the placebo arm who experienced rebleeding was nearly double that on the esomeprazole arm. The p value is based on Mantel-Haenszel test stratified only for type of endoscopic treatment used (single vs. combination). Although the primary endpoint was analyzed for the first 72 hours on study, rebleeding events were also collected in the subsequent 27 days when patients on both treatment arms took oral esomeprazole. Most of the rebleeds on study did occur in the first 72 hours of the study (22 on esomeprazole and 40 on placebo). On days 4-7, the number dropped to 5 in the patients who had been randomized to the IV esomeprazole and 20 on the placebo arm. There were 2 rebleeds on Days 8-30 in the IV esomeprazole arm and 3 on the placebo arm.

The initial review issues described earlier in this section prompted careful evaluation of the robustness of the p value associated with the treatment difference observed in this single study, which was not highly statistically significant, p= 0.026. The reviewers examined the strength of the observed outcome through a series of carefully selected sensitivity analyses, which are summarized below:

1) To address the concern that the Forrest Class I vs. II stratification, which was in the prespecified analysis, had been changed after closing the study, the reviewers conducted an analysis utilizing the original planned analysis, incorporating pooled Forrest Class I and II. This analysis yielded efficacy results similar to those presented by the applicant in this NDA utilizing the modified Statistical Analysis plan, p=0.027. (The p value shifted minimally from 0.026.)
2) To address the issue of collapsing the four Forrest categories into two stratification categories, the reviewers adjusted the primary efficacy analysis utilizing all four classification categories in the model. This analysis also incorporated the applicant's prespecified stratification factor of type of endoscopic treatment. The results of this exploratory analysis yielded a nonsignificant p-value of 0.169. The treatment effect remained -4.4% for proportion of treatment effect esomeprazole minus placebo.
3) Regarding the concerns about the variation in standard of care across countries and centers, the reviewers explored the following:

a. Dropping all patients treated with only epinephrine injection from the analysis, since this stand alone treatment is no longer considered sufficient therapy in the U.S. This reduced the population by 143 in the esomeprazole arm and by 142 in the placebo arm. The overall treatment effect remained -4.5% (esomeprazole minus placebo), but the p value shifted to 0.067. This shift, however, might be anticipated with dropping approximately a third of the patients from the ITT analysis.
b. Dropping the center from the Netherlands, Site 0102, which had the largest treatment effect in favor of esomeprazole, 30.9%, from the analysis. The number of patients randomized at this site was 53 of the total 764 ITT population. Dropping this site from the analysis resulted in a slightly diminished overall treatment effect, -3.73% ((5% CI= -7.67, 0.10) (esomeprazole minus placebo), and a shift in the p value to 0.06.
c. Adding country as a stratification factor to explore the treatment effect by country. (The reviewers could not do a similar analysis by center because only a limited number of centers had randomized >12 subjects.) When country was added as a stratification factor to the model that incorporated the applicant's original prespecified analysis stratification factors of endoscopic treatment (single vs. combination) and pooled Forrest Class (I vs. II), the p-value shifted to non-significant, p=0.058. The treatment effect remained -4.4% for proportion of treatment effect esomeprazole minus placebo. If the model incorporated adjustment for the Forrest class by individual classification – Ia, Ib, IIa, IIb – and country, the p value shifted to 0.327.

4) The reviewers evaluated subgroup analyses to examine the trial for consistency of the observed outcome among important subgroups. The treatment effect for esomeprazole was most pronounced in younger patients, less than age 65 (6% rebleed vs. 12% rebleed). In patients over the age of 65 (total N = 372), the rebleed rate was 6% on the esomeprazole arm and 8% on the placebo arm.

I concur with the reviewers' conclusion that the efficacy outcome from this single trial is not adequately robust to stand alone as evidence to support that Nexium IV for Injection is effective treatment to prevent rebleeding in the population studied. The p value of the applicant's primary efficacy analysis was not highly statistically significant at 0.026, and the proposed indication is unique enough to make it difficult to draw upon prior efficacy outcomes in different clinical situations to support that the observation in this single study is in fact real. I concur with the reviewers' conclusion that the efficacy data submitted in this application does not provide statistically persuasive evidence of the efficacy of Nexium IV for Injection (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

The clinical reviewers also expressed concern that an adequate dose had not yet been defined by the applicant because the 24 hour pharmacodynamic studies in healthy volunteers indicated that a pH >6, the target to optimize hemostasis, was not achieved for a substantial proportion of the total 24 hour period, and was sustained for one hour in a minority of subjects. The pharmacodynamic studies were only 24 hours in duration, and it appeared that at the end of 24

hours there was a trend upward to pH of 6 in the final hours on treatment. To explore whether the desired pharmacodynamic and associated therapeutic effect might be delayed until after the initial 24 hours on treatment, an exploratory analysis was conducted to compare the proportion of rebleeding that occurred in the first 24 hours vs. beyond 24 hours. These data are summarized in the table below. Over ¾ of patients who experienced rebleeding on the esomeprazole infusion, had the event in the first 24 hours of treatment, compared to ½ of the patients who rebled on the placebo arm. The proportion of patients that experienced rebleeding in the first 24 hours was very similar between esomeprazole and placebo.

	Esomeprazole	Placebo
N	375	389
Number of patients with Rebleed in the overall 72 hour period	22 (5.9%)*	40 (10.3%)
Number of patients with Rebleed in the first 24 hours	17 (4.5%)	21 (5.4%)
Number of patients with Rebleed from >24hours to 72 hours.	5 (1.3%)	19 (4.9%)

*percentage of patients in the study arm that experienced rebleed

The majority of additional rebleeds on the placebo arm occurred in the subsequent 12 hours beyond 24 hours, as shown in the summary table below, which shows cumulative rebleeding over sequential cumulative time periods. There were 11 additional rebleeds on the placebo arm in that follow-on 12 hours, as demonstrated by comparing the number of rebleeds in 36 hours to the number in the first 24 hours. In contrast there was only 1 additional rebleed in the subsequent 12 hours beyond the first 24 hour period on the esomeprazole arm.

APPEARS THIS WAY ON ORIGINAL

Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 24, 36, 48, 60, and 72 hours for ITT Population

	Esomeprazole (N=375)	Placebo (N=389)	Esomeprazole – Placebo 95% C.I.
Rebleed within 24 Hours			
% No Rebleed (n)[1]	95.5% (358)	94.6% (368)	
% Rebleed (n)[1]	4.5% (17)	5.4% (21)	
Treatment Difference vs. Placebo (95% C.I.)[1]			-0.9% (-4.1%, 2.3%)
Rebleed within 36 Hours			
% No Rebleed (n)[1]	95.2% (357)	91.8% (357)	
% Rebleed (n)[1]	4.8% (18)	8.2% (32)	
Treatment Difference vs. Placebo (95% C.I.)[1]			-3.4% (-7.1%, 0.087%)
Rebleed within 48 Hours			
% No Rebleed (n)[1]	94.9% (356)	90.8% (353)	
% Rebleed (n)[1]	5.1% (19)	9.2% (36)	
Treatment Difference vs. Placebo (95% C.I.)[1]			-4.2% (-8.0%, -0.54%)
Rebleed within 60 Hours			
% No Rebleed (n)[1]	94.7% (355)	90.5% (352)	
% Rebleed (n)[1]	5.3% (20)	9.5% (37)	
Treatment Difference vs. Placebo (95% C.I.)[1]			-4.2% (-8.0%, -0.46%)
Rebleed within 72 Hours			
% No Rebleed (n)[1]	94.1% (353)	89.7% (349)	
% Rebleed (n)[1]	5.9% (22)	10.3% (40)	
Treatment Difference vs. Placebo (95% C.I.)[1]			-4.4% (-8.3%, -0.6%)

[1] Percentages and 95% confidence interval are sample based.

These data suggest that there might be a delayed therapeutic benefit from esomeprazole that is accrued after 24 hours - when the pH may well be more consistently sustained at a higher level. However the pharmacodynamic data from the dose escalation study suggests a flattening of the pharmacodynamic effect with dose escalation, at least for the time intervals presented in this review (0-3 hours) and (0-24 hours), and for the infusional dose levels studied. The efficacy data and the PK/PD data suggest that additional dose exploration for the first 24 hour period might result in identification of a more effective dose.

8. Safety

The safety data base for this new dose regimen is limited to the single phase 3 study submitted, in which 371 were treated with the proposed 3 day intravenous regimen and received the loading dose, and the two phase PK/PD trials, in which the combined studies treated 63 patients with the proposed loading dose and infusion level or higher dose for only a 24 hour exposure. Of the 371 patients treated with esomeprazole in the phase 3 trial, 362 received both the loading dose and the follow on esomeprazole infusion. The total dose that will be administered with this new dosage regimen, combining the loading dose and the follow on

infusion, is 652 mg of esomeprazole over a 3 day period, or 268 mg in the first 24 hours, followed by 192 mg/24 hours in the following two days. This contrasts with the maximum approved dose for the current Nexium IV indication, 80 mg/24 hours, up to 10 days.

In the phase 3 trial the adverse events – types and proportions – were similar between arms, except for a higher rate of gastrointestinal rebleed related events in the placebo arm and a higher rate of vascular disorders related to phlebitis and infusion site reactions in the esomeprazole arm (3.5% vs. 0%). The proportion of patients with SAEs characterized as gastrointestinal disorders was 4.8% on the esomeprazole arm and 7.7% on the placebo arm. The overwhelming majority of these SAEs were bleeds from duodenal or gastric ulcers. On the esomeprazole arm, 75% (12/16) of the SAE bleeds in the first 72 hours were secondary to duodenal ulcers. On the placebo arm, 56% (14/25) were secondary to duodenal ulcers.

An additional observation in this study was that there were two psychotic events in patients treated on the esomeprazole arm vs. one on the placebo arm. One occurred in a 73 year old on Day 3. Another 73 year old developed acute psychosis on the first day of treatment. A literature search found only one case of psychosis reported in an individual who was taking lansoprazole as part of a triple therapy regimen for H. pylori. The authors concluded the psychosis may have been secondary to a drug-drug interaction between clarithromycin and the individual's routine medication, amitriptyline. The authors found in their literature search for clarithromycin that there had been a report in the literature of psychosis in a patient who was taking clarithromycin and omeprazole.

A slightly higher rate of hypoglycemia, inadequate control of diabetes mellitus, and abnormal potassium levels was observed in the patients on the infusional esomeprazole arm of this study. In addition there was a higher rate of hepatobiliary adverse events on the esomeprazole arm than the placebo arm – 1.1% vs. 0.5%. The adverse events on the esomeprazole arm in this category included cholecystitis, steatosis, alcoholic cirrhosis and "hepatocellular damage". The latter event was graded as mild and there were no abnormal liver enzymes or bilirubin reported associated with this event. It is unclear whether this event was of any significance. The events on the placebo arm were hepatic cyst and post cholecystectomy syndrome.

The safety profile appears acceptable. Although the exposures with this dosing regimen are much higher than other approved regimens, the duration of exposure is short – 3 days. The pharmacology reviewer evaluated a 14 day intravenous infusional study of the esomeprazole dose 80 mg/kg/day conducted in rats to evaluate the higher exposure. This submitted nonclinical study revealed no new adverse events in the animals exposed to this higher dosing regimen relative to what is already known about the toxicities associated with PPIs. Animals demonstrated decreased activity, tremors, incoordination, and increased weights of the liver, stomach, adrenals and kidneys. No histopathologic treatment related changes were noted.

9. Advisory Committee Meeting

There was no advisory committee meeting for this supplemental application.

10. Pediatrics

The applicant requested a waiver of pediatric studies because "studies are impossible or highly impractical because the number of patients is so small and geographically dispersed." The clinical reviewers did not agree and will request that a pediatric program be developed for this indication because upper gastrointestinal bleeding occurs in the pediatric population and they anticipate that the product will be used in the pediatric population. This application was not discussed at PeRC because it is not going to be approved during this review cycle.

11. Other Relevant Regulatory Issues

There were no DSI audits requested. The financial Disclosure review noted that one investigator had reported receiving significant payments from the applicant. The investigator was Dr. Ernst J. Kuipers, MD, PhD, the PI from site 0102 in Rotterdam Netherlands. This site was discussed above in the clinical/statistical summary review. The favorable results from this site, prompted an exploratory analysis to evaluate the impact of removal of the data from this site to evaluate the impact on the observed outcome. Dropping this site from the analysis resulted in a slightly diminished overall treatment effect, -3.73% (5% CI= -7.67, 0.10) proportion of rebleeding (esomeprazole minus placebo), and a shift in the p value to 0.06.

12. Labeling

This supplement will not be approved at this time, so no labeling negotiations were held with the applicant. The applicant has proposed (b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Complete Response

- Risk Benefit Assessment – I concur with the clinical and biostatistical reviewers that the applicant has not provided sufficient evidence in this application to establish that Nexium IV, administered in the proposed dose of 80 mg intravenous loading dose over 30 minute infusion, followed by 8 mg/hour for 3 days, is effective (b) (4)

  The p value from the single phase 3 study submitted to support this application was not highly statistically persuasive and was not found to be robust in multiple sensitivity analyses. The sensitivity analyses selected were meaningful as they addressed potential confounders in the conduct of the trial and its analysis.

I concur with the reviewers that the applicant should conduct at least one additional phase 3 trial to replicate the findings of the study submitted in this supplement. It is also possible that the applicant could further optimize the dose and administration schedule to better achieve the pharmacodynamic goal of maintaining the gastric pH at a level >6, particularly in the first 24 hours of treatment. I concur with the reviewers that additional PK/PD studies should be conducted in the target population of patients and should incorporate clinical outcome endpoints.

The following comments describing this NDA supplement's deficiencies will be conveyed in the Complete Response letter:

CLINICAL and STATISTICAL

Our review finds that the primary efficacy results for this non-U.S. single study do not provide substantial evidence of efficacy. For a single study to stand alone as substantial evidence of efficacy, it should demonstrate highly statistically significant and clinically meaningful results. Consistency should be demonstrated across subgroups and secondary endpoints. The study should also show internal consistency in demonstrating the treatment effect across study centers. The single study that you have submitted does not meet these criteria for providing substantial evidence for the following reasons:

1. Highly statistically significant results were not demonstrated. Although your protocol specified analysis showed a reduction of 4.4% in the rate of clinically significant rebleeding within 72 hours after hemostasis compared to placebo ($p = .03$), that reduction was not highly significant, e.g., $p < .001$. In addition, the observed outcome was not found to be robust when subjected to the sensitivity analyses listed below:

    a. It is appropriate to account for country-to-country variation, so the protocol specified analysis was further stratified by country. This resulted in an insignificant treatment effect ($p=0.06$), although the absolute reduction in rebleeding remained 4.4%.

    b. When the protocol specified analysis was further stratified (retaining stratification by country in the model) using Forrest classification as four separate categories (Forrest Ia, Ib, IIa, and IIb) instead of two (Forrest I and Forrest II), an insignificant treatment effect was observed ($p=0.11$). The absolute reduction in rebleeding remained 4.4%. We believe the appropriate adjustment for Forrest classification should be by each individual Forrest category because each category has a different risk of rebleeding events. Even if this stratified analysis was conducted without incorporation of country in the model, the p value still shifted to a less persuasive value of $p= 0.05$.

2. The study lacked internal consistency across study centers. Despite similar patient demographics and disease characteristics, marked variability in the incidence of rebleeding, i.e., the primary endpoint, and treatment effect was observed in different countries and among leading centers. The treatment effect varied widely from -25% to +12% by country and from -31% to +20% in the larger centers that enrolled more than 10 patients. There is no clear explanation for why this occurred, although physician expertise and standards of care may have played a role.

3. The study lacked internal consistency in demonstrating the treatment effect in the important subgroup of patients aged 65 and older. In this subgroup, the proportion of patients that experienced rebleeding in the first 72 hours was 6.2% on the esomeprazole arm and 8.4% on the placebo arm. In contrast, in patients aged less than 65 the proportion of patients that experienced rebleeding in the esomeprazole arm was 5.5%, while on the placebo arm the proportion was 11.9%.

4. The study lacked internal consistency in demonstrating the treatment effect in important secondary efficacy outcomes that were evaluated in the first 72 hours. The proportion of patients who underwent surgery for rebleeding was a prespecified secondary endpoint and the observed outcome for this endpoint was similar between study arms. This analysis was not found to be statistically significant, $p = 0.31$. The secondary analysis comparing number of blood units transfused in the first 72 hours demonstrated a lower number of units infused on the esomeprazole arm (492) relative to placebo (738), $p=0.05$, and the secondary analysis that compared the proportion of patients who required endoscopic retreatment in the first 72 hours demonstrated a decreased rate of endoscopic retreatment (4.3%) on the esomeprazole arm relative to placebo (8.2%), $p=0.02$. Although the secondary analyses of number of blood units transfused and endoscopic retreatment appear nominally significant, there was no prespecified plan to adjust for multiple comparisons. Taking a conservative approach, these p values are not significant after a Bonferroni adjustment to account for multiple comparisons.

5. One center, Site 0102 in the Netherlands reported the largest treatment effect in all centers that participated in this study, -31% rebleeding events, favoring the esomeprazole arm of the study. The investigator from this site, Dr. Ernest J. Kuipers, MD, Ph.D., reported having accepted significant payments from Astra Zeneca. When we conducted a sensitivity analysis to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, we found that the overall treatment effect observed in the study decreased to -3.73% (95% CI = -7.67, 0.10) and the p value shifted to 0.06.

6. We identified additional study design and conduct concerns that further limit the study's ability to provide persuasive evidence that esomeprazole is effective for the proposed indication. These issues are listed below

   a. Endoscopic epinephrine injection is currently not an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers. More than a third of the patients in this study were treated with endoscopic epinephrine injection as single therapy. This draws into question the applicability of the outcome observed in this trial to current care of patients with an upper gastrointestinal bleed from a gastric or duodenal ulcer in the United States today.

   b. Although the inclusion criteria excluded patients with more than a single ulcer, a substantial proportion of the randomized patients had multiple ulcers and there was an imbalance between study arms in this prognostic factor that favored the esomeprazole arm. Fewer patients on the esomeprazole arm had multiple ulcers, 13.6%, relative to the placebo arm, 18.5%. This raises concerns regarding the study conduct in this international trial.

   c. Despite randomization, small imbalances in important prognostic factors were observed between the two study arms. The imbalances favored the esomeprazole treatment arm. These prognostic factors included Grade 1a stigmata of risk of rebleeding (esomeprazole=7.5%, placebo=10.3%) and large ulcers (esomeprazole=7.7%, placebo=10.3%).

   d. The lack of an exclusion criterion for intravenous administration of a proton pump inhibitor within 24 hours prior to enrollment is a potential confounding factor for the observed efficacy outcome. Although this was addressed with an amendment during the course of the study, the amendment only excluded patients who had received intravenous doses greater than 40 mg within 24 hours prior to enrollment.

7. There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. (b) (4)

(b) (4)

These deficiencies cannot be addressed adequately through additional analyses of the data in hand. We conclude that further clinical data from at least one additional adequate and well controlled study that provides persuasive and consistent evidence of efficacy will be needed to address all of the deficiencies in your application.

The following comments will be conveyed to describe how to address the deficiencies:

1. Conduct at least one additional, adequate, and well-controlled study to demonstrate the proposed clinical benefit of Nexium IV for (b) (4) The study should include some U.S. centers and the study design and analysis plan should address the deficiencies described in this letter above.

2. You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two pharmacokinetic/pharmacodynamic (PK/PD) studies that you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3 study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment.

   For the reasons stated above, conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data.

3. Study site 0102 in the Netherlands, which reported the greatest treatment effect in the major randomized, placebo controlled trial that you submitted for our review, will need to be inspected by the Division of Scientific Investigations (DSI) because

Dr. Ernst J. Kuipers, MD, PhD, the investigator at that site, has disclosed that he has accepted significant payments from Astra Zeneca. This inspection would be requested as part of our review of any future submission that includes this study as a critical component of establishing the efficacy of Nexium IV for the proposed indication. A recommendation from the DSI inspector that the data from this site can be used for determining the efficacy and safety of Nexium IV will be needed if this study will be used to support a future marketing application. This assessment will be an important component of a future determination of whether this study can stand as one of two adequate and well controlled trials for the proposed indication.

4. Conduct a pharmacokinetic study in a sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.

5. For this application, we note that you requested a waiver for pediatric patients under the age of 18 years for the following reasons:

- Small number of pediatric patients.
- Geographically widespread distribution of pediatric patients.

It is unlikely that a full waiver of pediatric studies will be granted on re-submission. The incidence of H.pylori related peptic ulcer disease in the pediatric population is low; however, peptic ulcers secondary to long term use of steroids, NSAIDs, and chronic renal failure are not uncommon. Pediatric patients are administered intravenous proton pump inhibitors (PPI) prophylactically before starting high dose steroids and for upper gastrointestinal bleeding.

Therefore, please submit a pediatric plan with your complete response.

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

/s/

Donna Griebel
11/26/2008 05:37:05 PM
DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

OFFICER/EMPLOYEE LIST

NDA 21689/S-014
Nexium IV

Officer/Employee List

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list.

Barley, Stacy
Best, Jeanine A
Bloom, Raanan
Bugin, Kevin
Chakder, Sushanta K
Holquist, Carol A
Jappar, Dilara
Klemm, Kathleen
Langille, Stephen
Lee, Sue Chih H
Merchant, Lubna
Oleszczuk, Zachary
Peterson, Aisha
Phillips, Chantal
Riley, Bryan S
Sachs, Hari
Taylor, Amy
Taylor, Kellie
Wynn, Erica L

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 20, 2013
From	Robert P. Fiorentino, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA # **Supplement#**	NDA # 21689 Supplement 014
Applicant	AstraZeneca
Date of Submission	December 14, 2012
PDUFA Goal Date	September 14, 2013 (3 month extension granted 05/08/2013 based on the 4/22/2013 solicited major amendment)
Proprietary Name / Established (USAN) names	NEXIUM IV Esomeprazole sodium
Dosage forms / Strength	80 mg IV infused over 30 minutes followed by an infusion of 8 mg/h for 71.5 hours
Applicant's Proposed Indication	NEXIUM I.V. for Injection is indicated for (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.
Recommendation	Approval

Contents

1. Introduction

This is the third review cycle for Supplement 14 of NDA 21689. This Supplement previously received a Complete Response (CR) on 11/26/2008 and 06/16/2011. The response to the second CR was submitted 12/14/2012 as a Class 2 resubmission. A solicited Major Amendment was received on 4/22/2013 that resulted in a 3 month review extension.

The following Primary Reviewers and their respective disciplines provided reviews for this review cycle that are discussed in my CDTL memo:

Clinical
- Aisha Peterson-Johnson, review signed 07/15/2013

Statistics
- Lisa Kammerman, review signed 08/27/2013

Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 and Division of Pharmacometrics
- Sandhya Apparaju, Ph.D. (Clinical Pharmacology Reviewer)
- Kevin Krudys, Ph.D. (Pharmacometrics Reviewer)
    - Joint review signed 07/20/2013

Nonclinical Pharmacology/Toxicology
- Sushanta Chakder, signed 07/22/2013

CMC / ONDQA Div II, Branch VI
- Yong Wang, review signed 06/06/2013

Office of Prescription Drug Promotion (OPDP)
- Meeta Patel, PharmD, signed 08/20/2013

Division of Medication Error Prevention and Analysis (DMEPA)
- Denise V. Baugh, PharmD, BCPS, review signed 06/18/2013

2. Background

For information on the background of this efficacy supplement, the reader is referred to the previous CDTL Memorandum by Dr. Lynne Yao submitted on 06/16/2011 during the second review cycle. The reader is also referred to the clinical review by Aisha Peterson Johnson submitted this cycle (dated 07/15/2013).

Following the second Complete Response (CR) on 06/16/2011, the sponsor submitted a request for a dispute resolution regarding the CR. FDA denied this request and recommend that a post-action meeting be held between the FDA and applicant. A post-action meeting was held on 03/22/2012. Although FDA initially proposed bringing this Supplement to an Advisory Committee, the sponsor indicated that they planned on submitting “additional data in response to the Complete Response letter.” They also stated that “[t]his information will include additional

PK, PD and clinical data (*H. pylori*) to address the relevance of the Lau study to the US population."

The applicant submitted an outline of their planned response to the CR and DGIEP had a teleconference with the sponsor on June 12, 2012 to discuss the adequacy of the proposal as a response to the CR. In general the discussion focused on providing specific analyses that could support the use of the "Lau study" as supportive evidence of efficacy, despite the concerns about the generalizability of the Lau study population to that evaluated in Study 01 (the original study conducted by the applicant and submitted to the sNDA).

As a result of the June 12, 2012 meeting, the sponsor submitted on June 13, 2012 a request for a six month extension of the one year CR response time from June 16, 2012, to December 16, 2012, in accordance with 21 CFR 314.110. DGIEP found the proposed extension date to be acceptable.

Applicant submitted their response to the June 16, 2011, CR Letter on December 14, 2012.

3. CMC / Device

There are no unresolved CMC issues and no additional CMC data was reviewed during this review cycle.

4. Nonclinical Pharmacology / Toxicology

No additional nonclinical pharmacology or toxicology studies were submitted or reviewed during this review cycle. (b) (4)

(b) (4)

(b) (4)

Dr. Chakder notes in his Non-Clinical review that (b) (4) studies reviewed previously under the initial submission and is acceptable. He also summarizes previous animal data that supports the safety of the proposed IV dose in humans. In rats, intravenous doses of 18-36 times, on a mg/kg basis (3-6 times based on body surface area), as the proposed continuous i.v. infusion daily clinical dose was well tolerated with minimal adverse effects. In dogs, esomeprazole sodium was tolerated well following continuous intravenous infusion for 14 or 28 days at doses several fold higher than the proposed daily i.v. infusion dose. The highest tolerable

dose of esomeprazole in a continuous infusion study in dogs was about 8 times, on a mg/kg basis (4.2 times based on body surface area), as the proposed daily i.v. clinical dose.

5. Clinical Pharmacology / Biopharmaceutics

Clinical Pharmacology and Pharmacometrics submitted a joint review and the primary reviewers were Sandhya Apparaju and Kevin Krudys (review signed July 20, 2013). Overall, the Clinical Pharmacology review concluded that based on the available PK and PD data among Chinese and Caucasian populations, there is no strong evidence to conclude that the ethnicity factor could contribute to differences in clinical outcomes between the phase 3 trial 001 and the Lau et al. trial. In addition, this submission addresses dosing recommendations in hepatic impairment subgroups, an issue pending from earlier review cycles.

The Clinical Pharmacology review of Cycle 3 resubmission focused on the review of PK and PD outcomes from a PK/PD study in Chinese volunteers (Study D961500007, or "Study 07"), the previously reviewed dose-ranging PK/PD study in Caucasians (Study D961500015, or "Study 15") as well as cross-study comparisons of data in the overall populations and subgroups where possible (i.e., known *H. pylori* status, CYP2C19 status). See Table 1 for an overview of the design and population of Study 07 and Study 15. The stated goal of their review was to determine whether there is sufficient PK/PD information available through which the findings from the Lau et al. study, which included only Chinese patients, can be generalized to the U.S. population. Note that no PK/PD data directly from the Lau study were available for review.

Table 1. Overview of Study D961500007 and Study D961500015

D9615L00007: Chinese 'healthy' subject PK/PD study; 2006	**D96150015: Caucasian (healthy) subject PK/PD study; 2004**
• Open-label, single dose, randomized, crossover study (with at least 6 days of washout) • Drug: IV Esomeprazole • Treatment regimens: – 40 mg/3 min; – 40 mg/30 min, BID – 40 mg/30 min + 8 mg/h for 23.5 h – 80 mg/30 min + 4 mg/h for 23.5 h – **80 mg/30 min + 8 mg/h for 23.5 h** – Sample size: N = 20 • Gender: 14 males; 6 females • Race: All Chinese • CYP2C19 status: EMs(homozygote): 7; IMs(heterozygote): 11; PMs: 2 • *H. pylori* status: Positive: 9; Negative: 11 • PK: Cmax, Css, AUC24, Clearance • PD: gastric pH related endpoints: time above pH 4, 5, 6, 7 etc.	• Open, randomized, five-way crossover study (washout of at least 13 days) • Drug: IV Esomeprazole • Treatment regimens: – 40 mg/30 min + 8 mg/h for 23.5h; – 80 mg/30 min + 4 mg/h for 23.5 h – **80 mg/30 min + 8 mg/h for 23.5 h** – 120 mg/30 min + 8 mg/h for 23.5 h – 120 mg/120 min + 8 mg/h for 23.5h • Sample size: N= 26 • Gender: 20 males; 6 Females • Race: All Caucasians • CYP2C19 status: EMs(homozygote): 17; IMs(heterozygote): 8; PMs: 1 • *H. pylori* status: All negative • PK: Cmax, Css, AUC24, Clearance • PD: gastric pH related endpoints: time above pH 4, 6, 7 etc.

For Study 07 and Study 15, the primary outcome variable was the percent of time with pH >6 over the 24 hour study period. The Applicant also separately documented the % of time over 24 hours with pH ≥ 7.0 in these studies. As noted by the Clinical Pharmacology review, available *in*

vitro data suggests that target pH for optimal clot stabilization occurs at pH 6.4- 6.8 (Green et al., Gastroenterology 1978).

Data from Studies 07 and 15 allowed the clinical pharmacology reviewers to make limited PK/PD comparisons in the *H. pylori* and CYP2C19 subgroups. In the study of Chinese patients, both *H. pylori* positive and negative healthy patients were enrolled. However, in the study of Caucasian patients, only *H. pylori* negative, healthy patients were enrolled.

In general, the Clinical pharmacology reviewers concluded that the pharmacodynamic (PD) outcomes observed in Caucasian and Chinese populations were comparable. Specifically, for the proposed regimen, for Chinese patients in Study 07, the mean percentage of time with pH >6 from 0-24 hrs was 50% (n=19), compared with 52% (n=24) observed in Caucasian patients in Study 15. There was a higher C_{max} observed in Chinese subjects when compared to Caucasian subjects. The clinical pharmacology reviewers noted that this difference could be due to the Chinese subjects having a lower median height and weight than the Caucasian subjects (164 cm/64kg vs. 177 cm/72kg).

For those subjects in Study 07 who received the comparable dose as that proposed for NEXIUM IV (80 mg/30 min + 8 mg/h for 23.5 h), the PD variables by *H. pylori* status are presented in Table 2 (as "Proposed Regimen E"). There was a trend for larger PD outcomes in *H. pylori* positive Chinese subjects.

Table 2. Pharmacodynamic Variables by *H. pylori* status, Study 07 (Chinese healthy subjects)

Proposed Regimen E	H. Pylori Positive (n = 9)	H. Pylori Negative (n = 11)
% time when pH >4 over 24 h	98.37 ± 0.54	93.69 ± 5.05
% time when pH >6 over 24 h	59.12 ± 9.56	46.7 ± 20.4
% time when pH> 6 over first 3 h	82.77 ± 5.01	49.4 ± 33.6
% time when pH>7 over 24 h	18.75 ± 9.26	11.14 ± 8.56
Mean pH over 24 h	6.25 ± 0.23	5.84 ± 0.61

There were no PK differences across *H. pylori* subgroups in healthy Chinese volunteers and a comparable primary PD outcome (% time when pH >6 over 24 h) in the overall and *H. pylori*-negative Chinese vs. Caucasians. Although the clinical pharmacology review notes that the % time when pH >7 over 24 h appears higher in Chinese subjects. Table 3 presents the data for proposed Regimen (80 mg/30 min followed by 8 mg/h infusion) for PK/PD Studies 07 and 15.

Table 3. PD Parameters in *H. pylori* negative Chinese (Study 07) and Caucasian subjects (Study 15)

PD outcome	**Chinese *Overall (H. pylori +, -)* (n = 19)**	**Chinese *H. Pylori* (neg) (n = 11)**	**Caucasian *Overall (H. pylori* neg) (n= 24)**
% time when pH >4 over 24 h	95 ± 4.6	93.69 ± 5.05	86.1 ± 11.3
% time when pH >6 over 24 h	48 ± 17.4	46.7 ± 20.4	46.6 ± 26.5
% time when pH >6 over first 3 h	65 ± 28.6	49.4 ± 33.6	43.4 ± 26.1
% time when pH >7 over 24 h	13.3 ± 10.6	11.14 ± 8.56	4.0 ± 7.5

Key Clinical Pharmacology Conclusions

The impact of H. pylori status on clinical outcomes:

Better PD response (via assessment of intragastric pH) was observed in subjects in the Chinese PK/PD Study 007 who were *H. pylori* positive, compared to *H. pylori* negative Chinese subjects. The Clinical Pharmacology reviewers were not certain that this PD difference translates into better clinical outcomes but they note that the phase 3 trial and the Lau et al. trial did show "better" efficacy in *H. pylori* positive patients (see Additional Efficacy Analyses in Section 7). Overall, the Clinical Pharmacology reviewers did not appear to believe that *H. pylori* status could have contributed to observed differences in efficacy outcomes between the two trials "because the proportion of *H. pylori* positive patients was similar between the two trials (approximately 65% in the active treatment groups, and ~55% in the placebo groups)."

The impact of CYP2C19 polymorphism on outcomes:

Differences in CYP2C19 polymorphism across Chinese and Caucasian subjects are unlikely to be an issue, as PK differences between genotypes were modest and an exposure-response (E-R) correlation was absent at the high intravenous doses evaluated for this indication.

The impact of parietal cell mass differences:

While the clinical pharmacologists state that they do not have concrete data to conclude one way or the other regarding the impact of parietal cell mass differences across ethnicities, they note that the PD response was *generally* similar between the two PK/PD studies (Study 07 in Chinese and Study 15 in Caucasians). There were however, some differences in a few of the secondary PD outcomes assessed including % time during the first 3 hrs when pH was > 6 or % time over 24 hours with pH>7, which appeared to be better in the Chinese population compared to Caucasians.

Dosing recommendations in hepatic impairment subgroups:

(b) (4)

Instead, intravenous dosing recommendations from the clinical pharmacology reviewers are based on i.v. omeprazole data in patients with hepatic impairment as well as a PK/PD bridge between these two drugs ("Study 004") and are as follows:

- Mild hepatic impairment (C-P, A): 80 mg over 30 min + 6 mg/h over 71.5 h
- Moderate hepatic impairment (C-P, B): 80 mg over 30 min + 6 mg/h over 71.5 h
- Severe hepatic impairment (C-P, C): 80 mg over 30 min + 4 mg/h over 71.5 h

6. Clinical Microbiology

During the first review cycle, the product quality microbiology reviewer recommended approval of Nexium IV for the proposed indication. See the full review by Dr. Bryan Riley [electronically signed March 23, 2011 and May 4, 2011(addendum)].

7. Clinical / Statistical Efficacy

Overview of Efficacy Evaluations

The reader is referred to the clinical reviews submitted during previous review cycles for a detailed account of the clinical studies submitted to this sNDA.

Briefly, in addition to the applicant-conducted trial D961DC00001 (referred to herein as, "Study 01") submitted to the initial sNDA submission, the review team reviewed three key *omeprazole* clinical trials. Two of these (Studies 840 and 841) were Scandinavian trials conducted in the early 1990's. The third, referred to by the reviewers as "the Lau trial," was considered the strongest evidence submitted to support efficacy in the indication, in addition to Study 01. However, this trial was a single center trial conducted in Hong Kong. The Lau trial was published in the New England Journal of Medicine in 2000, nine years before the IV esomeprazole Study 01 was published.

Table 4. Key Clinical Trials Reviewed

Trial Name	Trial Type	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population
D961DC00001 (TRIAL 01)	Safety and Efficacy	Multicenter International Prospective Randomized Double-blind, Parallel Group, Placebo-controlled	Esomeprazole (a bolus 80mg over 30 min followed by a continuous infusion of 8mg/hr for 71.5 hours) or Placebo Follow-up treatment after I.V. Esomeprazole with Oral Esomeprazole 40mg once daily for 27 days	767 Randomized 764 Treated	Patients who had undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer classified as Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment modalities varied.)
Lau, et. al.	Safety and Efficacy	Single Center (Hong Kong) Randomized Double-blind, Parallel Group Placebo-controlled	Omeprazole (a bolus intravenous injection of 80mg over 30 min followed by a continuous 8mg/hr infusion for 71.5 hours) or Placebo Follow-up therapy after I.V. Omeprazole infusion with oral 20mg Omeprazole once daily for 8 weeks	320 Planned 240 Randomized	Hospitalized Patients who had undergone successful endoscopic treatment of a bleeding peptic ulcer. Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment was injection epinephrine followed by thermocoagulation)
Trial I-840	Safety and Efficacy	Multicenter International Double Blind Parallel Group Placebo Control	Omeprazole 80mg given intravenously as a bolus dose over 30 minutes followed by 8mg/hr for 71.5 hours or Placebo Follow-up therapy after I.V. Omeprazole infusion with oral 20mg Omeprazole once daily for 21 days. (Oral therapy started at 48hours)	350 Planned 274 Randomized	Hemodynamic ally unstable outpatients and inpatients with PUB endoscopically classified as Forrest Ia, Ib, IIa, or IIb. (Endoscopic treatments varied. Pre-entry endoscopic treatment only in patients classified as Forrest Ia or IIa)
Trial I-841 (study stopped prematurely due to safety monitoring)	Safety and Efficacy	Multicenter International Randomized Double-Blind Parallel Group Placebo-Controlled	Omeprazole 80mg given intravenously as a bolus over 30 minutes followed by continuous infusion of 8mg/hr for 3 to 5 days. (If there were signs of bleeding during day 2 or 3 the infusion was given for 120 hours) Follow-up therapy after I.V. Omeprazole with Omeprazole 20mg daily for 21 days	400 Planned 333 Randomized	Patients ≥ 60 years old with endoscopic signs of peptic ulcer bleeding and clinical symptoms of upper gastrointestinal bleeding. (Forrest Ia, Ib, IIa, IIb) (Endoscopic treatments varied. Pre-entry endoscopic intervention was only to be used in patients with bleeding classified as Forrest Ia)

Source: Reproduced from the Cycle 2 Clinical Review, Dr. Erica Wynn, p21, DARRTS, 14 June 2011

The results of the 4 trials are presented in Table 5. A more detailed tabulation of key study features are provided in the Appendix.

Table 5. Rebleeding Within 72 Hours of Therapeutic Endoscopy

Study	Study Drug*	Placebo	Treatment Difference
01	5.9% (22/376)	10.3% (40/389)	-4.4%
Lau	4.2% (5/120)	20.0% (24/120)	-15.8%
840 / 841 [combined] All patients with endoscopic therapy	16.7% (17/102)	30.6% (34/111)	-13.9%
Only patients with endoscopic therapy as given in Study 01	13.6% (3/22)	23.3% (7/30)	-9.7%

*esomeprazole in Study 01; omeprazole in Lau study, Study 840, and Study 841
Source: Data reproduced from Clinical and Statistical review and Dr. Peterson's presentation at CDER Regulatory Briefing on April 19, 2013

Despite the favorable outcomes observed in all 4 trials, the Division expressed concern (as noted in the CR letter) about the generalizability of the clinical trial reported by Lau et al. due to the "ethnically homogenous" population of this study. The Division again stated that the deficiency could be addressed with an additional, adequate, well controlled clinical trial. The applicant voiced ethical concerns of conducting another controlled trial in the target population and instead proposed to submit available pharmacokinetic/pharmacodynamics evidence to bridge the two populations (Asians and Caucasians) in order to support the applicability of Lau et al. data to the U.S. population. These data were submitted and extensively reviewed in the third cycle.

The clinical review by Dr. Aisha Peterson Johnson for this current cycle addresses each of the applicant's CR responses and also focuses on the additional information submitted this cycle in support of the Lau et al study. The Clinical Review discussion of the CR items is described below.

Adequacy of Studies 840 and 841 to Support the Proposed Indication for NEXIUM IV

As noted by Dr. Peterson Johnson, while similarities between Study 01 and Trials I-840 and I-841 exist, there are differences in, among other things, entry criteria, patient demographics, endoscopic treatments administered, and primary endpoint. The primary endpoint for the I-840 and I-841 trials was "overall outcome of treatment" as measured using a ranking scale whereby each patient was ranked for his/her worst outcome. Not all patients in Trials I-840 and I-841 received endoscopic treatment. This was considered an important difference because in Study 01, successful hemostasis was required for study inclusion. Successful hemostasis in Study 01 required, in part, endoscopic treatment with injection therapy (epinephrine, dilution 1:10000) and/or one of the following: coagulation with heater probe, electrocautery, or hemoclips.

Table 6.

Trial Name	Brief Description
Trial I-840	▪ Omeprazole IV vs. placebo ▪ Hemodynamically unstable patients ▪ Therapeutic endoscopy only for Forrest Ia, IIa
Trial I-841	▪ Omeprazole IV vs. placebo, treatment for 72 hours or 120 hours ▪ Patients ≥ 60 years old ▪ Therapeutic endoscopy only for Forrest Ia

There was considerable effort performed in the previous cycle to identify a subset of patients in Trials I-840 and I-841 that closely matched those in Study 01. For I-840 and I-841 combined, only 52 patients received an endoscopic treatment that was allowed in Study 01. In this subpopulation the numerical treatment benefit (reduction in rebleeding) was -9.7%, compared to the overall study population of -13.9%.

In contrast to the 52 patients selected by FDA reviewers last cycle, the applicant considered it more relevant to include an analysis of the 137 patients who received the same treatment modalities as in Study 01 (with or without additional endoscopic treatment). In this population proposed by the applicant, the treatment difference was -15.6%. The statistical reviewer this cycle noted in her review, "Whether this exploratory analysis should be limited to the 52 subjects identified by the clinical review team in cycle 2 or should be expanded to the 137 subjects identified in the Applicant's response is a clinical decision."

Although the numerical benefit trended in the same direction (with similar magnitude) regardless of the subgroup analyzed, the clinical reviewer for cycle 2, Dr. Erica Wynn, concluded that no substantive comparisons between Study 01 and Trials I-840 and I-841 could be made. However in her review this cycle, Dr. Peterson-Johnson notes, "[d]espite the differences between Study 01 and Studies 840/841 (described above), the rebleeding results of Trials I-840 and I-841 provide supportive evidence of efficacy for Nexium IV for the proposed indication." She also notes that "while not statistically significant, the trend is important and provides supportive evidence for the efficacy of Nexium IV for the proposed indication."

Generalizability of the Results of the Lau et al. Trial to the U.S. Population

The review team was concerned that compared with Caucasian populations, [East] Asian populations are known to have a lower parietal cell mass, a higher prevalence of *H. pylori* infection, and a higher prevalence of cytochrome 2C19 genetic polymorphism, and that these factors could be expected to influence the pharmacodynamic effect of PPIs. It was believed that these factors could have made the positive results of the Lau trial less generalizable to the U.S. patient population and a number of exploratory analyses were performed.

However these factors were reviewed in detail in the Clinical Pharmacology and Biopharmaceutics reviews described previously.

Inconsistency in Rebleeding Rates Between Study D961DC00001 and the Lau et al. trials

The review team was concerned that the differences in rebleeding rates between Study 01 and the Lau trial, specifically in the placebo rates (10.3% vs. 20%, respectively), would make generalizability of the Lau trial to the US population invalid or raise questions regarding the use of the Lau trial as a "supportive" study.

In their response to the FDA CR letter, the sponsor performed a two-step analysis to determine why the relative risk for rebleeding differed between Study 01 and the Lau trial.

As a first step of the regression analysis, the magnitude of the difference was calculated by the Applicant. Table 7 shows the event rate at day 3 in the two studies, when only "study drug" (placebo vs. omeprazole or esomeprazole, respectively) and "study" (the study reported by Lau et al. vs. Study D961DC00001) are included as factors. In this model the point estimate for

”study” (0.686) indicates a tendency for a reduced overall risk of rebleeding in Study 01 (i.e., ~31% *lower* relative risk in having a rebleed in Study 01 vs. Lau, *independent* of study drug), although this is not statistically significant. Probably more important, this analysis also appears to show that subjects who received placebo had a ~2.4-times higher risk of rebleeding compared to those that received PPI (esomeprazole or omeprazole), *independent* of the study in which the subjects were enrolled.

Table 7. Relative Risk for rebleeding in the D961DC00001 study and the Lau et al study - Reduced model - Cox regression

Explanatory variable	Relative risk	Lower 95% CI	Upper 95% CI	p-value
Study	0.686	0.442	1.067	0.0944
Study drug	2.381	1.519	3.734	0.0002

Lau study=1 and D961DC00001 study=2. Study drug=1 for esomeprazole/omeprazole, 2=placebo
Source: Applicant, Response to Complete Response Letter, 7 December 2012, Table 5, page 20

In a second step, potential risk factors for recurrent bleeding were included in the analysis. Table 8 includes, in addition to the two factors in Table 7, also other such potential risk factors. In this model the difference in rebleeding rate between the studies appears to be explained by factors other than “study.” After adjusting for other possible explanatory variables, the estimated risk for rebleeding in Study 01 relative to the Lau study is close to 1. The strongest predictor is ASA grade IV, and the applicant notes that patients with ASA grade IV were not included in Study 01. Applicant further states the following: “When designing study D961DC00001, inclusion of severely ill patients with ASA grade IV was not considered feasible, as this would not be accepted, due to ethical considerations, at all planned sites of this multi-national study.”

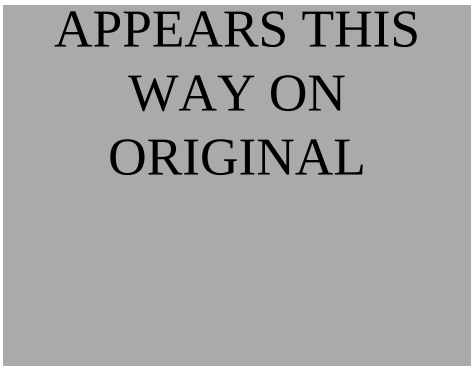


Table 8. Relative Risk for rebleeding in the D961DC00001 study and the Lau et al study –Expanded model, Cox regression

Explanatory variable	Relative risk	Lower 95% CI	Upper 95% CI	p-value
Study	0.979	0.543	1.768	0.9451
Study drug	2.290	1.416	3.703	0.0007
Age	0.993	0.977	1.009	0.3962
Sex	1.169	0.723	1.890	0.5229
Hospitalized	0.330	0.130	0.835	0.0193
Previous ulcer bleeding	1.277	0.683	2.387	0.4442
ASA grade II	1.395	0.776	2.509	0.2658
ASA grade III	2.256	1.132	4.497	0.0207
ASA grade IV	3.968	1.425	11.052	0.0083
H. pylori	0.612	0.385	0.973	0.0379
Forrest Ia	2.177	1.031	4.601	0.0415
Forrest IIa	1.773	1.031	3.050	0.0386
Forrest IIb	2.453	1.282	4.694	0.0067
NSAID (incl aspirin)	1.395	0.782	2.489	0.2601
Aspirin	1.112	0.595	2.081	0.7391
Warfarin	0.675	0.159	2.875	0.5952

Lau study=1 and D961DC00001 study=2. Study drug=1 for esomeprazole/omeprazole, 2=placebo. Sex=1 for male and sex=2 for female. ASA II, ASA III and ASA IV compared to ASA I. H. pylori variable collapsed into 2 main classes Hp=0 for Negative and Hp=1 for Positive or Trace. Forrest class Ia , Forrest class IIa and Forrest class IIb compared to Forrest class Ib. Hospitalized, Previous ulcer bleeding, NSAID, Aspirin and Warfarin , answers: 0=no, 1=yes.

Source: Applicant, Response to Complete Response Letter, 7 December 2012, Table 6, page 21

I also note that the relative risk associated with the study drug (compared to placebo) does not appear to change between the two analyses, suggesting fairly robust estimate of treatment benefit (2.381 to 2.290) for the PPI, with very small p-values.

However, the statistical reviewer did not agree with the Applicant's approach (to the regression model) to identifying possible reasons for the differences in placebo rebleeding rates between the Lau et al. trial and Study 01 and considered any type of cross-study analyses to be exploratory in nature. Therefore, she concluded that the results of such analyses "should not be given much weight in deciding whether the results of Lau can be generalized to a broader population."

Differences in efficacy outcome between Lau and Study 01 in subgroups of patients ≥65 years of age and the subgroup of patients with Forrest Ib classification

Previous reviewers were concerned about differences in treatment benefit in patients ≥ 65 years of age between the Lau study (-19.7%) and Study 01 (-2.2%). However, as noted by the clinical reviewer, the risk factor shown to have the greatest positive association with risk of rebleeding correlates directly with age – ASA grade IV. However, no ASA grade IV patients were allowed in Study 01 and 20.5% of patients ≥65 years old in the Lau Study were classified as ASA grade IV. Regardless, these cross study comparisons between subgroups should be viewed with caution however the trend for therapeutic benefit in subjects ≥ 65 in Study 01 is still in the *same direction* as the overall results (i.e., -2.2% vs. -4.4%).

In addition, as noted by the clinical reviewer, Forrest Ib patients have a higher risk of rebleeding and therefore represent an important subgroup. The Applicant stated that "the effect of iv esomeprazole in Forrest Ib patients in study D961DC00001 is lower than anticipated and difficult to explain." In their response to the Complete Response Letter, the Applicant provided possible explanations for the difference in effect size seen in Forrest Ib patients in Study 01 compared to Lau, 0.5% vs. 10%, respectively. Their arguments appear speculative in nature (as *post hoc* explanations for retrospective subgroup analyses tend to be). However I am unconvinced that the outcomes of the Forrest Ib subgroup analyses within Study 01 have established that the drug would be ineffective in these patients, (b) (4)

Other Issues Identified within the CR Letter

The reader is referred to the clinical review this cycle and biometric review from previous cycles for discussions related to Items 6 and 7 from the CR letter. The fact that observational studies were submitted to the application or that *post hoc* analyses removing one or more sites from the primary analysis result in a different p-value, do not in themselves suggest that the overall results or conclusions are invalid.

Additional Efficacy Analyses

An April 10, 2013 information request sent to the applicant requested the proportion of subjects by treatment arm who re-bleed within 3, 6, 12 and 24 hours for Study 01 and the Lau et al. study.

The number of re-bleedings by specified time period in Study 01 is presented in Table 9. There does not appear to be substantial difference in rebleeding between the two arms of Study 01 until 24-48 hours.

Table 9. D961DC00001 - Proportion of subjects who Re-Bleed within 3, 6, 12, 24, 48 and 72 hours, ITT population

Re-bleed within (hours)	Esomeprazole n/N(%)	Placebo n/N(%)
3	3/375 (0.8%)	3/389 (0.8%)
6	6/375 (1.6%)	5/389 (1.3%)
12	9/375 (2.4%)	10/389 (2.6%)
24	17/375 (4.5%)	20/389 (5.1%)
48	19/375 (5.1%)	35/389 (9%)
72	22/375 (5.9%)	40/389 (10.3%)

mdbmpe 15APR13:08:45:54.54 "D961DC00001 - proportion of subjects who rebleed"

Source: Applicant, Response to Information Request, dated 04/22/2013

In the Lau et al. study, data on re-bleeding was not collected as a continuous variable over time, but as events within consecutive 24-hour periods after randomization. Data for the first 3 consecutive 24 hour periods is given in Table 10. Note that in the Lau study there was a clear difference in rebleeding rates at the 24 hour timepoint.

Table 10. Lau et al - Proportion of subjects who Re-Bleed within 24, 48 and 72 hours, ITT population

Re-bleed within (hours)	Omeprazole n/N(%)	Placebo n/N(%)
24	3/120 (2.5%)	17/120 (14.2%)
48	3/120 (2.5%)	21/120 (17.5%)
72	5/120 (4.2%)	24/120 (20%)

mdbmpe 15APR13:09:01:07.26 "LAU - proportion of subjects who rebleed"

Source: Applicant, Response to Information Request, dated 04/22/2013

The applicant also stratifies these data by *H. pylori* status. This analysis for Study 01 is presented in Table 11):

Table 11. D961DC00001 - Proportion of subjects who Re-Bleed within 3, 6, 12, 24, 48 and 72 hours (subgrouped by *H. pylori* status), ITT population

Re-bleed within (hours)	Esomeprazole n/N(%)		Placebo n/N(%)	
	H. pylori(+)	H. pylori(-)	H. pylori(+)	H. pylori(-)
3	2/264 (0.8%)			3/119 (2.5%)
6	3/264 (1.1%)	2/92 (2.2%)	1/252 (0.4%)	4/119 (3.4%)
12	4/264 (1.5%)	4/92 (4.3%)	4/252 (1.6%)	6/119 (5%)
24	9/264 (3.4%)	7/92 (7.6%)	6/252 (2.4%)	12/119 (10.1%)
48	10/264 (3.8%)	7/92 (7.6%)	18/252 (7.1%)	13/119 (10.9%)
72	11/264 (4.2%)	9/92 (9.8%)	21/252 (8.3%)	14/119 (11.8%)

19 Ezomeprazole subjects have missing H.pylori status, 2 of them rebleed within 72 hours
18 Placebo subjects have missing H.pylori status, 5 of them rebleed within 72 hours

mdbmpe 17APR13:10:07:26.18 "D961DC00001 - proportion of subjects who rebleed w HPstatus"

Source: Applicant, Response to Information Request, dated 04/22/2013

Figure 1 presents the KM estimates of rebleeding events, by *H. pylori* status, in Study 01.

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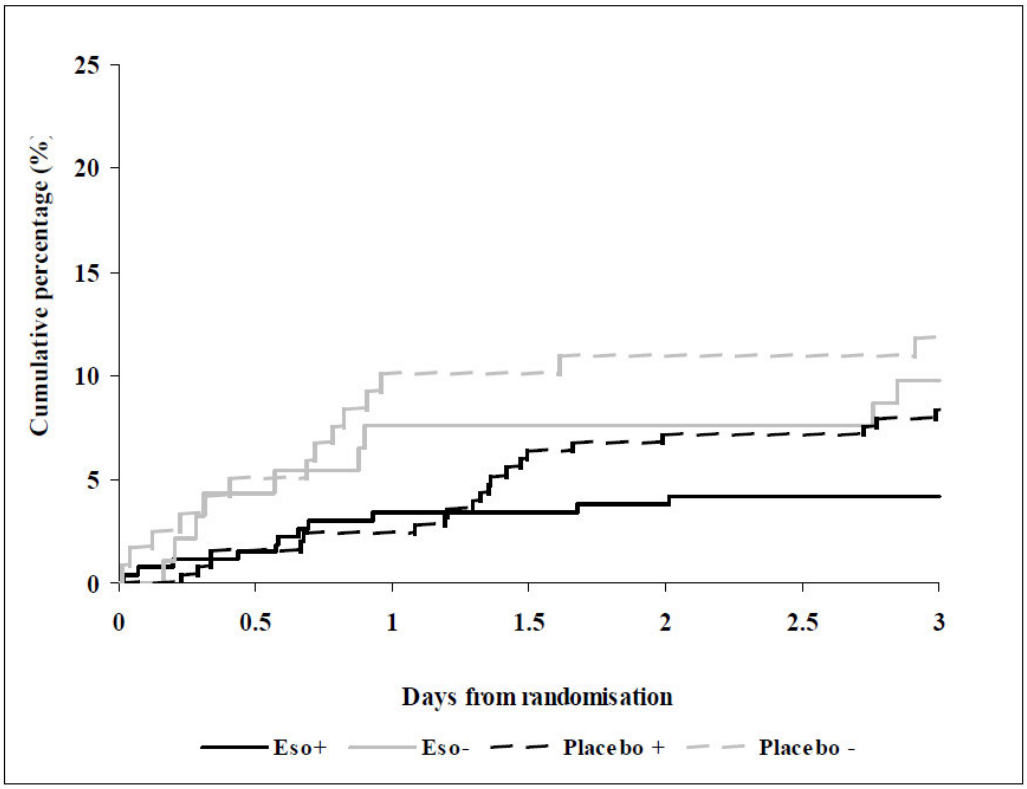
Figure 1. KM estimates of rebleeding events by *H. pylori* status in Study D961DC00001



Source: Applicant, Response to Information Request, dated 04/22/2013

Table 12 presents the proportion of subjects in the Lau study who re-bleed, by *H. pylori* status. Note that continuous data on time of rebleed was not available for the Lau et al study as it was for Study 01.

Table 12. Lau et al - Proportion of subjects who Re-Bleed within 24, 48 and 72 hours (subgrouped by H. pylori status), ITT population

Re-bleed within (hours)	Omeprazole n/N(%)		Placebo n/N(%)	
	H. pylori(+)	H. pylori(-)	H. pylori(+)	H. pylori(-)
24		2/39 (5.1%)	9/64 (14.1%)	7/54 (13%)
48		2/39 (5.1%)	11/64 (17.2%)	9/54 (16.7%)
72	1/78 (1.3%)	3/39 (7.7%)	11/64 (17.2%)	12/54 (22.2%)

3 Omeprazole subjects have missing H. pylori status and 1 of them rebleed within 72 hours
3 Placebo subjects have missing H. pylori status and 1 of them rebleed within 72 hours
mdbmpe 17APR13:10:36:12.25 "LAU - proportion of subjects who rebleed w HPstatus"

Source: Applicant, Response to Information Request, dated 04/22/2013

DGIEP also requested that for those subjects who met the definition of a clinically significant rebleed in Study 01 and Lau et al., to tabulate, by study and treatment arm, the number of patients who met each criterion comprising the definition of a clinically significant rebleed.

This data is presented in Table 13 & Table 14. It does not appear that any single criterion by itself drove the observed outcome in either study. There appears to be significant overlap and redundancy in these criteria both between and within each study.

Table 13. D961DC00001 - Number(%) of subjects who had a clinically significant rebleed within 30 days, by diagnostic sub criterias and treatment arm, ITT population

Diagnostic sub criteria	Esomeprazole (n=29/N=375) n/N(%)	Placebo (n=53/N=389) n/N(%)
1 - Endoscopic verification: blood in stomach	13 / 375 (3.5%)	30 / 389 (7.7%)
2 - Endoscopic verification: active bleeding from a peptic ulcer	13 / 375 (3.5%)	25 / 389 (6.4%)
At least one of 1 or 2: Any endoscopic verification	18 / 375 (4.8%)	36 / 389 (9.3%)
3 - Vomiting of fresh blood/fresh blood in gastric tube/haematochezia/maelena	21 / 375 (5.6%)	39 / 389 (10%)
4 - Decrease in Hb>20g/L during 24h or lack of increase in Hb after transfusion	25 / 375 (6.7%)	44 / 389 (11.3%)
5 - Unstable circulation SBP ≤ 90mmHg/pulse ≥ 110/min	18 / 375 (4.8%)	28 / 389 (7.2%)
At least one of 3, 4 or 5: Any clinical sign	29 / 375 (7.7%)	53 / 389 (13.6%)
6 - Vomiting significant amounts (>200mL) of fresh blood as estimated by the investigator	8 / 375 (2.1%)	12 / 389 (3.1%)

mdbmpe 18APR13:12:16:46.91 "D961DC00001 - diagnostic criterias incl. any A anyB"

Source: Applicant, Response to Information Request, dated 04/22/2013

Table 14. Lau et al - Number(%) of subjects who had a clinically significant rebleed within 30 days, by diagnostic sub criteria and treatment arm, ITT population

Diagnostic sub criteria	Omeprazole (n=8/N=118) n/N(%)	Placebo (n=27/N=119) n/N(%)
Defined as rebleeders but no subcriterias can be found		2 / 119 (1.7%)*
1 - Associated condition at repeat endoscopy: Fresh blood	4 / 118 (3.4%)	8 / 119 (6.7%)
2 - Recent hemorrhage at repeat endoscopy: Spurter or Ooze	3 / 118 (2.5%)	13 / 119 (10.9%)
At least one of 1 or 2: Any endoscopic verification	6 / 118 (5.1%)	17 / 119 (14.3%)
3 - Rebleeding day 1-3: Fresh hematemesis	3 / 118 (2.5%)	2 / 119 (1.7%)
4 - Rebleeding day 1-3: Drop by 2mg/dl & melena	1 / 118 (0.8%)	9 / 119 (7.6%)
5 - Rebleeding day 1-3: Hypotension, tachycardia and melena	4 / 118 (3.4%)	10 / 119 (8.4%)
At least one of 3, 4 or 5: Any clinical sign	6 / 118 (5.1%)	20 / 119 (16.8%)
6 - Vomit significant amounts of fresh blood	1 / 118 (0.8%)	

Categories 3, 4 and 5 were assessed at day 1-3, but one on day 6

*Two subjects (IVP 141 and IVP 171) in the placebo group are defined as rebleeders but no details of criteria can be found

Source: Applicant, Response to Information Request, dated 04/22/2013

Since multiple criteria could be met to define a rebleeder for any given subject in either trial, the review team also asked the applicant to tabulate the number of patients in each treatment arm who met multiple criteria for rebleeding. Table 15 presents the number of subjects who met multiple criteria.

Table 15. D961DC00001 and Lau et al - Number(%) of subjects who had a clinically significant rebleed within 30 days, with multiple diagnostic sub criteria and treatment arm, ITT population

Total number of sub criteria met	D961DC00001		Lau et al	
	Esomeprazole (n=29/N=375) n/N(%)	Placebo (n=53/N=389 n/N(%)	Omeprazole (n=8/N=118) n/N(%)	Placebo (n=27/N=119) n/N(%)
Defined as rebleeders but no subcriteria can be found				2 / 119 (1.7%)
1			3 / 118 (2.5%)	12 / 119 (10.1%)
2	8 / 375 (2.1%)	17 / 389 (4.4%)	2 / 118 (1.7%)	9 / 119 (7.6%)
3	10 / 375 (2.7%)	14 / 389 (3.6%)	3 / 118 (2.5%)	4 / 119 (3.4%)
4	4 / 375 (1.1%)	11 / 389 (2.8%)		
5	6 / 375 (1.6%)	8 / 389 (2.1%)		
6	1 / 375 (0.3%)	3 / 389 (0.8%)		

mdbmpe 16APR13:12:51:03.90 "D961DC00001 - total n of combined detailed criterias"

Source: Applicant, Response to Information Request, dated 04/22/2013

DGIEP sent an Information Request on August 15, 2013 that requested, among other issues, further clarification on type of peptic ulcer bleeds observed at baseline and follow-up endoscopies.

Applicant notes that rebleeding events were documented by endoscopy in 43 of the 62 subjects who had clinically significant rebleeding within 72 hours. In all 43 cases the rebleeding location was in the *same location* (stomach or duodenum) as the baseline bleeding event.

Table 16 present the proportion of subjects who had rebleeds by baseline ulcer type (duodenal or gastric). The relative reduction in rebleeding rate between esomeprazole and placebo was similar for duodenal and gastric ulcers.

Table 16. Proportion of subjects by treatment with clinically significant rebleeding within 72 hours

Duodenum					
Treatment Group	No Rebleeding		Rebleeding		Total
	N*	%	N	%	N
Esomeprazole	202	93.5	14	6.5	216
Placebo	208	89.3	25	10.7	233
Gastric					
	No Rebleeding		Rebleeding		Total
	N*	%	N	%	N
Esomeprazole	150	94.9	8	5.1	158
Placebo	140	90.3	15	9.7	155
Combined					
	No Rebleeding		Rebleeding		
	N*	%	N	%	p-value**
Esomeprazole	352	94.1	22	5.9	0.0266
Placebo	348	89.7	40	10.3	

* One Esomeprazole and one Placebo subject were not included in the analyses because their baseline bleeding location could not be verified at endoscopy. Neither subject had a rebleed within 72 hours.
** Cochran-Maentel-Haenzel test stratified by baseline endoscopy bleeding location.

Source: Applicant response to IR dated August 15, 2013

The applicant also provided rebleeding events that were documented by endoscopy. It appears the majority of rebleeds was documented by endoscopy and appears to trend similarly with the overall results. Applicant also notes that in all 43 cases where rebleeding were endoscopically documented, the rebleeding location was in the same location (stomach or duodenum) as the baseline bleeding event. See Table 17.

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Table 17. Proportion of subjects by treatment with clinically significant rebleeding within 72 hours as documented by endoscopy

Duodenum					
Treatment Group	No Rebleeding		Rebleeding		Total
	N*	%	N	%	N
Esomeprazole	202	94.8	11	5.2	213
Placebo	208	92.9	16	7.1	224
Gastric					
	No Rebleeding		Rebleeding		Total
	N*	%	N	%	N
Esomeprazole	150	98.0	3	2.0	153
Placebo	140	91.5	13	8.5	153
Combined					
	No Rebleeding		Rebleeding		
	N*	%	N	%	p-value**
Esomeprazole	352	96.2	14	3.8	0.0246
Placebo	348	92.3	29	7.7	

* One Esomeprazole and one Placebo subject were not included in the analyses because their baseline bleeding location could not be verified at endoscopy. Neither subject had a rebleed within 72 hours.
** Cochran-Maentel-Haenzel test stratified by baseline endoscopy bleeding location.
Source: Applicant response to IR dated August 15, 2013

8. Safety

The Clinical reviewer for this cycle concluded that overall, no new safety signals were observed for Nexium IV in Study 01 or the Lau study. More detailed safety review of Study 01 was done in the first cycle by Dr. Anil Nayyar (review dated 11/18/2008) and a safety review of the Lau Study was performed during the last cycle by Dr. Erica Wynn (review dated 4/08/2011).

The CDTL reviewer last cycle (Dr. Lynne Yao, review dated 06/16/2011) concluded that, "[o]verall, the safety data available for esomeprazole contained within this submission were minimal. Based on review of the safety data submitted there were no new safety signals identified."

During this review cycle there was refocus on the safety data from Studies I-840 and I-841 given that these studies were terminated prematurely after an imbalance in mortality was detected in Study I-841. Eleven deaths were reported in the omeprazole arm compared with one death in the placebo arm. However this imbalance was not observed in the other three studies submitted to support approval of this NDA.

Table 18. Death by Day 30 (Study 01, Study Lau), Death by Day 21 (Studies 840/841)

Study Drug	Study 01	Study Lau	Study 840	Study 841
Esomeprazole/Omeprazole	0.8 (3/375)	4.2% (5/120)	6.2% (8/130)	7.4% (11/148)
Placebo	1.5% (6/389)	10.0% (12/120)	5.9% (8/135)	0.6% (1/162)

Source: Clinical Review, Table 25, page 36/43, Aisha Peterson, dated 07/15/2013.

The causes of deaths are presented in the clinical review and include MI, heart failure, stroke, pulmonary embolism and GI hemorrhage. The biologic basis of any such association between omeprazole and the CV events is not known. The Clinical reviewer concluded that the available data from these studies, as well as available postmarketing data, suggest that the mortality findings in Study I-841 were most likely due to chance.

9. Advisory Committee Meeting

An Advisory Meeting was not held to discuss this efficacy supplement.

10. Pediatrics

See previous CDTL memo by Dr. Lynne Yao for a discussion of the proposed pediatric plan submitted by the applicant. Briefly, the applicant submitted a waiver request in the initial submission because "studies are impossible or highly impractical because the number of patients is so small and geographically dispersed." At the time, the application was not discussed at PeRC because the review team planned a CR during this review cycle. During the second review cycle the applicant again request a full waiver. The applicant provided data on the number of projected hospitalized patients in the U.S. with pediatric peptic ulcer bleeds. This data was presented before the Pediatric Review Committee (PeRC) on February 16, 2011, and the committee concurred with the recommendation to provide full waiver to the applicant for the proposed indication.

11. Other Relevant Regulatory Issues

Regulatory Briefing

A CDER Regulatory Briefing was held on April 19, 2013. The purpose of this briefing is to discuss the adequacy of evidence provided to support approval of NEXIUM I.V. for the proposed indication, for which PPIs have become standard of care.

DGIEP provided a brief overview of the concerns that were raised during previous review cycles (Cycles 1 and 2). Also presented were the available PK/PD data in Chinese and Caucasian

subjects that were provided by the sponsor to support the applicability of the Lau et al. clinical trial data to the general U.S. population.

As noted in the meeting minutes from the Regulatory Briefing, the majority of the Regulatory Briefing Panel members concluded that the data presented represented substantial evidence of efficacy as described in the Evidence of Effectiveness Guidance document. A member with Clinical Pharmacology expertise commented that a larger PK/PD study in healthy subjects would be unlikely to provide additional relevant information from the Clinical Pharmacology perspective, noting that the PD effect of interest (increase in pH to specific levels) had been demonstrated. The majority of members also commented that the consistent effect across the studies supported the conclusion that efficacy had been demonstrated.

In addition, the Regulatory Briefing Panel members concluded that the mortality difference observed in Study 841 did not preclude approval because the observation did not constitute conclusive evidence of increased risk of mortality related to PPI or even a signal of an increased risk, since it was not a consistent finding across studies.

12. Labeling

Indication

The Applicant's original proposed indication for NEXIUM IV was (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers."

Claims regarding (b) (4) were removed (b) (4) (b) (4)

In addition, throughout the label the proposed term (b) (4) was changed to "bleeding gastric and duodenal ulcers."

Adverse Reactions

Table 3 was added to the table to reflect more broadly the adverse reactions observed in Study 01.

Dosing

Sections 2.2, 8.6 and 12.3 were revised to contain language regarding dosing in patients with hepatic impairment.

Animal Toxicology

(b)(4)

Clinical Studies

The review team negotiated with the applicant regarding acceptable presentation of clinical data included in Section 14.2

(b) (4)

Other Labeling Issues

At the time of finalization of this review, the team was discussing whether data obtained under NDA #202342 (esomeprazole strontium, approved 08/06/2013) should be incorporated into the NEXIUM IV label. More specifically, these discussions were in regard to Sections 8 and 13.2 of the esomeprazole strontium label, which contain data from juvenile rat toxicity studies conducted with esomeprazole magnesium and esomeprazole strontium.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Approval.

- **Risk Benefit Assessment**

NEXIUM I.V. is currently approved and indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively, as an alternative to oral therapy when oral NEXIUM is not possible or appropriate.

The review team this cycle performed a number of analyses that indicate that Study 01 can be used to label IV NEXIUM adequately for the treatment of bleeding gastric and duodenal ulcers. The Lau et al. trial, despite lacking an identical design to Study 01, nevertheless provides supportive evidence that omeprazole (a racemic mixture of which esomeprazole is half the content) is effective in the treatment of bleeding gastric or duodenal ulcers. Arguments that the Lau study population is not generalizable, as a whole, to a non-Chinese population do not appear to be supported strongly by the analyses performed by the review team this cycle, particularly the PK/PD analyses. The results from from Study 01 and Lau et al., and to a lesser extent Studies I-840 and I-841, suggest to me that intravenous esomeprazole or omeprazole has a measureable treatment advantage compared to placebo, across studies and various subgroups.

The applicant also makes the point that additional placebo-controlled trials would be impracticable or unfeasible. It shouldn't be taken lightly that published clinical practice guidelines, including the 2012 American College of Gastroenterology Guidelines[1] and the 2010 International Consensus Upper GI Bleeding Conference Group, strongly advocate the use of intravenous PPI drugs in preventing peptic ulcer re-bleeding after a successful endoscopic hemostasis. This reality does lend some support to the applicant's assertion.

FDA's, *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* notes the following in such circumstances in which a second adequate and well-controlled trial would be impractical [Section II(3)(c)]:

> A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

Actively bleeding gastric and duodenal ulcers could result in significant morbidity and mortality. As noted by the applicant, approximately 100 patients per 100,000 inhabitants are yearly admitted to hospitals due to significant upper GI bleeding, and approximately half of these bleedings are caused by gastric and/or duodenal ulcers (Rockall *et al* 1995, van Leerdam *et al* 2003). The mortality rate within 30 days in these patients is approximately 5 to 10%.

Further, as concluded by the review team, the proposed dosing regimen of NEXIUM IV for bleeding gastric or duodenal ulcers appears to be safe, providing a favorable risk: benefit profile.

As noted previously, at the time of finalization of this review, the team was discussing whether animal data obtained under NDA #202342 (esomeprazole strontium) should be incorporated into the NEXIUM IV label. Because of these ongoing discussions, an action was not taken on the PDUFA goal date of September 14, 2013.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A REMS is not recommend.

- **Recommendation for other Postmarketing Requirements and Commitments**

At the time of finalization of my review, no Postmarketing Requirements or Commitments were recommended.

[1] *Am J Gastroenterol* 2012; 107:345–360

- **Recommended Comments to Applicant**

None.

14. Appendix

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Table 19. Key Study Design Features (Studies 01, Lau, 840, and 841)

	01	Lau	840	841
Definition of endpoint criterion	Blood in the stomach or a verified active bleeding from a peptic ulcer (Forrest class Ia, Ib) **Or** At least 2 of the following: • Vomiting of fresh blood or fresh blood in a gastric tube or hematochezia or melena after a normal stool • Decrease in hemoglobin >20g/l or (hematocrit >6%) despite ≥ 2 units of blood has been transfused during 24 hours • Unstable circulation systolic blood pressure ≤90mm Hg or pulse≥110/min (after having had a stable circulation) **Or** Hematemesis (vomiting of significant amount of (>200ml) of fresh blood)	Fresh hematemesis Hypotension: Systolic Blood Pressure<90 Tachycardia PR>110 and Melena Drop in hemoglobin by 20g/l in 24 hours and melena	Moderate: • Hematemesis • Significant amount of coffee grounds or red blood in the nasogastric tube • Hemoglobin falling 16g/l or more • Neither tachycardia or hypertension Severe: • Voluminous hematemesis, red blood in the nasogastric tube or in stools • Unstable circulation or rapid transfusions required to prevent it.	Hemodynamically unstable and/or Hb fall>10g/l over 12 hours Fresh Blood (macroscopic in the nasogastric tube or fresh hematemesis) Blood transfusion was necessary to maintain the hemoglobin level.
Therapeutic endoscopic procedures	Injection therapy (epinephrine) and/or one of the following: coagulation with heater probe, electrocautery, hemoclips.	Injection therapy (epinephrine) followed by captive thermocoagulation with heater probe	Preferably injection technique but thermal coagulation or electrocoagulation allowed	Eg: sclerotherapy, heater probe
Drug and dosing	Placebo or Esomeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)	Placebo or Omeprazole (a bolus IV injection of 80mg followed by a continuous infusion of 8mg/hr for 72 hours)	Placebo or Omeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)	Placebo or Omeprazole (a bolus infusion of 80mg over 30mg followed by a continuous infusion of 8mg/hr for 71.5 hours). If signs of rebleeding occurred within 48 hours the continuous infusion was given for 120 hours

	01	Lau	840	841
Oral Follow-Up Treatment After IV treatment	Esomeprazole (40 mg once daily for 27 days)	Omeprazole (20 mg once daily for 8 weeks)	After 48 hr IV therapy, all patients received omeprazole (20mg once daily until follow-up visit Day21)	Omeprazole (20 mg once daily until follow-up visit, day 21)
Inclusion criteria Age (years) Signs of Gastrointestinal Bleeding Forrest Classification of Bleeding Ulcers Successful endoscopic hemostasis	≥18 years Within 24 hours prior to endoscopy Ia, Ib, IIa, or IIb Yes	≥ 16 years Within 24 hours after admission endoscopy performed Ia, Ib, IIa, or IIb Yes	>18 years Within 12 hours prior to endoscopy Ia, Ib, IIa, or IIb Only Forrest Ia, IIa	>60 years Within 48 hours prior to admission Ia, Ib, IIa, or IIb Only Forrest Ia

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/s/

ROBERT FIORENTINO
09/20/2013

Cross-Discipline Team Leader Review

Date	June 16, 2011
From	Lynne P. Yao, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-689 Supplement S014/ Complete Response Submission
Applicant	AstraZeneca LP
Date of Submission	September 15, 2010
PDUFA Goal Date	June 16, 2011
Proprietary Name / **Established (USAN) names**	Nexium, I.V. Esomeprazole Sodium, I.V.
Dosage forms / Strength	Lyophilized powder for Injection/ 20 and 40 mg vials
Proposed Indication(s)	1. (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.
Recommended:	*Complete Response*

1. Introduction

This memorandum reviews the information submitted by the applicant, AstraZeneca, in response to a Complete Response Letter issued on November 26, 2008, for Nexium I.V. (esomeprazole sodium I.V.), NDA 21-689/S014, for (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. This review focuses on the deficiencies cited in the Complete Response Letter issued and the adequacy of the responses provided by the applicant regarding these deficiencies. The Complete Response Letter noted deficiencies in clinical, statistical, and clinical pharmacology areas. These deficiencies and the applicant's responses will be the focus of this memo.

The applicant's complete response was submitted on September 15, 2010, and was designated for standard review, with a PDUFA date of March 16, 2011. However, additional data received from the applicant on February 14, 2011 based on an information request sent to the applicant triggered a major amendment, with an extension of the PDUFA date to June 16, 2011.

Both the clinical and statistical reviewers have recommended that a Complete Response action be taken for the current submission. This memo reviews the recommendations made by each review discipline and documents my concurrence with the clinical and statistical teams' recommendations for a Complete Response action. The clinical pharmacology team, however, concluded that the information submitted to address the clinical pharmacology deficiencies was adequate.

2. Background

A. Clinical Background

Peptic ulcer is the most common cause of upper gastrointestinal bleeding. Up to 20% of patients with a bleeding peptic ulcer will require endoscopy because of active continuous bleeding, or recurrent episodes of bleeding.[1] It has been established that specific populations are at higher risk of bleeding from peptic ulcers and for rebleeding after endoscopic treatment for peptic ulcers. These risk factors include older age (age >65 years), poor overall health status, comorbid illnesses, ulcer size and hemodynamic instability (i.e. shock, low initial hemoglobin level, requirement for blood transfusions). Additionally, the risk of rebleeding has also been demonstrated to be associated with the findings on endoscopy and Laine and Peterson reported a review of the prognosis for rebleeding associated with the Forrest classification categories.[2,3] This publication reported that 55% (17-100) of actively bleeding

[1] Lau, et al, Effect of Intravenous Omeprazole on Recurrent Bleeding after Endoscopic Treatment of Bleeding Peptic Ulcers, N. Engl. J. Med., 2000, Aug 3; 343(5): 310-316
[2] Laine L., Peterson W, Bleeding Peptic Ulcer, N. Engl. J. Med., 1994, Sep 15;331(11):717-27
[3] Forrest JA, Finlayson ND, Shearman DJ, Endoscopy in gastrointestinal bleeding, Lancet, 1974, 17:394-397.

ulcers rebleed, that ulcers associated with a visible vessel (Forrest II) are associated with a 43% (0-81) risk of rebleeding, and those with adherent clot (Forrest IIb) a 22% (14-36) risk of rebleeding (see table 1). These risk levels were based on review of multiple publications and the associated range of risk of rebleed for each level is large. It is important to note that each of the individual classifications in this scheme are associated a distinct risk of rebleeding.

Table 1: Forrest Classification of Gastric Ulcer Hemorrhage with Prognosis

	Forrest Classification	Rebleeding Incidence if untreated
Type I: Active Bleeding	Type Ia: Spurting bleeding Type Ib: Oozing bleeding	100% 55% (17 -100%)
Type II: Recent Bleeding	Type IIa: Non-bleeding visible vessel Type IIb: Adherent Sentinel Clot Type IIc: Black base vessel (Hematin covered flat spot)	43% (8 – 81%) 22% (14 -36%) 10% (0 -13%)
Type III: No bleeding	Type III: No stigma	5% (0 – 10%)

copied from clinical review by E. Wynn

Treatment for bleeding peptic ulcers includes both conservative management, endoscopic treatment, and surgery. Endoscopic treatment is usually provided within 24 hours of inpatient hospitalization and treatments used include injection with epinephrine, thermocautery, and hemoclips. The clinical reviewer noted that in a recently published clinical guideline, injection therapy with epinephrine is useful only as adjunct therapy in combination with other modalities (e.g. thermocautery, hemoclips).[4]

Several investigators have studied the use of proton pump inhibitors (PPIs) to decrease the risk of rebleeding of peptic ulcers. The mechanism of action of the presumed effect of PPIs in the reduction of risk of rebleeding of peptic ulcers is based on in vitro and animal studies that demonstrate that platelet aggregation is decreased at ≤6.8 and that fibrinolysis increases at lower pH. Therefore, maintenance of a higher intragastric pH through the actions of PPIs may enhance clot formation in the stomach and duodenum, leading to a decreased risk of rebleeding. The clinical reviewer noted that several studies have been published evaluating the use of intravenous PPI to decrease the risk of bleeding of peptic ulcers; however, these studies have been confounded by heterogeneity of patient populations studied, specific PPI treatment regimen, and the timing and/or type of endoscopic intervention used.

B. Regulatory Background

Initial Submission

The original sNDA (21-689/S014) was submitted on May 29, 3008. The supplement was granted a standard review. On November 26, 2008, a Complete Response letter was issued because of significant clinical and clinical pharmacology deficiencies. These deficiencies included:

[4] Barkun A, Bardou M, Kuipers, E, et al, "International Consensus Recommendations on the Management of Patients with Nonvariceal Upper Gastrointestinal Bleeding." *Ann. Intern. Med.* 2010;152:101-113.

1. Lack of a highly statistically significant result of a single study to support the efficacy of the product for the proposed indication.
2. Lack of robustness of clinical efficacy when evaluated using important sensitivity analyses including country-to-country variation and appropriate stratification by patient characteristics (i.e., Forrest classification)
3. Lack of internal consistency and wide variability of efficacy results across study centers
4. Lack of treatment effect in patients 65 years of age and older, a group considered to be at higher risk for rebleeding events
5. Lack of effect in important secondary efficacy outcomes including the proportion of patients who underwent surgery for rebleeding, the number of units of blood required in the first 72 hours, and the proportion of patients who required endoscopic retreatment in the first 72 hours, after Bonferroni adjustment to account for multiple comparisons
6. Potential impact of results from a study site with a primary investigator with significant financial disclosures. Removal of this site from the analysis resulted in a decrease in the observed treatment effect to -3.7% and a p-value that increased to 0.06.
7. Nonstandard endoscopic treatments within the study
8. Inclusion of a substantial number of patients that had multiple ulcers at the time of endoscopy despite clear exclusion criteria that stated that patients with multiple ulcers on endoscopy should be excluded from the study. Fewer patients with multiple ulcers were randomized to the treatment group and may have favored the esomeprazole arm.
9. Imbalances in baseline factors for risk of rebleeding that favored the treatment arm (i.e., large ulcers, and grade Ia stigmata for risk of rebleeding).
10. Allowance for use of I.V. PPI therapy within 24 hours of enrollment of the study.
11. Inadequate information to permit proper dosing in patients with hepatic impairment.

Recommendations to address the deficiencies were:

1. Conduct at least one additional adequate and well-controlled study to demonstrate the proposed benefit of NEXIUM I.V. for (b) (4)
2. Consider if the dose evaluated in the pivotal trial was adequate to achieve the desired efficacy. Conduct an additional dose finding study in the target population to evaluate dose optimization.
3. Study site 0102 in the Netherlands, which reported the greatest treatment effect will need to be inspected by the Division of Scientific Investigations (DSI).
4. Conduct a pharmacokinetic study in sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.

Additionally, the Complete Response letter recommended the submission of the following additional information:

1. Submit a pediatric plan

2. Submit Safety update as described in 21CFR 314.50(d)(5)(vi)(b) to include data from all nonclinical and clinical data trials of the drug under consideration regardless of indication, dosage form, or dose level

The following list outlines the discussions between the division and the applicant regarding the information to be included in the complete response submission:

- June 11, 2009 – Type C meeting held between the Division and applicant to discuss a path forward for the application. The applicant proposed a reanalysis of the data from D961DC00001 (b) (4) The Division rejected the applicant's proposal (b) (4) The Division also stated that the study data from a published study by Lau, et al, could be included but would be considered as supportive only because it was a single center trial and was not conducted using esomeprazole. The Division proposed that one path forward would be for the applicant to review and reanalyze the data from previously conducted well-controlled trials using esomeprazole. The applicant agreed to propose and submit a preliminary response to the CR letter for FDA review.

- July 14, 2009 – The applicant submitted a proposal for the information to be included to address the deficiencies noted in the Complete Response letter.

- December 03, 2009 – An advice letter was issued to the applicant that included the following recommendations:
    1. Provide supportive data, including clinical study reports (CSRs) for each trial included in the new submission. Submit justification describing how the supportive evidence is similar to that of trial D961DC00001 (the pivotal trial reviewed with the original efficacy supplement submission). Present a summary of a head to head comparison between the submitted trials and D961DC00001 evaluating the patient population, therapeutic endoscopic procedures, dosing of drug, endpoints criteria, and efficacy results.
    2. Provide criteria used to define a clinically significant rebleed event in each trial and the timing of all clinically significant rebleeding events
    3. Provide information on rebleeding events during the first 72 hours post-endoscopy using Forrest's classification criteria. Also provide separate tables for the percent of patients with clinically significant rebleeding events by age, race, and gender for each trial.
    4. Provide additional supportive evidence of efficacy for specified variables:
        - Proportion % (n) of mortalities within 72 hours and 30 days
        - Proportion % (n) who had surgery due to a rebleeding event within 72 hours and 30 days
        - Proportion % (n) who had endoscopic re-treatment due to a rebleeding event within 72 hours and 30 days
        - Number of blood units transfused within 72 hours and 30 days

5. Provide complete case report forms (CRFs) for patients who died, sustained a serious adverse event (SAE) and/or rebleeding event at any time during the trial.
6. Provide datasets in a format similar to those in the original submission.

Current Submission
The applicant submitted their Complete Response for supplement S014 on September 15, 2011. The current submission included the following information:

1. Pharmacologic bridging studies to assess the pharmacodynamic comparability between intravenous omeprazole and intravenous esomeprazole
2. Three clinical studies evaluating intravenous *omeprazole*: one published in the literature by Lau, et al, and two studies (I-840 and I-841) conducted by the applicant
3. Observational data from use of intravenous esomeprazole in patients with peptic ulcer bleed
4. A systematic review of available trials from any proton pump inhibitor for the proposed indication
5. Additional observational data from other data sources including healthcare and administrative databases, and hospital networks with field-based studies.

This memo will review the data included in the applicant's complete response. The Complete Response letter contained no product quality or pharmacology/toxicology deficiencies; therefore, no reviews were required from these disciplines. The following reviewers provided discipline specific reviews for the submission:

Clinical Review by E. Wynn, dated June 14, 2011
Statistical Review by L. Kammerman, with concurrence by M. Welch, dated June 15, 2011
Clinical Pharmacology Review by D. Jappar, with concurrence by S.C. Lee dated May 26, 2011
Pediatric and Maternal Health Staff consult review by A. Taylor, with concurrence by L. Mathis, dated January 18, 2011
Division of Scientific Investigation (DSI) consult by J. Lee dated April 8, 2011.
Office of Surveillance and Epidemiology consult by J. Ju, dated, January 28, 2011

3. CMC/Device

Current Submission
There were no product quality issues cited in the Complete Response letter. Thus, there were no product quality issues reviewed in the applicant's current submission. The product quality microbiology review initially noted potential deficiencies related to the applicant's proposed storage times for the reconstituted product. However, the applicant addressed the reviewer's concerns adequately and the reviewer concluded that the supplement be approved.

4. Nonclinical Pharmacology/Toxicology

Current Submission
There were no nonclinical issues cited in the Complete Response letter. Thus, there were no nonclinical issues reviewed in the applicant's current submission.

5. Clinical Pharmacology/Biopharmaceutics

Initial Submission
The reader is referred to the clinical pharmacology review by T. M. Chen, dated November 25, 2008 for complete details.

The original sNDA submission included one clinical pharmacology study that evaluated the following:

1. PK and PD parameters of esomeprazole, IV, given as a loading of dose of 40 mg, 80 mg, and 120 mg, over 30 minutes in healthy subjects
2. PK and PD parameters of esomeprazole, IV, given as a loading dose as described above, followed by a continuous infusion of either 4mg/hr or 8 mg/hr for 72 hours in healthy subjects

Additionally, data pertinent to the sNDA reviewed in previous submissions includes the following:

1. PK and PD parameters of esomeprazole, IV, given once daily for 5 days at doses of 20 and 40 mg to healthy subjects
2. PK and PD parameters of esomeprazole, PO, given once daily for 5 days at doses of 20 and 40 mg to healthy subjects

The overall results of these studies are presented in table 2. It is important to note that intragastric pH levels above 4 were achieved at least 80% of the 24-hour treatment period for all treatment regimens studied. However, intragastric pH levels above 6 were only achieved for roughly half of the 24-hour period. These pharmacodynamic findings suggest that the optimal dose may not have been achieved because nonclinical studies, as stated above, suggest that a pH of at least 6.4 is required to maximize hemostasis in the upper gastrointestinal tract. Nevertheless, there was a reduction of rebleeding events in the single phase 3 trial despite the substantial proportion of time that intragastric pH ≤6 (see section 4, Clinical/Statistical-Efficacy). However, the small treatment effect noted in the single phase 3 trial may be partly explained by an inadequate dose.

Table 2: Estimates of mean percentage of time with intragastric pH>4, pH>6, pH>7 with intravenous infusion of esomeprazole at 5 different infusion combinations in healthy subjects, during the 24 hour period by dose level

	Esomeprazole Regimen	Estimate
pH>4 (0-24)	40 mg + 8 mg/h	82%
	80 mg + 4 mg/h	80%
	80 mg + 8 mg/h	90%
	120 mg (30 min)+ 8 mg/h	84%
pH>6 (**0-3hr**)	40 mg + 8 mg/h	25%
	80 mg + 4 mg/h	35%
	80 mg + 8 mg/h	46%
	120 mg (30 min)+ 8 mg/h	46%
pH>6 (**0-24h**)	40 mg + 8 mg/h	46%
	80 mg + 4 mg/h	44%
	80 mg + 8 mg/h	52%
	120 mg (30 min)+ 8 mg/h	49%
pH>7 (0-24h)	40 mg + 8 mg/h	2%
	80 mg + 4 mg/h	4%
	80 mg + 8 mg/h	5%
	120 mg (30 min)+ 8 mg/h	4%

copied from division director memo by D. Griebel

The clinical pharmacology reviewer also noted that although the PK/PD studies were limited to 24 hours of exposure to Nexium, the PK/PD for the dose regimen had been adequately characterized. The reviewer noted that the studies were only performed in healthy volunteers, and not the target population and expressed concern that it is not possible to correlate the PD in healthy subjects compared to patients who have bleeding peptic ulcers. The clinical pharmacology reviewer also expressed concern that patients with moderate or severe hepatic impairment were excluded from the pivotal trial. Therefore, PK data from this population were not available for this new dose regimen.

Based on these concerns, the following clinical pharmacology deficiencies were cited in the Complete Response letter:

1. You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two pharmacokinetic/pharmacodynamic (PK/PD) studies that you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3

study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment.

2. There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment.

Thus, the Complete Response letter included the following clinical pharmacology deficiencies that must be addressed by the applicant in their resubmission:

1. Conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data.

2. Conduct a pharmacokinetic study in a sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.

Current Submission
The reader is referred to the clinical pharmacology review by D. Jappar, dated May 26, 2011 for complete details.

The applicant submitted data and literature references for PK/PD bridging between omeprazole and esomeprazole in order to use the results of intravenous omeprazole data to support the proposed indication for esomeprazole. The applicant submitted data comparing PK and PD parameters of short-term intravenous infusion of esomeprazole and omepraozole; the PK and effect on intragastric pH of esomeprazole, 80 mg as a bolus intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/hour for 23.5 hours was compared to that of corresponding dosage regimen of intravenous omeprazole in Study D961DC00004; and oral studies (which will not be reviewed in this memo).

Study D961DC00004 was a double-blind, randomized, 2-way crossover, single-center (Switzerland) comparative study of esomeprazole and omeprazole given as short-term intravenous infusion of 80 mg over 30 minutes followed by continuous infusion of 8 mg/hour for 23.5 hours regarding the effect on 24-hour intragastric pH and pharmacokinetics in 39 healthy male and female volunteers with washout period of 13 days between the treatments. The clinical pharmacology reviewer noted that the geometric mean Cmax and AUCt of esomeprazole were 14% higher compared to omeprazole; 95.47 vs. 83.97 μmol*h/L for AUC and 12.82 vs. 11.28 μmol/L for Cmax. Esomeprazole and omeprazole has similar intragastric pH compared to time profiles and median intragastric pH (5.9 vs. 5.8). Therefore, no

substantive differences were noted between the two treatments with respect to both PK and PD parameters when given as 80 mg bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/hour for 23.5 hours. However, clinical reviewer also noted that there was less interindividual variability for esomeprazole compared to omeprazole regarding AUC and percentage of time with intragastric pH>4.

D9615C00018 was a single-center, open-label, randomized, two-way cross-over study comparing the effect of single 30-minutes intravenous infusion of esomeprazole 40 mg and omeprazole 40 mg under fasting conditions. The clinical pharmacology reviewer noted that following single dose of 30 minutes intravenous infusion, esomeprazole 40 mg had higher exposure (36% for AUC and 18% for Cmax) and longer half-life (12%) compared to omeprazole. Regarding PD parameters, both esomeprazole and omeprazole resulted in a significant reduction in peak acid output and basal acid output from the baseline, with more significant effect from esomeprazole compared to omeprazole. The more pronounced PD effect of esomeprazole likely is a reflection of its higher AUC compared to omeprazole.

Study SH-QBE-0061 was a two-center, open-label, randomized, two-way cross-over study to compare PK of single and multiple dose of 40 mg esomeprazole and 40 mg omeprazole administered as a short term intravenous infusion for 30 minutes once daily for five days in healthy male subjects. The clinical pharmacology reviewer noted that following once daily intravenous administration of 40 mg esomeprazole or 40 mg omeprazole over 30 minutes for 5 days, AUC was higher for esomeprazole than for omeprazole on both day 1 and day 5 in extensive metabolizers. However, in poor metabolizers, the effect on AUC was contradictory. Moreover, the observed difference in AUC between poor and extensive metabolizers for esomeprazole was less than for omeprazole. However, there were only 2 subjects in poor metabolizer group to make a definitive conclusion.

The clinical reviewer concluded that extent of differences between the PK/PD parameters of esomeprazole compared to omeprazole were dependent on the route of administration. There were no major differences in PK and PD parameters (AUCt and Cmax of esomeprazole were only 14% higher than those for omeprazole) in studies evaluating continuous intravenous infusion (80 mg as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/hour for 23.5 hours). However, following short term intravenous infusion over 30 minutes, AUC and Cmax of 40 mg esomeprazole were 36-43% and 12- 18% higher than those of 40 mg omeprazole, respectively. Higher AUC of esomeprazole was also reflected in its higher PD effect. For the various administration routes and dosing regimens studied, the acid suppression effect of esomeprazole was similar to or greater than that of omeprazole when given at the same dose. Therefore, clinical studies evaluating intravenous omeprazole would be likely to demonstrate a similar or smaller treatment effect than studies evaluating esomeprazole. The clinical reviewer concluded that overall, a reasonable PD bridging is established between omeprazole and esomeprazole for the proposed IV dosing regimen.

Additionally, the applicant submitted data and literature references to address the use of esomprazole for the proposed indication in patients with hepatic impairment. The applicant submitted data from two studies; use of oral esomeprazole in hepatic impairment patients

(study SH-QBE-0026, Sjövall et al 2002), and another study with intravenous omeprazole in hepatic impairment patients (CSR I-1226, Piqué et al 2002).

When esomeprazole 40 mg was given orally for 5 days to hepatic impairment patients, overall, the AUC increased with the degree of the liver impairment. However, Cmax was not influenced significantly by the degree of liver impairment. The AUC in patients with severe hepatic insufficiency were about 2-3 fold higher compared to patients with normal hepatic function. When intravenous omeprazole, 80 mg, was infused over 30 minutes followed by a constant infusion of 8 mg/hour up to 24 hours in hepatic impairment patients, higher omeprazole AUC was noted in patients with hepatic impairment compared to subjects with normal liver function. Additionally, the omeprazole AUC increased with the degree of the liver impairment. Patient with mild to moderate hepatic impairment had an approximately 1.46 fold (46%) and 1.74 fold (74%) higher mean AUC compared to the patients with normal liver function whereas the patients with severe hepatic impairment function had almost 2 fold higher mean AUC compared to the patients with normal hepatic function. Mean omeprazole Cmax values, however, were less influenced by the severity of hepatic impairment. The clinical pharmacology reviewer concluded (b) (4) Therefore, the clinical pharmacology reviewer recommended that the applicant resubmit the modeling and simulation results of previously collected data to support an estimate of the proper constant infusion rate in patients with moderate and severe hepatic impairment.

In a dose finding study submitted and reviewed during the last review cycle, the applicant proposed the recommended dose for patients with normal liver function (80 mg infusion over 30 minutes followed by a 8 mg/hr constant infusion) showed 50% higher AUC (111 vs. 74 µmol*h/L) and comparable Cmax compared to the recommended dose for patients with severe hepatic impairment (80 mg infused over 30 min followed by 4 mg/hr constant infusion).

Based on these findings, the applicant has proposed the following dose adjustment for esomeprazole in patients with hepatic impairment:

1. (b) (4)
2. A dose reduction for patients with severe hepatic impairment to 80 mg infused over 30 min followed by a maximum continuous infusion dose of 4 mg/hour (b) (4)
3. (b) (4)

The clinical reviewer concluded that the data provided supported the proposed dosing recommendations for patients with hepatic impairment. However, clinical reviewer noted concern regarding the proposed continuous intravenous infusion rate of esomeprazole for both patients with moderate (b) (4) and severe (4 mg/hour) hepatic impairment. Therefore, the clinical pharmacology reviewer recommended that the applicant conduct further modeling and

simulation based on previously collected data in order to estimate the proper constant infusion rate in patients with moderate and severe hepatic impairment.

Finally, the applicant provided information to address the deficiency relating to the optimal dose of esomeprazole for the proposed indication. The applicant argued that healthy subjects would be more likely to H. pylori negative and that the acid suppressive effects of PPIs are less pronounced than in patients who are H. pylori positive.[5] Based on the provided literature, clinical pharmacology reviewer agreed that the acid suppressive effect of the proposed esomeprazole is expected to be more pronounced when given to bleeding peptic ulcer patients than given to *H. pylori* negative healthy subjects as in this dose finding study. After further internal discussion, the clinical pharmacology review team concurred with applicant's explanation and agrees that no further dose finding study in target population is necessary. However, I do not agree that all patients with bleeding peptic ulcers are H. pylori positive. Thus, it cannot be assumed that the effect of esomeprazole is expected to be more pronounced in bleeding peptic ulcer patients compared to healthy patients. I conclude that the data the applicant has presented to not completely support their dose selection as the optimal dose of esomeprazole.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this complete response submission or the initial submission because esomeprazole is not intended as an antimicrobial product.

7. Clinical/Statistical- Efficacy

Initial Submission

The reader is referred to the clinical review by A. Nayyar dated November 17, 2008 and the statistical review by S. Castillo dated November 13, 2008 for complete details.

The data used to support the proposed indication in the initial sNDA submission was a single randomized, placebo-controlled study. The primary endpoint of the study was the proportion of patients who experienced clinically significant rebleeding in the first 72 hours after endoscopic treatment. Major enrollment criteria included presence of a single gastrointestinal bleeding from a peptic ulcer (gastric or duodenal) classified by Forrest classification as Ia, Ib, IIa, or IIb (see table 1); patients with multiple ulcers were excluded. Intervention for the ulcer must have included injection with epinephrine and/or one of the following: heater probe, electrocautery, or hemoclips. Patients were randomized to receive treatment with esomeprazole, 80 mg, IV over 30 minutes followed by a constant infusion of 8 mg/hr for the remainder of the 72 hour treatment period or placebo.

There were 767 patients enrolled at 91centers outside the U.S.; approximately 2/3 were male, nearly 90% presented with melena, and approximately 60% had duodenal ulcers. As stated above, patients were to be excluded from the study if multiple ulcers were present at

[5] Gillen D, Wirz A, Neithercut W, Ardill J, McColl K; Helicobacter pylori infection potentiates the inhibition of gastric acid secretion by omeprazole; Gut, 1999;44:468-475

endoscopy. However, 14% on the esomeprazole arm had multiple ulcers compared to 19% on the placebo arm. Data were missing for this descriptor in 8% of randomized esomeprazole patients and 6% of placebo patients.

The overall efficacy results are presented in table 3. Treatment with esomeprazole resulted in a decreased the incidence of rebleeding at 72 hours of 4.4% compared to placebo treatment and that the result was statistically significant (p=0.0256, Mantel-Haenszel test stratified only for type of endoscopic treatment used).

Table 3: Incidence of rebleeding within the first 72 hours after endoscopic intervention

	Esomeprazole	Placebo	Treatment Effect Esomeprazole minus Placebo (with 95% CI)
N	375	389	
% Rebleed (n)	5.9% (22)	10.3% (40)	-4.4% (CI = -8.3%, -0.6%)
p-value			0.0256

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However, the clinical and statistical reviewers uncovered several issues that questioned the robustness of the efficacy finding, and the clinical and statistical reviewer concluded that this single study did not provide substantial evidence of efficacy for the proposed indication. The limitations and deficiencies of the study were summarized in the Complete Response letter as follows:

"Our review finds that the primary efficacy results for this non-U.S. single study do not provide substantial evidence of efficacy. For a single study to stand alone as substantial evidence of efficacy, it should demonstrate highly statistically significant and clinically meaningful results.
Consistency should be demonstrated across subgroups and secondary endpoints. The study should also show internal consistency in demonstrating the treatment effect across study centers.

The single study that you have submitted does not meet these criteria for providing substantial evidence for the following reasons:

1. Highly statistically significant results were not demonstrated. Although your protocol specified analysis showed a reduction of 4.4% in the rate of clinically significant rebleeding within 72 hours after hemostasis compared to placebo (p = .03), that reduction was not highly significant, e.g., p < .001. In addition, the observed outcome was not found to be robust when subjected to the sensitivity analyses listed below:
   a. It is appropriate to account for country-to-country variation, so the protocol specified analysis was further stratified by country. This resulted in an insignificant treatment effect (p=0.06), although the absolute reduction in rebleeding remained 4.4%.
   b. When the protocol specified analysis was further stratified (retaining stratification by country in the model) using Forrest classification as four separate categories

(Forrest Ia, Ib, IIa, and IIb) instead of two (Forrest I and Forrest II), an insignificant treatment effect was observed (p=0.11). The absolute reduction in rebleeding remained 4.4%. We believe the appropriate adjustment for Forrest classification should be by each individual Forrest category because each category has a different risk of rebleeding events. Even if this stratified analysis was conducted without incorporation of country in the model, the p value still shifted to a less persuasive value of p= 0.05.

2. The study lacked internal consistency across study centers. Despite similar patient demographics and disease characteristics, marked variability in the incidence of rebleeding, i.e., the primary endpoint, and treatment effect was observed in different countries and among leading centers. The treatment effect varied widely from -25% to +12% by country and from -31% to +20% in the larger centers that enrolled more than 10 patients. There is no clear explanation for why this occurred, although physician expertise and standards of care may have played a role.

3. The study lacked internal consistency in demonstrating the treatment effect in the important subgroup of patients aged 65 and older. In this subgroup, the proportion of patients that experienced rebleeding in the first 72 hours was 6.2% on the esomeprazole arm and 8.4% on the placebo arm. In contrast, in patients aged less than 65 the proportion of patients that experienced rebleeding in the esomeprazole arm was 5.5%, while on the placebo arm the proportion was 11.9%.

4. The study lacked internal consistency in demonstrating the treatment effect in important secondary efficacy outcomes that were evaluated in the first 72 hours. The proportion of patients who underwent surgery for rebleeding was a prespecified secondary endpoint and the observed outcome for this endpoint was similar between study arms. This analysis was not found to be statistically significant, p = 0.31. The secondary analysis comparing number of blood units transfused in the first 72 hours demonstrated a lower number of units infused on the esomeprazole arm (492) relative to placebo (738), p=0.05, and the secondary analysis that compared the proportion of patients who required endoscopic retreatment in the first 72 hours demonstrated a decreased rate of endoscopic retreatment (4.3%) on the esomeprazole arm relative to placebo (8.2%), p=0.02. Although the secondary analyses of number of blood units transfused and endoscopic retreatment appear nominally significant, there was no prespecified plan to adjust for multiple comparisons. Taking a conservative approach, these p values are not significant after a Bonferroni adjustment to account for multiple comparisons.

5. One center, Site 0102 in the Netherlands reported the largest treatment effect in all centers that participated in this study, -31% rebleeding events, favoring the esomeprazole arm of the study. The investigator from this site, Dr. Ernest J. Kuipers, MD, Ph.D., reported having accepted significant payments from Astra Zeneca. When we conducted a sensitivity analysis to explore the impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center

from the efficacy analysis, we found that the overall treatment effect observed in the study decreased to -3.73% (95% CI = -7.67, 0.10) and the p value shifted to 0.06.

6. We identified additional study design and conduct concerns that further limit the study's ability to provide persuasive evidence that esomeprazole is effective for the proposed indication. These issues are listed below:
   a. Endoscopic epinephrine injection is currently not an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers. More than a third of the patients in this study were treated with endoscopic epinephrine injection as single therapy. This draws into question the applicability of the outcome observed in this trial to current care of patients with an upper gastrointestinal bleed from a gastric or duodenal ulcer in the United States today.
   b. Although the inclusion criteria excluded patients with more than a single ulcer, a substantial proportion of the randomized patients had multiple ulcers and there was an imbalance between study arms in this prognostic factor that favored the esomeprazole arm. Fewer patients on the esomeprazole arm had multiple ulcers, 13.6%, relative to the placebo arm, 18.5%. This raises concerns regarding the study conduct in this international trial.
   c. Despite randomization, small imbalances in important prognostic factors were observed between the two study arms. The imbalances favored the esomeprazole treatment arm. These prognostic factors included Grade 1a stigmata of risk of rebleeding (esomeprazole=7.5%, placebo=10.3%) and large ulcers (esomeprazole=7.7%, placebo=10.3%).
   d. The lack of an exclusion criterion for intravenous administration of a proton pump inhibitor within 24 hours prior to enrollment is a potential confounding factor for the observed efficacy outcome. Although this was addressed with an amendment during the course of the study, the amendment only excluded patients who had received intravenous doses greater than 40 mg within 24 hours prior to enrollment.

7. There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment."

These deficiencies were communicated in a Complete Response letter issued on November 26, 2008. Additionally, the letter included recommendations to resolve these clinical deficiencies:

8. Conduct at least one additional, adequate, and well-controlled study to demonstrate the proposed clinical benefit of Nexium IV for (b) (4) The study should include some U.S. centers and the study design and analysis plan should address the deficiencies described in this letter above.

9. You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two pharmacokinetic/pharmacodynamic (PK/PD) studies that you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3 study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment.

   For the reasons stated above, conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data.

In addition to these recommendations to address clinical deficiencies, the letter also stated that additional site inspections would be required if data from a specific site in the Netherlands would be used to support of any future submissions as described below:

10. Study site 0102 in the Netherlands, which reported the greatest treatment effect in the major randomized, placebo controlled trial that you submitted for our review, will need to be inspected by the Division of Scientific Investigations (DSI) because Dr. Ernst J. Kuipers, MD, PhD, the investigator at that site, has disclosed that he has accepted significant payments from Astra Zeneca. This inspection would be requested as part of our review of any future submission that includes this study as a critical component of establishing the efficacy of Nexium IV for the proposed indication. A recommendation from the DSI inspector that the data from this site can be used for determining the efficacy and safety of Nexium IV will be needed if this study will be used to support a future marketing application. This assessment will be an important component of a future determination of whether this study can stand as one of two adequate and well controlled trials for the proposed indication.

Current Submission

The reader is referred to the clinical review by E. Wynn, dated June 14, 2011 and the statistical review by L. Kammerman, dated June 15, 2011 for complete information.

After discussions with the division regarding the information that could be submitted as part of the complete response, the division agreed that data from previously conducted studies evaluating intravenous esomeprazole could be submitted. Additionally, previously conducted studies using intravenous omeprazole would be considered supportive. However, data from

these studies should ideally be from clinical trials with designs aimed at minimization of bias with similar target population, inclusion and exclusion criteria, primary efficacy measures, and drug dose administration.

The applicant submitted three clinical studies for review as the primary information in support of their complete response. The design of the three studies and the original study (Study D961DC00001) are listed in table 4. As noted by the clinical reviewer, all three of these studies were conducted using intravenous omeprazole, not esomeprazole. The division had stated that studies in omeprazole would be considered supportive only. However, the applicant also submitted clinical pharmacology data (see section X) to support a bioequivalence bridge between intravenous omeprazole and intravenous esomeprazole. The clinical pharmacology reviewer concluded that the data supported the bioequivalence of these two formulations. Therefore, the three studies submitted using intravenous omeprazole could be used to support the efficacy of intravenous esomeprazole. This section will detail the findings from these three studies.

Table 4: Clinical studies included in the applicant's complete response submission

Trial Name	Trial Type	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population
D961DC0001 (TRIAL 01)	Safety and Efficacy	Multicenter International Prospective Randomized Double-blind, Parallel Group, Placebo-controlled	Esomeprazole (a bolus 80mg over 30 min followed by a continuous infusion of 8mg/hr for 71.5 hours) or Placebo Follow-up treatment after IV Esomeprazole with Oral Esomeprazole 40mg once daily for 27 days	767 Randomized 764 Treated	Patients who had undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer classified as Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment modalities varied.)
Lau, et. al.	Safety and Efficacy	Single Center (Hong Kong) Randomized Double-blind, Parallel Group Placebo-controlled	Omeprazole (a bolus intravenous injection of 80mg over 30 min followed by a continuous 8mg/hr infusion for 71.5 hours) or Placebo Follow-up therapy after IV Omeprazole infusion with oral 20mg Omeprazole once daily for 8 weeks	320 Planned 240 Randomized	Hospitalized Patients who had undergone successful endoscopic treatment of a bleeding peptic ulcer. Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment was injection epinephrine followed by thermocoagulation)
Trial I-840 (study stopped prematurely due to safety monitoring)	Safety and Efficacy	Multicenter International Double Blind Parallel Group Placebo Control	Omeprazole 80mg given intravenously as a bolus dose over 30 minutes followed by 8mg/hr for 71.5 hours or Placebo Follow-up therapy after IV Omeprazole infusion with oral 20mg Omeprazole once daily for 21 days. (Oral therapy started at 48hours)	350 Planned 274 Randomized	Hemodynamically unstable outpatients and inpatients with PUB endoscopically classified as Forrest Ia, Ib, IIa, or IIb. (Endoscopic treatments varied. Pre-entry endoscopic treatment only in patients classified as Forrest Ia or IIa)
Trial I-841	Safety and Efficacy	Multicenter International Randomized Double-Blind Parallel Group Placebo-Controlled	Omeprazole 80mg given intravenously as a bolus over 30 minutes followed by continuous infusion of 8mg/hr for 3 to 5 days. (If there were signs of bleeding during day 2 or 3 the infusion was given for 120 hours) Follow-up therapy after IV Omeprazole with Omeprazole 20mg daily for 21 days	400 Planned 333 Randomized	Patients ≥ 60 years old with endoscopic signs of peptic ulcer bleeding and clinical symptoms of upper gastrointestinal bleeding. (Forrest Ia, Ib, IIa, IIb) (Endoscopic treatments varied. Pre-entry endoscopic intervention was only to be used in patients with bleeding classified as Forrest Ia)

copied from clinical review by E. Wynn

Studies I-840 and I-841

These studies were conducted as multicenter, international, randomized, double-blind, parallel group, placebo-controlled studies. The studies were designed to evaluate the effect of intravenous omeprazole in patients with bleed peptic ulcers with respect to clinical outcomes such as mortality, surgery, need for repeat endoscopic treatment, and the number and amount of blood transfusions.

Eligibility, treatment and assessments

Both studies enrolled patients with endoscopically intervention for a bleeding peptic ulcer. In Study 840, patients enrolled must have been hemodynamically unstable outpatients and inpatients with PUB endoscopically classified as Forrest Ia, Ib, IIa, or IIb. Patients enrolled in Study I-841 must be over 60 years of age with evidence of bleeding. These enrollment criteria differed substantively compared to the original pivotal trial (see table 4). Additionally, the baseline endoscopic treatment used in I-840 and I-841 were also different from the original study (see table 4). The omeprazole treatment used in both studies was generally analogous to the esomeprazole treatment used in the pivotal study. However, in Study I-841, the continuous infusion could be continued up to 5 days if signs of bleeding were present at day 2 or 3.

Endpoints

The primary endpoints used in these studies were also different from the original pivotal trial. The primary endpoint for Studies I-840 and I-841 was the incidence of specific clinical outcomes 72 hours after endoscopic treatment for bleeding ulcer. These outcomes included death, operation, additional endoscopic treatment, and total blood transfusions required. However, the endpoint for the pivotal study was the proportion of patients with clinically significant rebleeding within 72 hours of continuous infusion of Esomeprazole or placebo.

The reviewer concluded that the differences in patient population, endoscopic treatments used at baseline, and primary endpoint measurement precluded the ability to make any substantive comparisons between these studies and the original pivotal trial. The applicant asserted that 137 patients randomized in trials I-840 and I-841 were treated with the comparable endoscopic modalities to those in the original pivotal trial. However, the clinical and statistical reviewer evaluated all the patients enrolled in the study and found 52 patients that had similar baseline enrollment criteria. Furthermore, of these 52 patients, only 14 had two endoscopic treatment modalities given at study entry. The clinical reviewer noted that differences in baseline treatment modality may lead to differences in risk of rebleeding. The reviewer cited a publication by Park, et al, that concluded that differences in endoscopic treatment modalities lead to different rebleeding rates. Specifically, the authors concluded that 1) the addition of a second modality to epinephrine is superior to epinephrine alone 2) mechanical therapy alone with either hemoclips or thermal therapy using a heater probe is similar to combination therapy with epinephrine and 3) combination therapy with injection therapy is superior to cautery using bipolar coagulation alone. Therefore, appropriate comparisons based on endoscopic treatment provided could only be made between patients in the studies with the same treatment. Only 14 patients in both studies met this criterion.

Results

There were 274 patients enrolled in study I-840 and 333 patients randomized in the I-841 study. However, study I-840 was stopped early due to an increase in mortality rate in the treatment group compared to the placebo group. This will be discussed more completely in section 11, Safety. As stated above, the applicant asserted that 137 patients randomized in trials I-840 and I-841 were treated with the comparable endoscopic treatment modalities to those in the original pivotal trial. However, the clinical and statistical reviewer agreed that only 52 patients matched the patients with comparable endoscopic treatment modalities from the original pivotal study. The clinical and statistical reviewer evaluated the efficacy outcome for these 52 matched patients. Again, as stated above, a more "appropriately" matched population only includes 14 patients, a number too small to draw any conclusions.

Baseline demographic data for the 52 matched patients is presented in table 5. The reviewer noted that there were baseline differences between the treatment groups. Patients in the omeprazole group had a higher mean age and a higher percentage were over the age of 65 years. There were also differences in the proportion of patients classified in each of the Forrest groups and more patients in the placebo group presented in shock. It is not clear how these baseline imbalances may have affected the study. However, the presence of these differences at baseline make the ability to draw conclusions from these limited patients even more difficult.

Table 5: Baseline Demographics for 52 patients in Trials I-840 and I-841 who received the same endoscopic treatment as Pivotal Trial

Characteristic	Omeprazole Group (n = 22)	Placebo Group (n = 30)
Male Sex – no. (%)	10 (45.5%)	18/30 (60%)
Female Sex – no. (%)	12 (54.5%)	12/30 (40%)
Mean Age – (years)	70.5	68.3
Patients ≥ 65 years – no. (%) < 65 years – no. (%)	17/22 (77.3%) 5/22 (22.7%)	19/30 (63.3%) 11/30 (36.7%)
Mean Hemoglobin (g/L) (Standard Deviation)	82.9 (32.3)	95.8 (32.4)
Number of Patients with Shock at Presentation	18/22 (81.8%)	26/30 (87%)
Number of Patients with Endoscopic Signs of Rebleeding Spurting Hemorrhage (Forrest Class Ia) Oozing Hemorrhage (Forrest Class Ib) Nonbleeding Visible Vessel (Forrest Class IIa) Clot with underlying vessel (Forrest Class IIb)	 2/22 (9.1%) 8/22 (36.4%) 1/22 (4.5%) 11/22 (50%)	 5/30 (16.7%) 9/30 (30.0%) 7/30 (23.3%) 9/30 (30.0%)
Number of Patient with Duodenal ulcer Gastric ulcer	 13/22 (59%) 9/22 (41%)	 15/30 (50%) 15/30 (50%)
Number of Patients with A Previous Ulcer	10/22 (45.4%)	17/30 (56.7%)
Number of Patients with A Previous Ulcer Complication	3/22 (13.6%)	3/30 (10%)
Number of Patients with Each Risk Factor for Bleeding Peptic Ulcer (%) Use of Cox-2 NSAID Use of Aspirin Use of Warfarin	 2/22 (9.1%) 5/22 (22.7%) 1/22 (4.5%)	 1/30 (3.3%) 6/30 (20%) 1/30 (3.3%)

The primary endpoint of the original pivotal trial, the proportion of patients with a rebleeding event in the first 72 hours was evaluated in the 52 patients from Study I-840 and I-841. The clinical and statistical reviewer noted that a smaller proportion 13.6% (3/22) of omeprazole-treated subjects had a rebleeding event within 72 hours as compared to placebo-treated subjects: 13.6% (3/22) vs. 23.3% (7/30). However, this difference was not statistically significant (p=0.4882, Fisher's Exact Test). The statistical reviewer concluded that the sample size was too small to permit meaningful analyses of subgroups.

Thus, no further subgroup analyses were performed in patients from these studies. Overall, the limitations in the study design, patient population studied, endpoints selected were sufficiently divergent to prevent a meaningful interpretation and comparison with the original pivotal trial.

Furthermore, even in the subset of patients who were matched for similar endoscopic treatments, there was a treatment effect that was not statistically significant.

It is also important to note that trial I-841 was also omitted from the review because of differences in the trial design as described above. Furthermore, the applicant stated that trial was terminated prematurely after 333 patients had been randomized due to a substantial imbalance between treatment groups in the number of deaths. The mortality rate was 6.9% in the omeprazole group and 0.6% in the placebo group. However, the applicant stated that an independent expert group, the primary investigators, and personnel from the company examined the data and determined that the difference in mortality was secondary to chance. Nevertheless, no new patients were enrolled in the trials and the Steering Committee decided not to resume enrollment. Regardless, the increase in mortality may be concerning for a potential safety signal and; furthermore, this study clearly does not provide additional support to the applicant's efficacy claim.

The Lau Trial

This study was a randomized, double-blind, placebo-controlled study conducted at a single center in Hong Kong, Prince of Wales Hospital, and was funded by an academic research grant. The clinical reviewer noted that an exact study protocol was not provided by the applicant and could not be reviewed. The purpose of the study was to evaluate the effect of intravenous omeprazole on the prevention of rebleeding by assessment of the rate of clinically significant rebleeding during the intravenous treatment period.

Eligibility, treatment and assessment

Enrollment criteria included hospitalized patients who had undergone successful endoscopic treatment of a bleeding peptic ulcer. Forrest Class Ia, Ib, IIa, or IIb. In this study, endoscopic treatment was injection epinephrine followed by thermocoagulation. These enrollment criteria were generally consistent with the enrollment criteria of the original pivotal trial. The treatment administered was omeprazole (a bolus intravenous injection of 80mg over 30 min followed by a continuous 8mg/hr infusion for 71.5 hours) or placebo. This treatment regimen was analogous to the treatment plan for esomeprazole used in the original pivotal trial. The patient population, use of specific endoscopic treatment modality and the treatments provided were generally comparable to the original pivotal trial.

Endpoints

The primary endpoint of the Lau trial, recurrent bleeding within 30 days following endoscopy, differed from the original pivotal trial. However, the proportion of patients having clinically significant rebleeding within the first 72 hours was measured as a secondary outcome, the primary endpoint for the original pivotal trial, was a secondary endpoint of the study. Thus comparisons of outcomes from the Lau trial and the original pivotal trial could be performed. The clinical reviewer noted that the studies overall were generally well-matched based on endoscopic procedures performed, and important inclusion criteria. There were minor differences in the clinical definition of rebleeding used in the two trials; however, in the Lau

trial, rebleeding was confirmed with endoscopy, which is more sensitive that confirmation of rebleeding based on clinical grounds (see table 6).

Table 6: Comparison of the Lau trial and trial D961DC00001

	Lau, et. al. 2000	D961DC00001
Definition of endpoint criterion	Fresh hematemesis Hypotension: Systolic Blood Pressure<90 Tachycardia PR>110 and Melena Drop in hemoglobin by 20g/l in 24 hours and melena	Blood in the stomach or a verified active bleeding from a peptic ulcer (Forrest class Ia, Ib) **Or** At least 2 of the following: • Vomiting of fresh blood or fresh blood in a gastric tube or hematochezia or melena after a normal stool • Decrease in hemoglobin >20g/l or (hematocrit >6%) despite ≥ 2 units of blood has been transfused during 24 hours • Unstable circulation systolic blood pressure ≤90mm Hg or pulse≥110/min (after having had a stable circulation) **Or** Hematemesis (vomiting of significant amount of (>200ml) of fresh blood)
Therapeutic endoscopic procedures	Injection therapy (epinephrine) followed by captive thermocoagulation with heater probe	Injection therapy (epinephrine) and/or one of the following: coagulation with heater probe, electrocautery, hemoclips.
Drug and dosing	Placebo or Omeprazole (a bolus I.V. injection of 80mg followed by a continuous infusion of 8mg/hr for 72 hours)	Placebo or Esomeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)
Oral Follow-Up Treatment After I.V. treatment	Omeprazole (20mg once daily for 8 weeks)	Esomeprazole (40mg once daily for 27 days)
Inclusion criteria **Age (years)** **Signs of Gastrointestinal Bleeding** **Forrest Classification of Bleeding Ulcers** **Successful endoscopic hemostasis**	 ≥ 16 years Within 24 hours after admission endoscopy performed Ia, Ib, IIa, or IIb Yes	 ≥18 years Within 24 hours prior to endoscopy Ia, Ib, IIa, or IIb Yes

Results

Overall, 240/739 patients who were admitted to the hospital during the study period with bleeding peptic ulcers were enrolled in the study. Of these, 267 patients received endoscopic treatment. Surgery was required for five patients in whom endoscopic treatment was unsuccessful. There were 22 patients not included in the trial; 10 had terminal cancer, 9 were moribund as a result of concomitant illnesses, and 3 did not provide consent. Two hundred forty were randomized to treatment (120 omeprazole and 120 placebo). With the exception of one patient in the placebo group, all patients completed their assigned infusion treatment according to the protocol. The eight week follow-up visit was completed for all but two patients in the omeprazole group and four in the placebo group. According to the article, 85 patients in the omeprazole group and 83 patients in the placebo group underwent follow-up endoscopy at 8 weeks. The demographic characteristics compared to the original pivotal trial

are presented in table 7. There were not substantive differences in gender or mean age. However, there were some differences in important baseline characteristics. The clinical reviewer noted that the Lau trial enrolled more patients over the age of 65 years in both treatment groups. In addition, both treatment groups in the Lau trial contained more patients who were hospitalized at the time of upper GI bleeding prior to endoscopy; were in shock at presentation; or on concomitant anticoagulation therapy. The clinical reviewer suggested that the older and sicker population enrolled in the Lau trial may explain the larger treatment effect in the primary outcome compared to the pivotal trial. It may also explain, at least in part, the differences between trials in mortality within 72 hours and within 30 days.

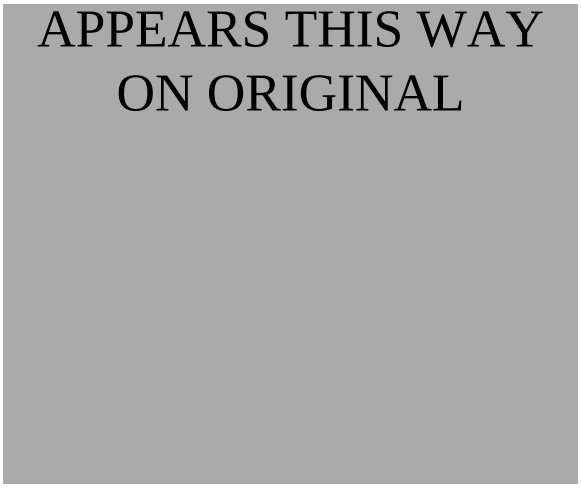

Table 7: Comparison Baseline Characteristics trial D96DC00001 and Lau Trial

Characteristic	Lau Trial		Trial D961DC00001	
	Omeprazole (N = 120)	Placebo (N = 120)	Esomeprazole (N = 375)	Placebo (N = 389)
Gender, n (%)				
Male	80 (66.7%)	80 (66.7%)	254 (67.7%)	268 (68.9%)
Female	40 (33.3%)	40 (33.3%)	121 (32.3%)	121 (31.1%)
Age, years				
Mean (SD)	64 (17.2)	67 (15.9)	62.1 (17.1)	60.2 (17.6)
Min – Max	18 – 99	22 - 95	18 - 95	18 – 98
Patients per age category, n (%)				
< 65 years	44 (36.7%)	40 (33.3%)	182 (48.5%)	210 (54.0%)
≥ 65 years	76 (63.3%)	80 (66.7%)	193 (51.5%)	179 (46.0%)
Shock at Presentation, n (%)				
No	104 (86.7%)	106 (88.3%)	356 (94.9%)	370 (95.1%)
Yes	16 (13.3%)	14 (11.7%)	19 (5.1%)	19 (4.9%)
H. pylori status, n (%)				
Negative	42 (35.0%)	56 (46.7%)	92 (24.5%)	119 (30.6%)
Positive	78 (65.0%)	64 (53.3%)	246 (65.6%)	226 (58.1%)
Trace			18 (4.8%)	26 (6.7%)
Missing			19 (5.1%)	18 (4.6%)
Forrest Class, n (%)				
Ia	14 (11.7%)	9 (7.7%)	28 (7.5%)	40 (10.3%)
Ib	50 (41.7%)	49 (40.8%)	166 (44.3%)	163 (41.9%)
IIa	38 (31.7%)	36 (30.0%)	136 (36.3%)	151 (38.8%)
IIb	18 (15.0%)	26 (21.7%)	42 (11.2%)	34 (8.7%)
Missing	0	0	3 (0.8%)	1 (0.3%)
Ulcer location, n (%)				
Gastric	53 (44.2%)	48 (40.0%)	157 (41.9%)	155 (39.8%)
Duodenal	67 (55.8%)	72 (60.0%)	216 (57.6%)	233 (59.9%)
Missing	0	0	2 (0.5%)	1 (0.3%)
Hemoglobin, g/L				
Mean (SD)	94.5 (27.2)	95 (25.7)	97.7 (24.9)	97.4 (25.9)
Hospitalized at time of UGI bleeding prior to enrollment, n(%)				
Not hospitalized	98 (81.7%)	97 (80.8%)	338 (90.1%)	354 (91.0%)
Hospitalized	22 (18.3%)	23 (19.2%)	37 (9.9%)	35 (9.0%)
Previous history of gastric or duodenal ulcer, n (%)	38 (31.7%)	45 (37.5%)	112 (29.9%)	118 (30.3%)
Previous ulcer bleeding, n (%)	36 (30.0%)	36 (30%)	---	--
Previous complications related to gastric or duodenal ulcer, n (%)	---	---	44 (11.7%)	41 (10.5%)
Medication use prior to enrollment, n(%)				
NSAIDs	39 (32.5%)	40 (33.3%)	151 (40.3%)	157 (40.4%)
Acetylsalicylic acid (dose unknown)	23 (19.2%)	18 (15.0%)	103 (27.5%)	103 (26.5%)
Warfarin	5 (4.2%)	5 (4.2%)	9 (2.4%)	13 (3.3%)

copied from clinical review by E. Wynn

The overall efficacy results of the Lau trial are presented in table 8. There was a 15.8% reduction in the incidence of recurrent bleeding in patients treated with intravenous omeprazole compared to placebo. This finding was both clinical and statistically significant.

There were also treatment differences based on Forrest classification but these differences did not reach statistical significance except with both Forrest Ia and Ib were combined and when IIa and II b were combined. Again, the clinical reviewer disagreed that combining these groups should be grouped because each group is associated with a different underlying risk of rebleeding.

Table 8: Efficacy results for the Lau trial

Efficacy Outcome	Omeprazole (N = 120)	Placebo (N = 120)	p-value
Number of patients with recurrent bleeding (%)			
By Day 3 (72 hours)	5 (4.2%)	24 (20.0%)	<0.001
By Day 7	7 (5.8%)	26 (21.7%)	<0.001
By Day 30*	8 (6.7%)	27 (22.5%)	<0.001
Recurrent Bleeding Within 30 days by Forrest Class (# patients/total #)			
Active bleeding ulcers (Forrest Ia + Ib)	3/64 (4.7%)	10/58 (17.2%)	0.04
Forrest Class Ia	2/14 (14.3%)	2/9 (22.2%)	1.00
Forrest Class Ib	1/50 (2.0%)	8/49 (16.3%)	0.02
Ulcers with nonbleeding visible vessels (Forrest IIa + IIb)	5/56 (8.9%)	17/62 (27.4%)	0.02
Forrest Class IIa	3/38 (7.9%)	9/36 (25.0%)	0.06
Forrest Class IIb	2/18 (11.1%)	8/26 (30.8%)	0.17
Recurrent Bleeding Within 3 days by Sex (#patients/total #)			
Male	2/80 (2.5%)	14/80 (17.5%)	
Female	3/40 (7.5%)	10/40 (25%)	
Recurrent Bleeding Within 3 days by Age (#patients/total#)			
≥ 65 years old	5/76 (6.6%)	21/80 (26.3%)	
< 65 years old	0/44	3/40 (7.5%)	
Recurrent Bleeding Within 30 days by Sex (#patients/total #)			
Male	5/80 (6.3%)	17/80 (21.3%)	<0.001
Female	3/40 (7.5%)	10/40(25.0%)	0.06
Recurrent Bleeding Within 30 days by Age(#patients/total#)			
≥ 65 years old	6/76 (7.9%)	24/80 (30.0%)	<0.001
< 65 years old	2/44 (4.6%)	3/40 (7.5%)	
Mean number of units of blood transfused within 30 days after endoscopic therapy (Standard Deviation)	1.7 (1.9)	2.4 (3.2)	0.03
Number of patients who died (%)			
Within 3 days	3/120 (2.5%)	0/120	
Within 30 days	5/120 (4.2%)	12/120 (10.0%)	0.13
Number of patients who had surgery due to rebleeding (%)			
Within 3 days	1/120 (0.8%)	5/120 (4.2%)	
Within 30 days	3/120 (2.5%)	8/120(6.7%)	
Number of patients who had endoscopic retreatment for rebleeding (%)			
Within 3 days	4/120(3.3%)	21/120 (17.5%)	
Within 30 days±	6/120 (5%)	23/120 (19.1%)	<0.001
Total Number of hospitalization days from date of endoscopy until the date of discharge	757	859	

copied from clinical review by E. Wynn

The clinical reviewer also compared the results of the Lau trial with the original pivotal trial. Both studies demonstrated a treatment effect; however, the Lau trial had an overall treatment

effect o f 15.8% while the original pivotal trial had an overall treatment effect of only 4.4%. It should be noted that the incidence of rebleeding in the placebo group for the Lau study (20%) was almost double the incidence of rebleeding in the original pivotal trial (10.3%). This difference may be due to the older and sicker population enrolled in the Lau trial as well as racial differences noted between the two study populations. Additionally, differences such as endoscopic technique but these differences cannot be reviewed as there are no data to assess the adequacy of the endoscopic technique. Also, the treatment effect by day 30 was also generally consistent within studies and between studies (see table 9).

Table 9: Proportion of patients with clinically significant rebleeding within 72 hours and 30 days, Trial D961DC00001 and the Lau Trial

Outcome Variable	Trial by Lau et al		Trial D961DC00001	
	Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)	Placebo (n = 389)
Patients with clinically significant rebleeding within 72 hours, n (%)	5 (4.2%)	24 (20%)	22 (5.9%)	40 (10.3%)
Patients with clinically significant rebleeding within 30 days	8 (6.7%)	27 (22.5%)	29 (7.7%)	53 (13.6%)

copied from clinical review by E. Wynn

Sensitivity analyses based on data from the original pivotal trial are presented in table 10. There were no substantive differences in the efficacy outcome based on race, age, or gender. However, in patients 65 years of age and older, there was a substantial difference in outcome in the original pivotal trial (2.2% decrease in rebleeding in the esomeprazole group) compared to the Lau trial (19.7% decrease in rebleeding in the omeprazole group).

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Table 10: Efficacy data from D961DC00001 based on race, age, and gender

Subgroup		Rebleed status	Eso[a] (n=375)	Placebo[b] (n=389)
Race	Caucasian	No rebleed	307(94.5%)	305(89.2%)
		Rebleed	18(5.5%)	37(10.8%)
	Black	No rebleed	3(75.0%)	5(100.0%)
		Rebleed	1(25.0%)	0(0.0%)
	Oriental	No rebleed	26(96.3%)	25(92.6%)
		Rebleed	1(3.7%)	2(7.4%)
	Other	No rebleed	17(89.5%)	14(93.3%)
		Rebleed	2(10.5%)	1(6.7%)
Age	<65	No rebleed	172(94.5%)	185(88.1%)
		Rebleed	10(5.5%)	25(11.9%)
	≥ 65	No rebleed	181(93.8%)	164(91.6%)
		Rebleed	12(6.2%)	15(8.4%)
Gender	Male	No rebleed	239(94.1%)	240(89.6%)
		Rebleed	15(5.9%)	28(10.4%)
	Female	No rebleed	114(94.2%)	109(90.1%)
		Rebleed	7(5.8%)	12(9.9%)

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

copied from original statistical review by S. Castillo

There were other substantive differences in outcomes in the original pivotal trial compared to the Lau trial as outlined in table 11. Despite similarities in percentages of patients in each age group and by Forrest classification between the two studies (see table 7), the efficacy outcomes for these groups differ dramatically. It is not clear why these differences are present, but these differences are concerning for some patient characteristics between the two trials that differ fundamentally and affect the outcome of the study. These inconsistencies raise questions about the reproducibility of the efficacy outcome.

Table 11: Comparison of proportion of patients with rebleeding or death in Trial D961DC00001 and the Lau Trial

Subgroup	D961DC00001		Lau trial	
	Esomeprazole	Placebo	Omeprazole	Placebo
Mortality within 3 days	0.3%	0.0%	2.5%	0%
Mortality within 30 days	0.8%	1.3%	4.2%	10%
Age ≥ 65 years within 3 days	6.2%	8.4%	7.9%	30%
Forrest class Ib	5.4%	4.9%	2.0%	12%

Additional efficacy data from other sources
The applicant also submitted data from other sources that support the use of intravenous omeprazole or intravenous esomeprazole. The sources of data to evaluate use of intravenous esomeprazole in routine clinical practice included data from various claims databases including Premier Perspective Comparative Database, Kaiser Permanente Medical Care Program Databases and Veteran Affairs Administration Medical Care System Databases in US, PHARMO Record Linkage System in the Netherlands and a field-based study using the Hospital Network in Spain. Additionally, the applicant included information from observational studies and a literature review of intravenous esomeprazole and omeprazole. These studies are not considered adequate and well-controlled and therefore would not be sufficient to stand alone as evidence of the effectiveness of the product. The reader is directed to the clinical review by E. Wynn for complete details of these data.

Conclusions
There were three clinical studies submitted in the Complete Response submission to support data from the original pivotal trial, D961DC00001. The first two studies, I-840 and I-841, differ from the original pivotal trial in several substantive ways including differences in the patient populations studied, differences in the endoscopic treatments used, and differences in the clinical endpoints. Even when patients with similar characteristics from these studies are evaluated, there is a treatment effect of approximately 10% that is not statistically persuasive (p=0.49). As described above, the data from the Lau trial are clinically and statistically persuasive; however, it is not clear that the data from this study are generalizable to the U.S. population because this study was performed at a single site in Hong Kong. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of *H. pylori* infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which may potentially lead to a larger treatment effect.[6] Therefore, the data presented by the applicant in this Complete Response submission do not adequately support the effect of intravenous esomeprazole for the reduction of risk of rebleeding of endoscopically treated peptic ulcers.

Furthermore, other differences in efficacy outcomes between the two studies are concerning. The major difference in treatment effect between D961DC00001 and the Lau trial is driven by the difference in baseline rebleeding rate in the placebo group. It is not clear why there is such a difference in the baseline rebleeding rate in these two groups. It may be partially explained by the differences in ethnicity as described above such as differences such as the age and baseline health status; all of which may impact on the risk of rebleeding. Additionally, there are substantive differences in the outcome based on Forrest classification (Ib), and in mortality at 30 days between the two studies. These subgroup analyses suggest that the populations studied in the two trials differ in ways that affected the outcome of the study. These differences increase the concern that the ability to generalize the results of this study to the

[6] Leontiadis GI, Sharma VK, Howden CW; Systematic review and meta-analysis: enhanced efficacy of proton-pump inhibitor therapy for peptic ulcer bleeding in Asia—a post hoc analysis from the Cochrane Collaboration.; *Alimen. Pharmacol. and Therap;* .2005; 21:1055-1061.

U.S. population is limited. Furthermore, these inconsistencies raise questions about the reproducibility of the efficacy outcome.

11. Safety

Initial Submission

The reader is referred to the clinical review by A. Nayyar dated November 17, 2008 and the statistical review by S. Castillo dated November 13, 2008 for complete details.

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The safety data base for the original submission included patients treated in the single pivotal trial, as well as PK/PD trials in healthy subjects. The total dose that was administered over 72 hours in the original pivotal trial was 652 mg of which 268 mg was given in the first 24 hours. This differs substantially from the approved intravenous esomeprazole dose of a maximum of 80 mg in 24 hours. The clinical reviewer noted that the types and proportions of adverse events in the original pivotal trial were similar between treatment arms, except the higher rate of gastrointestinal bleeding events in the placebo arm, and the higher rate of infusion site reactions in the treatment arm. The majority of SAEs in the trial were bleeds from duodenal or gastric ulcers. On the esomeprazole arm, 75% (12/16) of the SAE bleeds in the first 72 hours were secondary duodenal ulcers. On the placebo arm, 56% (14/25) were secondary to duodenal ulcers. The clinical reviewer concluded that the safety profile appears acceptable based on the data from a single trial. Although the exposures with this dosing regimen are much higher than other approved regimens, the duration of exposure is short, i.e., 3 days.

The Complete Response letter included the recommendation to submit the following additional safety data:

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Current Submission
The reader is referred to the clinical review by E. Wynn, dated June 14, 2011 for complete information.

The safety data in this submission includes safety data sets for study I-840 and I-841, safety data sets for Study D961DC00001, the original pivotal trial, case report forms for the Lau trial, and postmarketing safety information for esomeprazole. The safety data from the original pivotal trial were previously reviewed with the original submission as described above. The clinical reviewer did not review the safety data sets from study I-840 and I-841 because the studies were not used to support the efficacy of the product. Further more, the data contained in these studies as well as the Lau trial were using omeprazole, not esomeprazole. Therefore, there are little data on the safety of esomeprazole available for review in this submission. Nevertheless, clinical reviewer evaluated the safety data from the Lau trial and to the postmarketing safety data.

The reviewer noted that the case report forms for the Lau study did not identify the patient's treatment group assignment and thus made interpretation of association to treatment impossible. An information request was sent late in the review cycle for this information, and it will be reviewed with the next cycle. There were five patients in the omeprazole group who died within 30 days after the initial endoscopy. Twelve patients in the placebo group died within 30 days of the initial endoscopy to achieve hemostasis. None of the five deaths in the Omeprazole group were caused by recurrent bleeding. Four of the patients in the placebo group died after surgery (three following gastrectomy for recurrent bleeding and one after excision of a perforated ulcer). Two patients in the placebo group who were deemed unfit for surgery, died from recurrent bleeding. The remaining six patients died from complications related to the concurrent illnesses. All but two patients in the omeprazole group and four patients in the placebo group completed follow-up assessments at 8 weeks.

Postmarketing safety information
A total of 41 case reports describing 45 serious adverse events (SAEs) and 20 non-serious adverse events were identified in the applicant's most recent periodic safety update report. In nearly a quarter (10 of 41) of the case reports, the indication for use was gastrointestinal bleeding. Two of the reports were from clinical trials where esomeprazole had been given either as a concomitant drug or the indication was for used in pediatric patients. Three deaths were reported; one case of agranulocytosis, hematoma, and acute hepatitis. Doses were provided in 35 of the case reports and ranged from 20mg to 200mg daily. The time from initiation of the intravenous esomeprazole therapy to the onset of the adverse event ranged from 0 days to 61 days in cases in which the timing of the adverse event was recorded. Based on these data, no new safety concerns were uncovered in the postmarketing data.

Conclusions
Overall, the safety data available for esomeprazole contained within this submission were minimal. Based on review of the safety data submitted there were no new safety signals identified.

12. Advisory Committee Meeting

No advisory committee meeting was held during the initial or current review cycle to discuss this product.

13. Pediatrics

Initial Submission
The applicant requested a waiver of pediatric studies because "studies are impossible or highly impractical because the number of patients is so small and geographically dispersed." The clinical reviewers did not agree and will request that a pediatric program be developed for this indication because upper gastrointestinal bleeding occurs in the pediatric population and they anticipate that the product will be used in the pediatric population. This application was not discussed at PeRC because it is not going to be approved during this review cycle.

Current Submission
The applicant again requested a full waiver for pediatric studies for the same reasons as listed above. The review division consulted the Pediatric and Maternal Health Staff (PMHS) to evaluate the feasibility of pediatric studies for the proposed indication; (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. The PMHS reviewer noted that the applicant provided incidence rates from Germany and Sweden for peptic ulcers in pediatric patients of 4.3/100,000 and 0.5/100,000 respectively and that only a fraction of these patients would have bleeding from their peptic ulcer disease. The applicant also provided data from a claims data

base (Premier Perspective™ database) that provides the projected number of pediatric patients with bleeding peptic ulcer in the U.S. (see table 10).

Table 10: US projected number of hospitalized patients with Pediatric PUB (primary discharge diagnosis only)

Age group	2004	2005	2006	2007	2008
< 1	(b) (4)				
1 to 3					
4 to 11					
12 to 17					
Total					

copied from PMHS reviewer consult by A. Taylor

Based on these data, the PMHS reviewer concluded that studies in pediatric patients who undergo therapeutic endoscopy for acute bleeding gastric or duodenal ulcers are impossible or highly impracticable because the number of patients is so small or the patients are geographically dispersed. Thus, the PMHS reviewer recommended that a full waiver should be granted to the applicant for the proposed indication. However, if the applicant were to seek a broader indication such as (b) (4) (b) (4) pediatric studies may be feasible. Additionally, the PMHS reviewer noted that the Best Pharmaceuticals for Children Act (BPCA) is designed to provide an incentive to sponsors to conduct pediatric studies that may not be required under PREA. (b) (4) (b) (4) However, esomeprazole was granted pediatric exclusivity on May 1, 2009. Since esomeprazole is an enantiomer of omeprazole, the exclusivity granted to esomeprazole at that time was considered a second period of exclusivity for the moiety. Therefore, esomeprazole is not eligible for any further periods of exclusivity. The waiver request was presented before the Pediatric Review Committee on February 16, 2011, and the committee concurred with the recommendation to provide full waiver to the applicant for the proposed indication.

14. Other Relevant Regulatory Issues

A. Financial Disclosures

There were no additional financial disclosures submitted with the current complete response. However, during the last review cycle one investigator, Dr. Ernst J. Kuipers, reported receiving significant financial payments and was a principal investigator at a site in the original pivotal trial. This site, site 0102 in the Netherlands, reported the largest treatment effect in all centers that participated in this study, -31% rebleeding events, favoring the esomeprazole arm of the study. When a sensitivity analysis was conducted to explore the

impact of that center's data on the overall observed outcome of the study by removing the patients treated at that center from the efficacy analysis, the overall treatment effect observed in the study decreased to -3.73% (95% CI = -7.67, 0.10) and the p value shifted to 0.06. Therefore, the Complete Response letter recommended that this site be investigated during the current review cycle (see results of DSI review in section 4.B below).

B. DSI Audits

A DSI consult was obtained to inspect site 0102, a clinical site from the original pivotal study (see section 4.A above). The principal investigator, E.J. Kuipers received significant fianacial payments and this site reported the largest treatment effect in all centers that participated in the study. The DSI consult concluded that no significant deficiencies were observed and a Form FDA 483 was not issued. The study appeared to have been conducted in accordance with the study protocol and applicable good clinical practice regulations, including data collection and assurance of subject safety and welfare. The study data from Site 102 appear reliable with respect to the study protocol as written and submitted in the NDA.

However, the DSI consulted also noted that the final evaluation inspection report (EIR) from the field has not been received at DSI and the final classification remains pending. However, in an email correspondence with DSI on June 9, 2011, DSI confirmed that a final EIR was issued and that there are no changes to the original findings or recommendations.

C. Discipline Consults

To assist in the assessment of the need to conduct appropriate pediatric studies under PREA, consults were obtained from the PMHS staff (see review by A. Taylor for complete details), and from OSE, Division of Epidemiology (see review by J. Ju for complete details).

15. Labeling

Physician labeling

Final product labeling was not satisfactorily negotiated during the current review cycle because deficiencies in the submission leading to a Complete Response action precluded a complete review and negotiation of final labeling with the applicant. The applicant will be required to submit proposed physician labeling with their Complete Response.

Patient labeling

Currently, Nexium labeling contains patient labeling but no medication guide. Final patient labeling was not satisfactorily negotiated during the current review cycle. The applicant will be required to submit proposed physician labeling with their Complete Response.

16. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The current submission contains deficiencies that have not been satisfactorily addressed. These include clinical issues that have not been resolved. Therefore, I recommend that a Complete Response (CR) action be taken for this application.

Risk Benefit Assessment
I agree with the clinical and statistical reviewers' conclusions regarding the data submitted in the applicant's Complete Response. The data submitted do not provide adequate support for the applicant' proposed indication (see Recommended Comments to Applicant below). Additionally, the responses that the applicant provided to address the deficiencies noted in study D961DC00001 in the Complete Response letter were reviewed. The applicant's responses do not change the reasons cited in the Complete Response Letter that study D961DC00001, as a single adequate and well-controlled study, does not provide sufficient evidence to support the your proposed indication. Furthermore, the safety data provided by the applicant were not complete and an information request send to the applicant late in the review cycle could not be reviewed during the current cycle. Therefore, there are inadequate data to completely review the safety data. However, the missing safety data are not critically in assessing an updated safety profile for esomeprazole per se because the missing safety data are for omeprazole. Nevertheless, the safety data requested from the applicant will be reviewed, if necessary, in the next review cycle.

The clinical pharmacology reviewers concluded that the data submitted in the Complete Response were sufficient. However, the reviewer also recommended that additional modeling and simulation based on previously collected data be performed in order to estimate the proper constant infusion rate in patients with moderate and severe hepatic impairment. Based on the clinical pharmacology reviewer's recommendation for additional modeling data, I do not agree with the deficiencies have been completely addressed. However, the data have already been submitted but without sufficient time for the clinical pharmacology reviewer to evaluate the data. Therefore, the Complete Response letter should state that this information should be resubmitted with the next submission.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
Postmarketing risk management activities were not reviewed extensively during this review cycle because a Complete Response action is recommended. However, during the review of the submission, no specific issues that would require postmarketing risk management activities were identified. Therefore, specific risk management strategies will not be included in the Complete Response letter.

Recommendation for other Postmarketing Requirements and Commitments
Postmarketing requirements and commitments were not reviewed extensively during this review cycle because a Complete Response action is recommended. Therefore, specific recommendations for postmarketing requirements and commitments will not be included in the Complete Response letter.

Recommended Comments to Applicant

The additional data submitted do not provide substantial evidence of efficacy of your product for the proposed indication. The additional clinical data that you have submitted do not meet the criteria for providing substantial evidence for the following reasons:

1. Trials I-840 and I-841 differ from the efficacy trial, D961DC00001, submitted in the sNDA on May 29, 2008 in several important ways, including the endoscopic treatments administered, and the primary endpoints evaluated. Therefore, these trials were not adequately designed to support the proposed indication.

2. When patients from trial I-840 and I-841 are matched to the population enrolled in the original efficacy trial based on enrollment criteria, too few patients remain to provide adequate power to show a statistically significant treatment effect. Of the combined total of 607 patients enrolled in the studies, only 52 patients had similar baseline enrollment criteria. The proportion of omeprazole-treated patients who had a rebleeding event within 72 hours was 13.6% (3/22). Although this proportion was lower than that observed in the placebo-treated patients, 23.3% (7/30), the difference was not statistically significant (p=0.49, Fisher's Exact Test).

3. The clinical trial reported by Lau, et al.[7] is comparable in design to D961DC00001 and the trial provides evidence of efficacy of intravenous omeprazole for the proposed indication. However, the study was conducted at a single center in Hong Kong and the population enrolled was ethnically homogeneous. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of *H. pylori* infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which may potentially lead to a larger treatment effect observed in the Lau trial. Therefore, the ability to generalize the results of this study to the U.S. population is limited.

4. There is a substantive difference in the rebleeding rate in the placebo group (20%) of the trial reported by Lau, et al. compared to the original efficacy trial (10%). It is not clear why the rebleeding rate in the Lau, et al. trial is double the rate observed in D961DC00001. It may be partially explained by the differences in Asian populations described in #3 above, or by differences in factors such as age and baseline health status, which may impact on the risk of rebleeding. Additionally, operational factors such as differences in endoscopic technique may also affect the risk of rebleeding.

5. There were substantive differences in the efficacy outcomes within important subgroups in the clinical trial reported by Lau, et al. compared to D961DC00001. These inconsistencies raise questions about the reproducibility of the efficacy outcome.

[7] Lau J, Sun J, Lee K, et al, Effect of Intravenous Omeprazole on Recurrent Bleeding after Endoscopic Treatment of Bleeding Peptic Ulcers, N. Engl. J. Med., 2000, Aug 3; 343(5): 310-316

a. In the subgroup of patients 65 years of age and older, the decrease in proportion of patients with rebleeding within 72 hours in the esomeprazole arm relative to placebo was 2.2% in D961DC00001. In contrast, the decrease in the same subgroup treated with omeprazole relative to placebo in the trial reported by Lau, et al. was 19.7%.

b. In the subgroup of patients with Forrest Ib classification, there were similar proportions of patients with rebleeding within 72 hours in the esomeprazole and placebo arms in D961DC00001 (a 0.5% difference). In contrast, there was a decrease in the proportion of patients with rebleeding within 3 days in the esomeprazole arm relative to placebo of 10% in the trial reported by Lau, et al.

6. The information from observational studies and literature reviews of intravenous esomeprazole and omeprazole were not considered adequate to constitute primary evidence of the efficacy of the product for the proposed indication.

7. We have reviewed your responses to the deficiencies cited in the November 26, 2008, Complete Response Letter regarding D961DC00001. Your responses do not change the reasons cited in the Complete Response Letter that study D961DC00001, as a single adequate and well-controlled study, does not provide sufficient evidence to support the your proposed indication. The following comments are responses to specific issues raised in your resubmission:

   a. Your assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers for D961DC00001 is not persuasive. The Breslow-Day test is not a powerful test for detecting lack of homogeneity. For this reason, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables further limits the usefulness of the test.

   b. You contend that the suboptimal pharmacodynamic (PD) effects of esomeprazole on gastric pH observed in the PK/PD studies submitted in the sNDA on May 29, 2008, can be attributed to the fact that the studies were performed in *Helicobacter pylori* negative healthy subjects, i.e., subjects in whom it would be more difficult to suppress intragastric acidity, and that a pH of 6 would have been more consistently achieved if the population studied had had peptic ulcer disease. We disagree because this position assumes that all patients with peptic ulcer disease have H. pylori. Not all patients with peptic ulcer disease are H. pylori positive, and the populations enrolled in the clinical trials you submitted to this NDA attest to this.
   c. A Division of Scientific Investigations (DSI) inspection was performed at site 0102 in the Netherlands because Dr. Ernst J. Kuipers, MD, PhD, the principal investigator at that site, disclosed that accepted significant payments from

AstraZeneca. The DSI investigation found that the data from this site were valid. Nevertheless, as stated in the Complete Response letter, the large impact from this small site on the overall efficacy of the trial suggests that the efficacy results are not robust and that the results from this single pivotal trial are not persuasive.

In order to address the deficiencies that have been identified in this sNDA, the following information should be included in the resubmission:

1. Conduct at at least one additional, adequate, and well-controlled trial to demonstrate the clinical benefit of Nexium® IV for (b) (4) The trial should include some U.S. centers, and should be designed to evaluate a specific population of patients with bleeding gastric or duodenal ulcers that would be most likely to benefit from treatment with esomeprazole.

Additional Comments:

The pharmacokinetic data in patients with hepatic impairment that you provided in the sNDA are not adequate to assess the recommended dose for continuous intravenous infusion of esomeprazole in patients with moderate and severe hepatic impairment.

The following information should be included in the resubmission:

1. Resubmit the modeling and simulation results of previously collected data to support an estimate of the proper constant infusion rate in patients with moderate and severe hepatic impairment

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/s/

LYNNE P YAO
06/16/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number	21-689
Priority or Standard	Priority
Submit Date(s)	14 December 2012
Received Date(s)	14 December 2012
PDUFA Goal Date	14 September 2013 (after 3 month extension)
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)/ Office of Drug Evaluation III
Reviewer Name(s)	Aisha Peterson Johnson MD, MPH, MBA
Review Completion Date	11 July 2013
Established Name	Esomeprazole sodium
Trade Name	Nexium I.V.
Therapeutic Class	Proton pump inhibitor
Applicant	AstraZeneca
Formulation(s)	Lyophilized Powder for Injection Solution
Dosing Regimen	80 mg IV infused over 30 minutes followed by an infusion of 8 mg/h for 71.5 hours
Indication(s)	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding of gastric or duodenal ulcers
Intended Population(s)	Adult patients with bleeding gastric or duodenal ulcers who have undergone therapeutic endoscopy

Template Version: March 6, 2009

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for Nexium® IV for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding of gastric or duodenal ulcers.

1.2 Risk Benefit Assessment

This is the third review cycle for this Application. The aggregate data submitted during Cycles 1, 2, and 3 support the conclusion that the benefit of Nexium IV at the proposed dose for reducing the risk of rebleeding following therapeutic endoscopy for acutely bleeding gastric or duodenal ulcers outweighs the risks.

The primary evidence submitted was Study 01. This randomized, placebo-controlled study used esomeprazole IV as the active study drug. This single study was adequately designed and the results were statistically significant in favor of esomeprazole. Secondary sources of evidence included the Lau Study and Studies 840 and 841. See Section 5.3 for a brief summary of the information submitted during Cycles 1 and 2.

For over 10 years, practice guidelines on the management of patients with ulcer bleeding (including those by the American College of Gastroenterology and the International Consensus Upper Gastrointestinal Bleeding Conference Group) [1,2] have included a strong recommendation for the use of IV PPI therapy following the achievement of endoscopic hemostasis to improve patient outcomes. Currently, two PPIs are available in an intravenous form—pantoprazole (Protonix®) and esomeprazole (Nexium®).

Proton pump inhibitors are a widely used class of medications which have long been used for GI diseases related to acid production. Short-term use of PPI has been found to be relatively safe and current warnings and precautions labeling for PPIs focuses primarily on events associated with the long term use of PPIs—B-12 deficiency, atropic gastritis, bone fracture, and hypomagnesemia. The proposed length of treatment with Nexium IV for (b) (4) rebleeding of gastric or duodenal ulcers after therapeutic endoscopy is 72 hours

1 Laine L, Jensen DM *Am J Gastroenterol* 2012; 107:345–360
2 Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P, International Consensus Upper Gastrointestinal Bleeding Conference Group; International Consensus Recommendations on the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding. *Ann Int Med* 2010; 152(2):101-113.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

See the following information from the Cycle 2 clinical review by Dr. Erica Wynn:

> "To comply with regulations under the Pediatric Research Equity Act (PREA), the applicant submitted a request for waiver of pediatric trials. In support of their waiver, the applicant submitted data on the occurrence of peptic ulcer bleeding in children and an analysis of two US pediatric databases exploring the incidence of pediatric peptic ulcer bleeding. Consults were obtained from the Pediatric Maternal Health Staff (PMHS) and the Office of Surveillance and Epidemiology (OSE). Both consultants concluded that the incidence of peptic ulcer bleeding in pediatric patients was uncommon. The reader is referred to the finalized PMHS consult by Dr. Amy Taylor dated March 2, 2011, and the OSE consult by Dr. Jing Ju dated February 1, 2011. Based on the information provided, this reviewer concurs with the PMHS consult, the OSE consult, and the applicant in that the number of pediatric PUB patients who are eligible to participate in a study is very limited and it may not be feasible to conduct trials in pediatric patients. In the opinion of this reviewer, the applicant's waiver request seems reasonable and should be granted for future trials. This issue was taken before the Pediatric Review Committee on February 16, 2011, and the committee concurred."

2 Introduction and Regulatory Background

2.1 Product Information

Nexium® (esomeprazole sodium) is the pure S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole (Prilosec®).

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

Nexium® IV was approved in the United States in 2005 for use in adults for short-term treatment (up to 10 days) of gastroesophageal reflux disease (GERD) in patients with a history of erosive esophagitis as an alternative when oral therapy is not possible or appropriate.

2.2 Tables of Currently Available Treatments for Proposed Indications

See first and second cycle reviews.

2.3 Availability of Proposed Active Ingredient in the United States

See first and second cycle reviews.

2.4 Important Safety Issues With Consideration to Related Drugs

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

- Symptomatic response does not preclude presence of gastric malignancy.
- Atrophic gastritis has been noted with long-term omeprazole therapy.
- Observational studies suggest that PPI therapy may be associated with an increased risk of *Clostridium difficile* associated diarrhea.
- The concomitant use of Clopidogrel and PPIs should be avoided due to the inhibition of CYP2C19 activity. CYPC2C19 is necessary for the metabolism of clopidogrel to its active metabolite.
- Hypomagnesemia, symptomatic and asymptomatic, has been reported in patients treated with a PPI.
- The concomitant use of St. John's Wort and Rifampin with a PPI should be avoided due to the induction of CYP2C19 or CYP3A4 which can lead to decreased concentrations of the PPI.
- Serum chromagranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors.
- Patients treated with a PPI and Warfarin may need to be monitored for increases INR and prothrombin time due to the risk of abnormal bleeding.
- Long-term PPI therapy has been associated with increased risk of osteoporosis-related hip fracture.

In addition, prescribers should be warned against the concomitant use of certain antiretroviral drugs and drugs for which gastric pH can affect bioavailability. See individual product labeling for further details. Additionally, the concomitant use of PPIs and clopidogrel has been associated with an increased risk of adverse outcomes following acute coronary syndrome.[3]

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1. Pre-submission Regulatory History, NDA 21-689, S-014

Date	Regulatory Action(s)
29 May 2008	The original supplemental NDA (S-014) submitted
26 November 2008	Complete Response Action, Cycle 1
11 June 2009	Type C, Post-Action Meeting Agency outlined that the following data may support a complete response: ▪ Literature reports ▪ Lau et al study (including data, CRFs, protocol, and SAP)
15 September 2010	Cycle 2 submitted by AstraZeneca
16 June 2011	Complete Response Action, Cycle 2
23 January 2012	Applicant requested formal dispute resolution regarding CR action dated 16 June 2011
30 January 2012	Agency denied dispute resolution request and recommended that Applicant request a post-action meeting to discuss concerns
06 April 2012	XXX
22 March 2012	Post Action Meeting ▪ Agency discussed the possibility of holding an Advisory Committee meeting to discuss the Division's recommendation to conduct an additional study ▪ Applicant described plan to submit PK, PD, and clinical data to address the relevance of the Lau study to the US population
23 April 2012	AZ submitted a proposed outline of their Cycle 3 Complete Response for preliminary Review
12 June 2012	Type C Meeting (tcon) to discuss Cycle 3 Complete Response submission. Key Agreement: The way forward to approval for this indication is to focus on the applicability of the Lau, et al. study to the US population, as identified in preliminary responses to the outline document and discussed at the meeting.
14 December 2012	Cycle 3 submitted by AstraZeneca

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

No new clinical trials were submitted in support of this cycle of the Application. Therefore, the Division of Scientific Investigations (DSI) did not perform any site audits.

3.2 Compliance with Good Clinical Practices

No new clinical trials were submitted in support of this Application. See the Cycle 1 clinical review by Dr. Anil Nayyar and the Cycle 2 review by Dr. Erica Wynn for compliance with good clinical practices information regarding the studies submitted during those cycles.

3.3 Financial Disclosures

No new clinical trials were submitted in support of this Application. See the Cycle 1 clinical review by Dr. Anil Nayyar and the Cycle 2 review by Dr. Erica Wynn for financial disclosure information regarding the studies submitted during those cycles.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no new data related to CMC submitted during the current review cycle. During the first review cycle, CMC recommended approval of Nexium for the proposed indication.

4.2 Clinical Microbiology

During the first review cycle, the product quality microboligy reviewer recommended approval of Nexium® for the proposed indication. See the full review by Dr. Bryan S. Riley in DARRTS (March 23, 2011 and May 4, 2011 addendum).

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical studies were submitted in support of this efficacy supplement. During the first review cycle, the pharmacotoxicology reviewer, Dr. Ke Zhang,

recommended approval of Nexium® for the proposed indication (see full review in DARRTS, 13 November 2008).

4.4 Clinical Pharmacology

During the second cycle review, the Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III) found the Application to be acceptable from a clinical pharmacology standpoint except for the label language, including the issue of dosage adjustment in hepatic impairment patients.

See the Cycle 3 Clinical Pharmacology review by Dr. Sandhya Apparaju in DARRTS. During the current review cycle, the Applicant submitted data to support the generalizability of the Chinese patient data submitted in Cycle 2 to the Caucasian population. These results are discussed in Section 6, Review of Efficacy.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Major Efficacy and Safety Trials Submitted During Review Cycles 1, 2, and 3

Trial Name	Trial Type	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population
D961DC00001 (TRIAL 01)	Safety and Efficacy	Multicenter International Prospective Randomized Double-blind, Parallel Group, Placebo-controlled	Esomeprazole (a bolus 80mg over 30 min followed by a continuous infusion of 8mg/hr for 71.5 hours) or Placebo Follow-up treatment after I.V. Esomeprazole with Oral Esomeprazole 40mg once daily for 27 days	767 Randomized 764 Treated	Patients who had undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer classified as Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment modalities varied.)
Lau, et. al.	Safety and Efficacy	Single Center (Hong Kong) Randomized Double-blind, Parallel Group Placebo-controlled	Omeprazole (a bolus intravenous injection of 80mg over 30 min followed by a continuous 8mg/hr infusion for 71.5 hours) or Placebo Follow-up therapy after I.V. Omeprazole infusion with oral 20mg Omeprazole once daily for 8 weeks	320 Planned 240 Randomized	Hospitalized Patients who had undergone successful endoscopic treatment of a bleeding peptic ulcer. Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment was injection epinephrine followed by thermocoagulation)
Trial I-840	Safety and Efficacy	Multicenter International Double Blind Parallel Group Placebo Control	Omeprazole 80mg given intravenously as a bolus dose over 30 minutes followed by 8mg/hr for 71.5 hours or Placebo Follow-up therapy after I.V. Omeprazole infusion with oral 20mg Omeprazole once daily for 21 days. (Oral therapy started at 48hours)	350 Planned 274 Randomized	Hemodynamic ally unstable outpatients and inpatients with PUB endoscopically classified as Forrest Ia, Ib, IIa, or IIb. (Endoscopic treatments varied. Pre-entry endoscopic treatment only in patients classified as Forrest Ia or IIa)
Trial I-841 (study stopped prematurely due to safety monitoring)	Safety and Efficacy	Multicenter International Randomized Double-Blind Parallel Group Placebo-Controlled	Omeprazole 80mg given intravenously as a bolus over 30 minutes followed by continuous infusion of 8mg/hr for 3 to 5 days. (If there were signs of bleeding during day 2 or 3 the infusion was given for 120 hours) Follow-up therapy after I.V. Omeprazole with Omeprazole 20mg daily for 21 days	400 Planned 333 Randomized	Patients ≥ 60 years old with endoscopic signs of peptic ulcer bleeding and clinical symptoms of upper gastrointestinal bleeding. (Forrest Ia, Ib, IIa, IIb) (Endoscopic treatments varied. Pre-entry endoscopic intervention was only to be used in patients with bleeding classified as Forrest Ia)

Electronically copied and reproduced from the Cycle 2 Clinical Review, Dr. Erica Wynn, p21, DARRTS, 14 June 2011

In addition to the clinical studies described in Table 2 above, the Applicant also submitted PK/PD studies (Studies 04, 07, and 15) and literature reviews.

5.2 Review Strategy

The 16 June 2011 Complete Response Letter (second cycle) stated that the additional data submitted by the Applicant in Cycle 2 did not provide substantial evidence of efficacy for Nexium IV for the proposed indication. The letter went on to specifically state the reasons why the submitted data were deemed inadequate.

The current clinical review will focus on the new *post-hoc* analyses submitted in support of the Cycle 3 re-submission. Each complete response item will be addressed in the order presented in the Complete Response Letter.

5.3 Discussion of Individual Studies/Clinical Trials

For a detailed review of the clinical trial results of studies submitted in previous cycles, see the full clinical reviews in DARRTS.

Below is a summary of the first and second review Cycles (excerpt from the Background Document for the CDER Regulatory Briefing held April 19, 2013):

> -Beginning of Regulatory Briefing excerpt-
>
> First Cycle
> During the first review cycle, the Applicant submitted a single adequate and well-controlled trial (Study 01). The primary efficacy endpoint in Study 01 was rebleeding within 72 hours of therapeutic endoscopy in patients who experienced peptic ulcer bleeding. (Clinically significant rebleeding was defined as an active bleed or blood in the stomach detected on EGD, hematemesis, hematochezia, melena, blood in gastric aspirate, hypotension or fall in hemoglobin greater than 2g/L in 24 hours.) For this study, 767 patients were randomized to esomeprazole or placebo. Overall, 5.9% of patients had rebleeding in the esomeprazole group compared to 10.3% in the placebo group. The difference between the treatment groups was -4.4%, with p-value of 0.03.
>
> The Division decided that the data from this trial failed to provide a level of evidence that rose to standards for a single study approval. A complete response letter was issued, and the Applicant was told the deficiency could be addressed by conducting an additional adequate and well-controlled study. The Sponsor responded that this would be impossible because use of high dose PPIs for the prevention of peptic ulcer rebleeding after therapeutic endoscopy is currently the standard of care. Clinical practice guidelines in the U.S. and internationally

recommend high dose intravenous PPIs as part of the treatment regimen of peptic ulcer bleeding. [Intravenous PPIs available in the U.S. include Nexium and Protonix (pantoprazole).] In a post-action meeting with the Applicant, the Division agreed that randomized, controlled trials investigating omeprazole for the same indication could be considered as supportive evidence, as long as an appropriate bridge was provided between esomeprazole and omeprazole. Esomeprazole is the S-isomer of omeprazole.

Second Cycle

In the second review cycle, the Applicant submitted five types of data:

- Pharmacokinetic/pharmacodynamic (PK/PD) bridging data between intravenous omeprazole and esomeprazole
- Data from the literature and trials conducted with intravenous omeprazole
- Observational data from use of intravenous esomeprazole in patients with peptic ulcer bleed
- A systematic review of available trials from any proton pump inhibitor
- Additional observational data from other data sources including healthcare and administrative databases, and hospital networks with field-based studies.

After reviewing the data, the clinical pharmacology and pharmacometrics reviewers concluded that the data submitted were sufficient to provide a reasonable pharmacodynamic bridge between omeprazole and esomeprazole for the proposed IV dosing regimen. With this bridge established, the submitted trials conducted with intravenous omeprazole were reviewed.

Three key omeprazole clinical trials were identified. Two (Study 840 and 841) were Scandinavian trials conducted in the early 1990's. These two studies are discussed further below. The third, referred to by the Division as "the Lau trial", was considered the strongest evidence submitted to support efficacy in the indication. However, this trial was a single center trial conducted in Hong Kong. The trial was published in the New England Journal of Medicine in 2000, nine years before the IV esomeprazole Study 01 was published. Although the primary endpoint of the Lau trial was not the same as Study 01, the Lau trial did provide data on the percentage of patients with clinically significant rebleeding within 72 hours following therapeutic endoscopy for peptic ulcer bleeding. In this all-Chinese population, 4.2% of omeprazole patients and 20.0% of placebo patients had clinical significant rebleeding within 72 hours of therapeutic endoscopy following peptic ulcer bleeding. The rebleed rate was similar, though numerically lower, in the omeprazole arm of the Lau trial than in the esomeprazole arm of Study 01. The rebleed rate in the placebo arm was strikingly higher in the Lau trial than in Study 01.

While the Lau trial provided supportive evidence of the effectiveness of omeprazole in the homogenous population, the Division questioned the generalizability of the results to the heterogenous U.S. population. Asians are known to have a lower parietal cell mass, higher prevalence of H. pylori infection, and a higher prevalence of CYP2C19 poor metabolizers. (Esomeprazole metabolism is significantly dependent upon CYP2C19.) The Division was particularly concerned that the first two factors could result in a higher proportion of the treated population achieving the high pH levels necessary to optimally stabilize clot. Further, the Lau study protocol was not available for review by the Division and there was no opportunity for a DSI inspection.

The trial designs of Scandinavian Studies 840 and 841 differed substantively from Trial 01. Areas of difference included entry criteria, patient demographics, and endoscopic treatments administered. The reviewers concluded that these differences precluded substantive comparisons between Study 01 and Studies 840 and 841. The statistical reviewer conducted exploratory analyses by using data from a small subset of 52 patients from these two trials who had received an endoscopic treatment allowed during Study 01. While no statistically significant difference in the proportion of patients with rebleeding at 72 hours between the omeprazole and placebo groups was observed in this analysis, the difference favored omeprazole and was similar in magnitude to the Lau study and Study 01.

Table 3. Rebleeding by 72 Hours after Therapeutic Endoscopy

Study	Study Drug	Placebo	Treatment Difference
01	5.9% (22/376)	10.3% (40/389)	-4.4%
Lau	4.2% (5/120)	20 % (24/120)	-15.8%
840/841	13.6% (3/22)	23.3% (7/30)	-9.7%

In the Complete Response letter issued to the sponsor at the end of cycle 2 review, the Division expressed concern about the generalizability of the clinical trial reported by Lau et al. due to the ethnically homogenous population (Asian) of this study. The Division again stated that the deficiency could be addressed with an additional, adequate, well controlled clinical trial. The applicant voiced ethical concerns of conducting another controlled trial in the target population and instead proposed to submit available pharmacokinetic/ pharmacodynamics

(PK/PD) evidence to bridge the two populations (Asians and Caucasians) in order to support the applicability of Lau et al. data to the U.S. population. These data were submitted in the third cycle.

-End of excerpt from Regulatory Briefing Background Document-

6 Review of Efficacy (Additional Analyses submitted in Response to CR Letter)

The seven items outlined in the Complete Response Letter (underlined) are discussed below. The discussion includes the Applicant's responses and this reviewer's comments.

6.1 Complete Response Item #1

Trials I-840 and I-841 differ from the efficacy trial, D961DC00001, submitted in the sNDA on May 29, 2008, in several important ways, including the endoscopic treatments administered and the primary endpoints evaluated. Therefore, these trials were not adequately designed to support the proposed indication.

Studies I-840 and I-841 were submitted by the Applicant during the second cycle and were reviewed in detail by Dr. Erica Wynn. In short, Trials I-840 and I-841 were conducted in the early 1990's in Scandinavia using omeprazole IV as the active study drug. These placebo-controlled trials were conducted using omeprazole IV 80 mg bolus (over 30 minutes) followed by an infusion of omeprazole 8 mg/hour for a total of 72 hours of IV treatment. (b)(4) Following the IV PPI phase, all patients were treated once daily with oral omeprazole 20 mg. Trial I-840 was conducted in hemodynamically unstable patients, while Trial I-841 was conducted in patients 60 years of age and older.

While similarities between Study 01 and Trials I-840 and I-841 exist, there are differences in many areas including entry criteria, patient demographics, endoscopic treatments administered, and primary endpoint. The primary endpoint for the Trials was "overall outcome of treatment" as measured using a ranking scale where each patient was ranked for his/her worst outcome. Not all patients in Trials I-840 and I-841 received endoscopic treatment. These differences led the clinical reviewer for cycle 2, Dr. Erica Wynn, to conclude that no substantive comparisons between Study 01 and Trials I-840 and I-841 could be made.

Despite these differences, the Applicant believes that Trials I-840/841 provide supportive evidence of efficacy for the proposed indication related to peptic ulcer bleeding (PUB) due to the fact that the studies show the beneficial effect of high-dose PPI treatment when added to a wide variety of endoscopic treatment regimens. During the second review cycle, the Applicant addressed the issue of differences related to different modalities of initial endoscopic therapy between Trials I-840/841 and Study 01by selecting a sub-sample of patients from Trials I-840/841 that received similar (or slightly more effective) endoscopic therapy as those used in Study 01. See Table 4 below. In these analyses, all subpopulations show a treatment difference in favor of the use of omeprazole (versus placebo).

Table 4. Trials I-840/841 Analysis Subpopulations

Patients included in Sub-population	Number of patients	Treatment Difference ^
All patients with endoscopic therapy	213	-13.9%
Patients with endoscopic therapy as given in Study 01 (including patients who received additional endoscopic therapy)	137	-15.6%
Patients with endoscopic therapy as given in Study 01 only	52	-9.7%

^Treatment difference= rebleeding rate in omeprazole patients – rebleeding rate in placebo patients

MO Comment: I agree with the Applicant that the similarities in study design between Study 01 and trials I-840 and I-841 do not entirely preclude relevant comparisons. Despite the differences between Study 01 and Studies 840/841 (described above), the rebleeding results of Trials I-840 and I-841 provide supportive evidence of efficacy for Nexium IV for the proposed indication. While rebleeding was not the primary endpoint for Trials I-840/84, the endpoint of severe rebleeding by Day 21 was a pre-specified secondary analysis. The severe rebleeding endpoint was defined as voluminous hematemesis, red blood in the nasogastric tube or in the stools, or unstable circulation (or rapid transfusion required to prevent unstable circulation). This endpoint definition is similar to the primary endpoint of clinically significant rebleeding used in the primary efficacy study (Study 01). See

Table 5 below.

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Table 5. Rebleeding Endpoint Definitions

Study	Rebleeding Endpoint	Rebleeding Definition
Study 01	Clinically Significant Rebleeding	▪ Endoscopy (need at least 1) o A1- Active bleed o A2- Blood in stomach ▪ Clinical (need at least 2) o B1- Hematemesis, hematochezia, melena, blood in gastric aspirate o B2- Fall in Hgb >2 g/L in 24 hours o B3- Hypotension (SBP<90, tachycardia HR>110) and melena ▪ Hematemesis: >200 mL of fresh blood
Trials I-840/841	Severe Rebleeding	▪ Voluminous hematemesis ▪ Red blood in the nasogastric tube or stools ▪ Unstable circulation (or rapid transfusion required to prevent unstable circulation

6.2 Complete Response Item #2

> When patients from Trials I-840 and I-841 are matched to the population enrolled in the original efficacy trial D961DC00001, based on enrolment criteria, too few patients remain to provide adequate power to show a statistically significant treatment effect. Of the combined total of 607 patients enrolled in the studies, only 52 patients met the enrolment criteria of D961DC00001. The proportion of omeprazole-treated patients in this subgroup who had a rebleeding event within 72 hours was 13.6% (3/22). Although this proportion was lower than that observed in the placebo-treated patients, 23.3% (7/30), the difference was not statistically significant (p=0.49, Fisher's Exact Test).

MO Comment:
For the 52 patients from Studies 840/841 who met the enrolment criteria for Study 01, the treatment difference was approximately 10%. The treatment difference observed in other subpopulations of Trials I-840/841 ranged from 10-15%. See Table 4 *above. These results suggest that the decrease in the rate of rebleeding seen with Nexium IV compared with placebo is not related to the initial endoscopic therapy used. And while not statistically significant, the trend is important and provides supportive evidence for the efficacy of Nexium IV for the proposed indication.*

6.3 Complete Response Item #3

> The clinical trial reported by Lau et al is comparable in design to D961DC00001 and the trial provides evidence of efficacy of intravenous omeprazole for the proposed indication. However, the trial was conducted at a single center in Hong Kong and the population enrolled was ethnically homogeneous. Other studies have demonstrated that Asian populations have a lower parietal cell mass; a higher prevalence of H. pylori infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which could have contributed to the larger treatment effect observed in the Lau trial. Therefore, the ability to generalize the results of this trial to the U.S. population is limited.

The Applicant acknowledges that compared with Caucasian populations, Asian populations are known to have a lower parietal cell mass, a higher prevalence of H. pylori infection, and a higher prevalence of cytochrome 2C19 genetic polymorphism. Each of these factors could be expected to influence the pharmacodynamics effect of PPIs.

No PK/PD data from the Lau study were available. Therefore, to help support the comparability of the two populations, the Applicant submitted PK and PD data from two Phase 1 studies in Chinese (Study 07) and Caucasian (Study 15) subjects. For Studies 07 (Chinese subjects) and 15 (Caucasian subjects) the primary outcome variable was the percent of time with pH >6 over the 24 hour study period. Data from Studies 07 and 15 also allowed the clinical pharmacology reviewers the ability to make limited PK/PD comparisons in the H. pylori and CYP2C19 subgroups. In the study of Chinese patients, both H. pylori positive and negative, healthy patients were enrolled. However, in the study of Caucasian patients, only H. pylori negative, healthy patients were enrolled.

The Clinical pharmacology reviewers concluded that the pharmacodynamic (PD) outcomes observed in Caucasian and Chinese populations were comparable.[4] Specifically, for Chinese patients in Study 07, the mean percentage of time with pH >6 was 48% (± 17.4) compared with 46.6% (± 26.5) observed in Caucasian patients in Study 15. See

[4] Slide #70, Regulatory Briefing, April 19, 2013.
http://inside.fda.gov:9003/downloads/CDER/OfficeoftheCenterDirector/RegulatoryBriefings/UCM348981.pdf

Table 11, below. There was a higher C_{max} observed in Chinese subjects when compared to Caucasian subjects. The difference could be due to the Chinese subjects having a lower median height and weight than the Caucasian subjects (164 cm/64kg, 177 cm/72kg).

H. pylori status

All Caucasian subjects in Study 15 were H. pylori negative. Both H. pylori negative and positive subjects were enrolled in the Chinese Study 07. There was a trend for larger PD outcomes in H. pylori positive subjects. In Study 07 (Chinese Subjects), the mean baseline pH in the H. pylori positive subjects was 1.67 compared with 1.47 in the H. pylori negative group. For the primary study endpoint, H. pylori positive patients were observed to have a higher percentage of time with pH >6 during the 24 hour study period. The mean pH over the study in H. pylori positive subjects (n=9) was 6.25 ± 0.23 compared with 5.84 ± 0.61 in H. pylori negative subjects (n=11). See Table 6 below.

Table 6. Pharmacodynamic Variables by H. pylori status, Study 07

Proposed Regimen E *	H. Pylori Positive (n = 9)	H. Pylori Negative (n = 11)
% time when pH >4 over 24 h	98.37 ± 0.54	93.69 ± 5.05
% time when pH >6 over 24 h	59.12 ± 9.56	46.7 ± 20.4
% time when pH> 6 over first 3 h	82.77 ± 5.01	49.4 ± 33.6
% time when pH>7 over 24 h	18.75 ± 9.26	11.14 ± 8.56
Mean pH over 24 h	6.25 ± 0.23	5.84 ± 0.61

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CYP2C19 status

CYP2C19 status was known for all subjects in both studies (07 and 15). Patients were categorized according to CYP2C19 status as extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM). In the Caucasian Study (15), there were 71% EMs, 25% IMs, and 4% PMs compared with 45%, 45%, and 10%, respectively in the Chinese study (07).

After reviewing the data of Caucasian patients in Study 15, the clinical pharmacology reviewers noted the following:

- Modestly higher systemic exposures (~ 17 % higher AUC) in IMs vs EMs
- Large variability in PD; differences in sample size (N = 17 EMs vs. N = 6 IMs)
- PD variability not due to H. pylori status (only H. pylori negative patients enrolled)
- PD variability unlikely to be due to PK differences (lack of Exposure-Response)

Table 7. PK/PD Parameters by CYP2C19 status in Caucasian Subjects, Study 15

	Overall	EM (n=17)	IM (n=6)	PM (n=1)
Cmax (umol/L)	14.2 ± 2.6	13.9 ± 3.0	14.5 ± 1.2	17.0
AUC 24 (umol.h/L)	109 ± 23.1	105.1 ± 18.8	123 ± 31.5	105.4
% time pH >6 over 24 h		45.2 ± 28.5	56.9 ± 13.9	7.4

Table adapted from Clinical Pharmacology Slides presented at CDER Regulatory Briefing, April 19, 2013

After reviewing the data of Chinese patients by CYP2C19 status in Study 07, the clinical pharmacology reviewers noted the following:

- Modestly higher systemic exposures (12- 20 % higher AUC) in IMs vs. EMs
- Similar primary PD outcome across genotypes (% time over 24 h when pH > 6)
- PD outcomes could be confounded by H. pylori status

Table 8. PK/PD Parameters by CYP2C19 status in Chinese Subjects, Study 07

PK/PD Variable	EMs (n=7)	IMs (n=10)	PMs (n=2)
% time pH >6 over 24 hours	50.6 ± 20.5	53.4 ± 17.7	51.6 ± 43.3
Cmax (ng/mL)	5953 ± 1257	7225 ± 1815	7655; 8037
AUC 24 (ng.h/mL)	36573 ± 8058	43032 ± 8790	47411; 46157

Table adapted from Clinical Pharmacology Slides presented at CDER Regulatory Briefing, April 19, 2013

The PK/PD results observed in Chinese subjects may be confounded by H. pylori status as both H. pylori positive and negative subjects were enrolled in Chinese Study 07. Therefore, to make a more direct comparison of PD parameters between Chinese and Caucasian patients, data from H. pylori negative Chinese and Caucasian patients was explored. The mean difference was very small (0.1%) for the primary outcome variable of Studies 17 and 05 (% time when pH >6 over 24 hours) between Chinese and Caucasian H. pylori negative subjects. See Table 9 below.

Table 9. PD Parameters in H. pylori negative Chinese and Caucasian subjects

PD outcome	**Chinese (n = 19)** ***Overall (+, -)***	**Chinese (n = 11)** ***H. Pylori* –ve**	**Caucasian(n= 24)** ***Overall (–ve)***
% time when pH >4 over 24 h	95 ± 4.6	93.69 ± 5.05	86.1 ± 11.3
% time when pH >6 over 24 h	48 ± 17.4	46.7 ± 20.4	46.6 ± 26.5
% time when pH> 6 over first 3 h	65 ± 28.6	49.4 ± 33.6	43.4 ± 26.1
% time when pH>7 over 24 h	13.3 ± 10.6	11.14 ± 8.56	4.0 ± 7.5

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When the PD parameters in H. pylori negative patients are explored by CYP2C19 status, the results for the % time pH >6 over 24 hours continues to be comparable between Caucasian and Chinese EMs and IMs. There were too few PMs in each group for relevant comparisons to be made. See Table 10 below.

Table 10. PD Parameters in H. pylori negative Subjects, by CYP2C19 status

A: CYP2C19 EMs/ *H.pylori* -ve	**Chinese (n = 5)**	**Caucasians (n = 17)**
% time when pH >6 over 24 h	44 ± 19.78	45.2 ± 28.5
% time when pH> 6 over first 3 h	42.9 ± 26.2	42.6 ± 24
% time when pH>7 over 24 h	7.48 ± 4.68	4.4 ± 8.5
B: CYP2C19 IMs/ *H.pylori* -ve	**Chinese (n = 5)**	**Caucasians (n = 6)**
% time when pH >6 over 24 h	50.1 ± 25.1	56.9 ± 13.9
% time when pH> 6 over first 3 h	52.7 ± 44.8	53 ± 28.3
% time when pH>7 over 24 h	16.1 ± 10.1	3.4 ± 4.9

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MO Comment:
The basic question to be answered is whether Nexium IV (80 mg bolus followed by 8 mg/h) can be expected to have similar effects on intragastric pH in Chinese and

Caucasian subjects. The ability of the PK/PD studies conducted in Chinese and Caucasian subjects to answer this question is limited for several reasons. First, the studies were conducted in healthy subjects, not PUB patients. Second, the studies involved a relatively small number of patients (24 Caucasian, 19 Chinese). Further, the Caucasian study did not enroll any patients with H. pylori infection.

Despite these limitations, the data from the PK/PD studies do show that Nexium IV has a similar effect on the primary PD outcome, % time pH > 6 over 24 hours, in Chinese and Caucasian subjects. This comparable effect persists regardless of CYP2C19 genotype. There was also a trend for larger PD effect seen in H. pylori positive subjects compared to H. pylori negative subjects. No exposure response relationship was noted. The PK/PD results provide sufficient evidence, in the opinion of this reviewer, that Nexium IV will affect intragastric pH similarly in Caucasian and Chinese patients. Therefore, the results of the Lau study can serve as supportive evidence of efficacy for the primary efficacy study--Study 01.

Table 11. Overall PD outcomes, Studies 07 and 15

PD outcome	Chinese Subjects H. pylori positive and negative (n =19)	Chinese Subjects H. pylori negative (n=11)	Caucasian Subjects H. pylori negative n=24
% time pH >6, over 24 hours (mean)	48 ± 17.4	46.7 ± 20.4	46.6 ± 26.5

Table adapted from Regulatory Briefing Presentation (April 19, 2013) by Dr. Sandhya Apparaju, clinical pharmacology reviewer.

6.4 Complete Response Item #4

> There is a substantive difference in the rebleeding rate in the placebo group (20%) of the trial reported by Lau et al compared to D961DC00001 (10%). It is not clear why the rebleeding rate in the Lau et al trial is double the rate observed in D961DC00001. It may be partially explained by the differences in Asian populations described in #3 above, or by differences in factors such as age and baseline health status, which may impact on the risk of rebleeding. Additionally, operational factors such as difference in endoscopic technique may affect the risk of rebleeding. This inconsistency in rebleeding rate between the trials also raises questions about the ability to generalize the results of this trial to the U.S. population.

To address this complete response item, the Applicant conducted a two-step risk factor analysis. These *post-hoc* analyses should be viewed as exploratory; therefore, no statistically valid conclusions can be drawn from the results. In the first step, only "study drug" (placebo/omeprazole-esomeprazole) and study (Study 01/Lau study) were included as risk factors. In this model, there was a tendency for a reduced risk of rebleeding in Study 01. See Table 12 below.

Table 12. Day 3- Relative Risk for Rebleeding in Study 01 and Lau et al- Reduced model- Cox regression

Explanatory variable	Relative risk	Lower 95% CI	Upper 95% CI	p-value
Study	0.686	0.442	1.067	0.0944
Study drug	2.381	1.519	3.734	0.0002

Lau study=1 and D961DC00001 study=2. Study drug=1 for esomeprazole/omeprazole, 2=placebo
mdbmpe 20NOV12:22:18:12.24 IVP_PUB Cox regression predicted risk for rebleeding_d3_rr_placebo

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In the second step of the Applicant's analysis, possible risk factors for recurrent bleeding were included. The relative risk for rebleeding attributable to Study 01 was

0.979. This value suggests that factors other than the study may have been largely responsible for the difference in placebo response rates seen Study 01 and Lau et al. The risk factor with the highest relative risk (strongest predictor of rebleeding) was American Society of Anesthesiologists (ASA) grade IV.

ASA grade IV (see Table 13 below) patients have severe systemic disease that is a constant threat to life. Study 01 was conducted a decade after the Lau trial and during that decade the use of IV PPI therapy in the setting of peptic ulcer bleeding continued to increase. Therefore, when Study 01 was conducted, ASA grade IV patients were excluded from the placebo-controlled study due to ethical considerations. In contrast, ASA Grade IV patients made up 16% of the Lau study population.

Table 13. American Society of Anesthesiologists (ASA) Grade Descriptions

Grade	Description
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes

The American Society of Anesthesiologists (ASA) system is a six-category physical status classification system for assessing the fitness of patients before surgery.

Table 14. Day 3- Relative Risk for rebleeding in Study 01 and Lau et al-Expanded model, Cox regression

Explanatory variable	Relative risk	Lower 95% CI	Upper 95% CI	p-value
Study	0.979	0.543	1.768	0.9451
Study drug	2.290	1.416	3.703	0.0007
Age	0.993	0.977	1.009	0.3962
Sex	1.169	0.723	1.890	0.5229
Hospitalized	0.330	0.130	0.835	0.0193
Previous ulcer bleeding	1.277	0.683	2.387	0.4442
ASA grade II	1.395	0.776	2.509	0.2658
ASA grade III	2.256	1.132	4.497	0.0207
ASA grade IV	3.968	1.425	11.052	0.0083
H. pylori	0.612	0.385	0.973	0.0379
Forrest Ia	2.177	1.031	4.601	0.0415
Forrest IIa	1.773	1.031	3.050	0.0386
Forrest IIb	2.453	1.282	4.694	0.0067
NSAID (incl aspirin)	1.395	0.782	2.489	0.2601
Aspirin	1.112	0.595	2.081	0.7391
Warfarin	0.675	0.159	2.875	0.5952

Lau study=1 and D961DC00001 study=2. Study drug=1 for esomeprazole/omeprazole, 2=placebo. Sex=1 for male and sex=2 for female. ASA II, ASA III and ASA IV compared to ASA I. H. pylori variable collapsed into 2 main classes Hp=0 for Negative and Hp=1 for Positive or Trace. Forrest class Ia , Forrest class IIa and Forrest class IIb compared to Forrest class Ib. Hospitalized, Previous ulcer bleeding, NSAID, Aspirin and Warfarin , answers: 0=no, 1=yes.

mdbmpe 20NOV12:22:09:14.17 IVP_PUB Cox regression predicted risk for rebleeding_d3_asagrade_forrest_Ibcomparator

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The Applicant analyzed Day 30 rebleeding results excluding ASA Grade IV patients to further explore how the inclusion of ASA Grade IV patients contributed to the difference in placebo group rebleeding rates in Studies 01 and Lau. By Day 30, 22.5% of the placebo patients in the Lau Study had had a rebleeding event, compared with 13.6% of the placebo patients in Study 01 (8.9% placebo rebleeding rate difference). If the sickest patients (ASA grade IV) are excluded from the Lau Study, the difference in Day 30 placebo rebleeding rates decreases to 3.4%. See Table 15 below. It is expected that Day 3 results will be similar given that for both studies the majority of the rebleeding events occurred in the first 72 hours.

Table 15. Rebleeding rate 01 Study and Lau Study, excluding ASA grade IV patients

Study	Day	Treatment	N	No Rebleeding	Rebleeding	95% CI for Rebleeding rate
Lau	30	Omeprazole	102	95 (93.1%)	7 (6.9%)	3% - 14%
D961DC00001	30	Esomeprazole	375	346 (92.3%)	29 (7.7%)	5% - 11%
Lau	30	Placebo	100	83 (83.0%)	17 (17.0%)	10% - 26%
D961DC00001	30	Placebo	389	336 (86.4%)	53 (13.6%)	10% - 17%

mdbmpe 20NOV12:22:59:46.72 PUB Lau rebleeding_konf_subgroup analyses_exkl_ASAIV

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MO Comment:

Understanding the cause of the difference in the rebleeding rate in the placebo group of the trial reported by Lau et al (20%) compared to Study 01 (10%) is important. The post-hoc factor analyses submitted by the Applicant may provide some evidence to suggest that the differences can be explained, in large part, by factors other than ethnic differences (such as those described in CRL #3 above). The results of the factor analyses support the conclusion that the Lau study can be viewed as supportive evidence for Study 01given that the Lau results can generalized to the US population. The statistical specifics of how the risk factor analyses were performed and therefore whether the results are able to provide adequate supportive evidence will be discussed in the statistical review.

6.5 Complete Response Item #5

There were substantive differences in the efficacy outcomes within important subgroups in the clinical trial reported by Lau et al compared to D961DC00001. These inconsistencies raise questions about the reproducibility of the efficacy outcome.

a) In the subgroup of patients 65 years and older, the decrease in proportion of patients with rebleeding within 72 hours in the esomeprazole arm relative to placebo was 2.2% in D961DC00001. In contrast, the decrease in the same subgroup treated with omeprazole relative to placebo in the trial reported by Lau et al was 19.7%.
b) In the subgroup of patients with Forrest Ib classification, there were similar proportions of patients with rebleeding within 72 hours in the esomeprazole and placebo arms in D961DC00001 (a 0.5% difference). In contrast, there was a decrease in the proportion of patients with rebleeding within 72 hours in the omeprazole arm relative to placebo of 10% in the trial reported by Lau et al. See Table 16, below.

As discussed above, the rate of rebleeding in placebo patients in Study 01 was approximately half that seen in placebo patients in the Lau study (10.3% and 20%, respectively). The discrepancy in placebo rebleeding rates between the two studies is reflected in the dissimilar treatment differences seen in Study 01 and the Lau Study (-4.4% and -15.8%, respectively). Subgroup analysis reveals that the treatment difference in patients 65 years and older taking esomeprazole was -2.2% in Study 01 compared with -19.7% in the Lau Study. The Applicant explored risk factors associated with rebleeding (see discussion of factor analyses above). In these analyses, the relative risk estimate for the factor “age” is 0.993 which suggests that age is not a risk

factor associated with rebleeding. However, the factor shown (in the analysis) to have the greatest positive association with risk of rebleeding correlates directly with age--ASA grade IV. No ASA grade IV patients were allowed in Study 01 and 20.5% of patients ≥65 years old in the Lau Study were classified as ASA grade IV.

MO Comment:
While the magnitude of the difference was smaller in patients >65 years old than the mean, the direction of the difference was consistent with the results of Study 01 and provide supportive evidence that IV PPIs are effective for the prevention of rebleeding.

Table 16. Rebleeding by Forrest class for Patients in Study 01

Day	Treatment	Ia	Ib	IIa	IIb
3	Esomeprazole	3/28 (10.7%)	9/166 (5.4%)	8/136 (5.9%)	2/42 (4.8%)
3	Placebo	9/40 (22.5%)	8/163 (4.9%)	17/151 (11.3%)	6/34 (17.6%)
7	Esomeprazole	4/28 (14.3%)	10/166 (6%)	9/136 (6.6%)	3/42 (7.1%)
7	Placebo	10/40 (25%)	14/163 (8.6%)	20/151 (13.2%)	6/34 (17.6%)
30	Esomeprazole	4/28 (14.3%)	10/166 (6%)	10/136 (7.4%)	4/42 (9.5%)
30	Placebo	10/40 (25%)	14/163 (8.6%)	21/151 (13.9%)	8/34 (23.5%)

In the D961DC00001 study 4 patients had missing values for Forrest class (3 in Eso and 1 in placebo)
PUB Forrest class vs rebleeding photojudge

Electronically copied and reproduced from Applicant's Response to Complete Response Letter submission, Table 16, p. 30

In their response to the Complete Response Letter, the Applicant provided possible explanations for the difference in effect size seen in Forrest Ib patients seen in Study 01 compared to Lau, 0.5% vs. 10%, respectively. The Applicant posits that the Lau study investigators may have been more experienced at identifying oozing bleeding from visible vessels (with a higher risk of rebleeding), while a higher proportion of bleeding from minute mucosal vessels (with a lower risk of rebleeding) were including in Study 01. No photo documentation is available from Lau Study. However, photo documentation is available from Study 01 and a *post-hoc* assessment of these photos was done by the Applicant. Photos were available for 273 of the 329 Forrest Ib patients of study 01. Two members of the Endpoint Committee for the study independently examined the photos to look for the presence or absence of additional stigmata of rebleeding (non-bleeding visible vessel or clot). According to the Applicant, the analysis showed that for Forrest Ib patients where there was agreement there was a higher rebleeding rate in the placebo group than in the group without agreement (13.7% vs. 5.7%, respectively). And there was a higher therapeutic effect of esomeprazole seen in patients where there was agreement compared with patients for which there was no agreement (8.6% vs. 0.5%, respectively).

MO Comment:
Forrest Ib patients have a higher risk of rebleeding and therefore represent an important subgroup. The Applicant's post-hoc analysis on agreement of independent observers

regarding the presence or absence of additional stigmata of bleeding in Study 01 does not persuade me that the small treatment difference seen in Forrest Ib patients is not real. However, the totality of the information from Study 01 and the Lau Study supports the position that Nexium IV is efficacious for the prevention of rebleeding in PUB. At Day 3, Day 7, and Day 30 in all Forrest subgroups, the proportion of placebo patients with rebleeding was higher than the proportion of IV PPI patients with rebleeding.

6.5 Complete Response Item #6

> The information from observational studies and literature reviews of intravenous esomeprazole and omeprazole were not considered adequate to constitute primary evidence of the efficacy of the product for the proposed indication.

The Applicant acknowledged in their response that the observational study data submitted during Cycle 2 were meant to serve as supportive evidence of efficacy.

MO Comment:
It is appropriate that the observational study data submitted during Cycle 2 serve only as secondary evidence of efficacy.

6.7 Complete Response Item #7

> We have reviewed your response to the deficiencies cited in the November 26, 2008, Complete Response Letter regarding trial D961DC00001. Your responses do not change our conclusion that D961DC00001, as a single adequate and well-controlled trial, does not provide sufficient evidence to support the proposed indication. The following comments are responses to specific issues raised in your resubmission:
>
> a. Your assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers for D961DC00001 is not persuasive. The Breslow-Day test is not a powerful test for detecting lack of homogeneity. For this reason, the lack of a statistical significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables further limit the usefulness of the test.
>
> b. A Division of Good Clinical Practice Compliance inspection was performed at site 0102 in the Netherlands because Dr. Ernst J. Kuipers, MD, PhD, the

principal investigator at that site, disclosed that he had accepted significant payments from AstraZeneca. The inspection found that the data from this site appear reliable. Nevertheless, as stated in the Complete Response letter, the large magnitude of treatment effect observed at this site, and the impact this site had on the overall efficacy of the trial, suggest that the efficacy results of D961DC00001 are not robust.

MO Comment:
Please see the biometrics reviews (Cycles 1, 2, and 3) for discussions regarding the Breslow-Day test, stratification variables, and other statistical issues.

The Division of Good Clinical Practice Compliance inspected site 0102 during the second review cycle and determined that the data from the site appeared reliable. The direction of the treatment difference supports the conclusion that Nexium IV is efficacious at the tested dose for (b) (4) *rebleeding of gastric and duodenal ulcers after therapeutic endoscopy.*

6.8 Additional Efficacy Considerations

6.8.1 Pharmacodynamic Endpoints

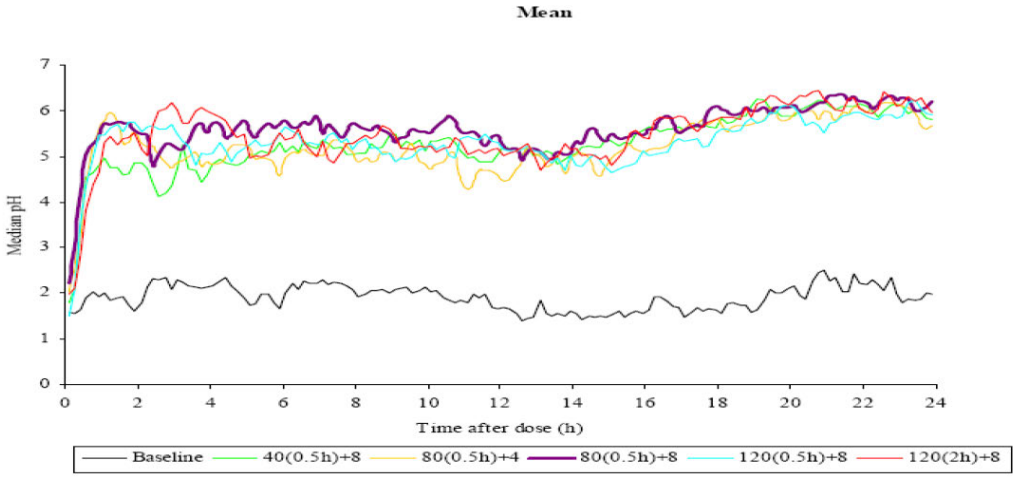
The primary endpoint for the PK/PD studies used to support dosing was the percentage of time subjects had a pH >6. However, *in vitro* studies showed that substantive impact on both plasma coagulation and platelet aggregation occurred at pH 6.4 – 6.8.[5] This suggests that a target pH for optimal clot stabilization would be greater than 6.8. A review of the mean time that subjects had a pH greater than 7 reveals that these values are generally much lower than the mean percent times subjects had a pH greater than 6 regardless of CYP2C19 and H. pylori status (48% vs 13.3% for Chinese subjects and 47% vs 4.0 percent for Caucasian subjects, mean values).

Given the results of the *in vitro* studies, PD results for the percent time pH >7 endpoints are particularly important. The relatively low percentage of time spent with a pH above 7 for both Chinese and Caucasian subjects suggests that a higher dose of esomeprazole might be necessary for the proposed indication to meet clot stabilization goals. The sponsor's dose-finding studies explored five dosing regimens (including two with higher bolus doses than the proposed dose). In these studies, the PD effect appeared to plateau at bolus doses higher than the proposed dose. During the second

[5] Green FW, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation: a poss ble contributor to prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978;74:38-44

cycle clinical pharmacology review, Dr. Dilara Jappar concluded that no further dose finding studies in the target population were necessary.

Figure 1. Median Intragastric pH Profiles at Baseline and during administration of Esomeprazole to Healthy Subjects, Treatments A-E (D9615C00015)



When we compare the results seen in Caucasian and Chinese subjects, it should be noted that there was a trend for Chinese subjects to have a higher percentage of time with a pH >7 over the 24 hour study period. This trend persisted regardless of CYP2C19 genotype or *H. pylori* status. See Table 17 and

Table 18 below.

Table 17. Mean % time pH >7 over 24 hours, by CYP2C19 status

	EMs	IMs	PMs
Study 07 (Chinese Subjects)	11.2 ± 7.8 (n=7)	16.4 ± 10.6 (n=10)	11.3; 4.6 (n=2)
Study 15 (Caucasian Subjects)	4.4±8.5 (n=17)	3.4±4.9 (n=6)	0.0 (n=1)

Table adapted from Regulatory Briefing Presentation (April 19, 2013) by Dr. Sandhya Apparaju, clinical pharmacology reviewer, Slides 66 and 67

Table 18. Mean % time pH >7 over 24 hours, by H. pylori status

	Overall	H. pylori positive	H. pylori negative
Study 07 (Chinese Subjects)	13.3 ± 10.6 n=19	18.75 ± 9.26 (n=9)	11.14 ± 8.56 (n=11)
Study 15 (Caucasian Subjects)	4.0 ± 7.5 n=24	All Caucasian subjects were H. pylori negative	

Table adapted from Regulatory Briefing Presentation (April 19, 2013) by Dr. Sandhya Apparaju, clinical pharmacology reviewer

MO Comment:
The generalizability of the PK/PD results to patients with bleeding gastric or duodenal may be limited by the fact that the studies included only healthy subjects. Higher bolus doses than the proposed bolus dose were studied, but no higher hourly infusion doses were studied than the 8mg/h proposed dose.

6.8.2 Time to Rebleeding

The cumulative number of rebleeding events that occur by 3 days and 30 days were the primary endpoints for Study 01 and the Lau study, respectively. Understanding at which timepoint within these broad time categories and comparing that to the pH was important. Rebleeding data at 3, 6, 9, 12, 24, and 48 hours was available for Study 01. Unfortunately, the Lau study data on rebleeding was not collected as a continuous variable over time, but as events within consecutive 24-hour periods after randomization.

In Study 01, the highest number of rebleeding events occurred between hours 12 and 24. A trend for most of the 3 day rebleeding events to occur within the first 24 hours was also seen in the Lau study. See Table 19 and Table 20 below.

Table 19. Proportion of patients with Rebleeding, Study 01

Re-bleed within (hours)	Esomeprazole n/N(%)	Placebo n/N(%)
3	3/375 (0.8%)	3/389 (0.8%)
6	6/375 (1.6%)	5/389 (1.3%)
12	9/375 (2.4%)	10/389 (2.6%)
24	17/375 (4.5%)	20/389 (5.1%)
48	19/375 (5.1%)	35/389 (9%)
72	22/375 (5.9%)	40/389 (10.3%)

Table 20. Proportion of Patients with Rebleeding, Lau *et al* Study

Re-bleed within (hours)	Omeprazole n/N(%)	Placebo n/N(%)
24	3/120 (2.5%)	17/120 (14.2%)
48	3/120 (2.5%)	21/120 (17.5%)
72	5/120 (4.2%)	24/120 (20%)

APPEARS THIS WAY ON ORIGINAL

MO Comment:
Of the 22 rebleeding events in the esomeprazole arm that occurred by Day 3, 77% occurred by 24 hours in Study 01. Of the 5 rebleeding events that occurred by Day 3 in the Lau study, 60% occurred by 24 hours. This data suggests that most of the benefit offered by the use of esomeprazole in this setting occurs early on. And this benefit is more directly related to increasing the pH than maintaining an increased pH. Therefore, continued dose-finding for the optimal maintenance dose is unnecessary. Further, the lack of further improvement in PD parameters seen with the 120 mg bolus dose supports the use of the proposed 80 mg bolus dose. I agree with the Dr. Dilara Jappar (Second cycle, pharmacology reviewer) that no further dose-finding is necessary unless those studies occur in the target population.

6.8.3 Rebleeding Definitions Used

An Information Request (IR) was sent to the Applicant during the current review cycle asking for a numeric breakdown for Study 01 and Lau study of how patients were diagnosed with rebleeding events. See Table 21 below for diagnostic criteria for rebleeding in Study 01 and the Lau study.

Table 21. Definition of Clinically Significant Rebleeding

Study 01	*Lau et al Study*
▪ Endoscopy (need at least 1) o A1- Active bleed o A2- Blood in stomach ▪ Clinical (need at least 2) o B1- Hematemesis, hematochezia, melena, blood in gastric aspirate o B2- Fall in Hgb >2 g/L in 24 hours o B3- Hypotension (SBP<90, tachycardia HR>110) and melena ▪ Hematemesis: >200 mL of fresh blood	▪ Vomiting of fresh blood ▪ Shock (systolic BP ≤90 mm Hg or pulse ≥110) with melena ▪ Drop in hemoglobin of 2 g/dL within 24 hours after a transfusion to 10 g/dL

Table 22. Number(%) of Patients with Clinically Significant Rebleeding within 30 days, by diagnostic sub-criteria and treatment arm, Study 01

Diagnostic sub criteria	Esomeprazole (n=29/N=375) n/N(%)	Placebo (n=53/N=389) n/N(%)
1 - Endoscopic verification: blood in stomach	13 / 375 (3.5%)	30 / 389 (7.7%)
2 - Endoscopic verification: active bleeding from a peptic ulcer	13 / 375 (3.5%)	25 / 389 (6.4%)
At least one of 1 or 2: Any endoscopic verification	18 / 375 (4.8%)	36 / 389 (9.3%)
3 - Vomiting of fresh blood/fresh blood in gastric tube/haematochezia/maelena	21 / 375 (5.6%)	39 / 389 (10%)
4 - Decrease in Hb>20g/L during 24h or lack of increase in Hb after transfusion	25 / 375 (6.7%)	44 / 389 (11.3%)
5 - Unstable circulation SBP ≤ 90mmHg/pulse ≥ 110/min	18 / 375 (4.8%)	28 / 389 (7.2%)
At least one of 3, 4 or 5: Any clinical sign	29 / 375 (7.7%)	53 / 389 (13.6%)
6 - Vomiting significant amounts (>200mL) of fresh blood as estimated by the investigator	8 / 375 (2.1%)	12 / 389 (3.1%)

Electronically copied and reproduced from Applicant's 22 April 2013 Response to Information Request, p 9.

Table 23. Number(%) of Patients with Clinically Significant Rebleeding within 30 days, by diagnostic sub-criteria and treatment arm, Lau *et al* Study

Diagnostic sub criteria	Omeprazole (n=8/N=118) n/N(%)	Placebo (n=27/N=119) n/N(%)
Defined as rebleeders but no subcriterias can be found		2 / 119 (1.7%)*
1 - Associated condition at repeat endoscopy: Fresh blood	4 / 118 (3.4%)	8 / 119 (6.7%)
2 - Recent hemorrhage at repeat endoscopy: Spurter or Ooze	3 / 118 (2.5%)	13 / 119 (10.9%)
At least one of 1 or 2: Any endoscopic verification	6 / 118 (5.1%)	17 / 119 (14.3%)
3 - Rebleeding day 1-3: Fresh hematemesis	3 / 118 (2.5%)	2 / 119 (1.7%)
4 - Rebleeding day 1-3: Drop by 2mg/dl & melena	1 / 118 (0.8%)	9 / 119 (7.6%)
5 - Rebleeding day 1-3: Hypotension, tachycardia and melena	4 / 118 (3.4%)	10 / 119 (8.4%)
At least one of 3, 4 or 5: Any clinical sign	6 / 118 (5.1%)	20 / 119 (16.8%)
6 - Vomit significant amounts of fresh blood	1 / 118 (0.8%)	

Categories 3, 4 and 5 were assessed at day 1-3, but one on day 6
*Two subjects (IVP 141 and IVP 171) in the placebo group are defined as rebleeders but no details of criteria can be found

Electronically copied and reproduced from Applicant's 22 April 2013 Response to Information Request, p 9.

MO Comment:
Review of the data on how rebleeding criteria were used to classify rebleeding events showed that most patients in both studies were diagnosed with rebleeding based on clinical signs and symptoms.

7 Review of Safety

Safety Summary

Overall, no new safety signals were observed for Nexium IV in Study 01 or the Lau Study. For a full safety review of Study 01, see the clinical review of Dr. Anil Nayyar in DARRTS (18 November 2008). For a fully safety review of the Lau Study, see the clinical review of Dr. Erica Wynn in DARRTS (08 April 2011).

At 72 hours after endoscopy, the mortality difference (active-placebo) varied from -0.3 to +2.5% across all 4 studies (See Table 24 below).

Table 24. Death by 72 Hours

Study Drug	Study 01	Study Lau	Study 840	Study 841
Esomeprazole/Omeprazole	0.5% (2/375)	2.5% (3/120)	1.5% (2/130)	0.6% (1/159)
Placebo	0.8% (3/389)	0	0	0.6% (1/163)

Reviewer's Table.

Both Studies 840 and 841, submitted as supportive evidence during cycle 2 (see clinical review by Dr. Erica Wynn in DARRTS, 08 April 2011), were terminated prematurely after an imbalance in mortality was detected in Study 841. Eleven deaths were reported in the omeprazole arm compared with one death in the placebo arm.

Table 25. Death by Day 30 (Study 01, Study Lau), Death by Day 21 (Studies 840/841)

Study Drug	Study 01	Study Lau	Study 840	Study 841
Esomeprazole/Omeprazole	0.8 (3/375)	4.2% (5/120)	6.2% (8/130)	7.4% (11/148)
Placebo	1.5% (6/389)	10.0% (12/120)	5.9% (8/135)	0.6% (1/162)

Reviewer's Table.

Of the 12 deaths reported in Study 841, only one in each treatment group was directly related to gastrointestinal bleeding (AE term, GI hemorrhage). Myocardial infarction was reported in five of the Nexium IV patient death narratives. For other AE terms reported in patients who died during Study 841, see Table 26 below.

Table 26. Death by Treatment Group (Study 841)

	Sex	Age (years)	Day of Onset	AE Term
Omeprazole IV*				
#1	M	78	2	Myocardial Infarction
#2	F	84	2	Myocardial Infarction, congestive heart failure
#3	M	85	3	GI hemorrhage
#4	M	68	2	Myocardial Infarction
#5	F	85	5	Myocardial Infarction
#6	M	72	7	Cardiac Failure
#7	F	78	6	Congestive Heart Failure
#8	M	79	13	Cerebral infarction
#9	M	77	19	Pulmonary Embolism
#10	M	84	7	Stroke
#11	M	82	8	Myocardial Infarction
Placebo IV#				
#1	F	85	2	GI hemorrhage

*Patients #5 through #11 randomized to omeprazole IV received omeprazole oral after omeprazole IV
#Patient #1 randomized to placebo IV did not receive omeprazole oral after placebo IV
Table electronically copied and reproduced from CDER, April 19, 2013 Regulatory Briefing Background Document

MO Comment:
An imbalance in deaths of the magnitude seen in Study 841 was not seen in Studies 840, 01, or Lau and is not previously known to be associated with the use of Nexium IV. Nexium IV is currently marketed and the postmarketing mortality data support the hypothesis that the mortality findings in Study 841 were a chance occurrence.

7.1 Methods

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

7.2 Adequacy of Safety Assessments

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

7.3 Major Safety Results

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

7.3.1 Deaths

See Section 7, Safety Summary, for a discussion of deaths in Studies 01, Lau, 840, and 841.

7.4 Supportive Safety Results

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

7.5 Other Safety Explorations

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

7.6 Additional Safety Evaluations

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

7.7 Additional Submissions / Safety Issues

See the First Cycle clinical review by Dr. Anil Nayyar and the Second Cycle clinical review by Dr. Erica Wynn.

8 Postmarket Experience

The Applicant submitted results of a search of the AstraZeneca global patient safety database. The search criteria used in this analysis included: medically confirmed case reports on esomeprazole iv for which new or significant follow-up information had been received by AstraZeneca during the period 1 May 2010 to 31 August 2012 and where esomeprazole iv was used for treatment of stress ulcer or gastrointestinal (GI) hemorrhage, and/or where an AE of GI hemorrhage was reported, and/or where a daily dosage of esomeprazole iv of ≥80 mg or an infusion rate of 8 mg/h was used. A total of 52 case reports describing 89 adverse events (AEs). The 52 case reports involved 38 non-serious AEs and 51 serious adverse events (SAEs). Overall, a review of these 52 case reports did not identify any new safety concerns regarding the use of esomeprazole IV in the setting of bleeding gastric or duodenal ulcers.

Of the events reported, three ended in death. See narratives in Table 27 below.

Table 27. Narratives of Reported Post-marketing Deaths, [redacted]

Case ID/Country/Primary Source/Age (years)/Gender	Primary Dose/Route	AE(s)	Narrative
2012SE09183 / South Africa / HP / 8 / Female	Intravenous (NOS)	Off label use; Death; Asthenia; Aphagia; Haematochezia; Pneumonia aspiration	A report was received from a healthcare professional via medical representative concerning an eight years old Female patient. The patient's medical history, concurrent diseases and concomitant medications were not reported. On an unknown date, the patient started receiving a treatment with intravenous Nexium IV (esomeprazole). The Nexium IV was administered to an 8 years old patient /off label use in the pediatric intensive care unit (preferred term: off label use). Reporter stated that patient was on Nexium IV for one day only. Patient was HIV positive. She had aspiration pneumonia (preferred term:pneumonia aspiration) and was very weak (preferred term:asthenia). She couldnt eat (preferred term:aphagia) and had blood in stools (preferred term:haematochezia). The patient died of an unknown cause on [redacted]
2012SE53889 / France / AUTH / 95 / Male	1 DF DAILY / Intravenous (not otherwise specified)	Cardiac arrest; Gastrointestinal haemorrhage; Gastric ulcer; Anaphylactic shock; Urticaria	Spontaneous serious succint report transmitted by French Medicine Agency concerning a 95-y-old male patient. Patient's medical history included coronary artery disease. On [redacted], the patient was hospitalized for unspecified reason. On unspecified date, the patient started on Nexium and Umuline intravenously. The patient then presented with anaphylactic schock and pelvis urticarian lesion requiring Polaramine and a bolus of 0.5 mg of Adrenaline IV. Nexium and Umuline were both discontinued and switched to Novorapid and Azantac leading to patient's full recovery for anaphylactic shock and urticaria. On [redacted], patient died due to cardio-circulatory arrest following digestive hemorrhage and gastric ulceration. French Medicine Agency considered the events of anaphylactic shock and urticaria as serious due to important medical event and suspected. Nexium and Umuline in their occurrence.
2012SE37310 / China / HP / 78 / Male	40 mg BID / Intravenous (not otherwise specified)	Anaphylactic shock	A report was received from a health professional concerning a 78 year old Chinese, male patient. The patient's medical history included cephalosporin allergy. The patient's concurrent disease provided as upper gastrointestinal hemorrhage, which was treated in a hospital. Concomitant medications included ceftriaxone sodium and tazobactam sodium for Nexium injection (esomeprazole sodium) (Lot. No.NH2456) 40mg + 0.9% NaCl solution 100ml two times a day were taken for acid inhibitory. On [redacted], before the first time of taking above drugs, the health professional did test for penicillin and no allergic reactions occurred. Then using of above drugs (which were injected with two tubes) started. After about half a minute taking above drugs, consciousness loss, pale face and dyspnea came out. The doctor thought it was anaphylactic shock (preferred term: anaphylactic shock) then stopped above injections immediately, which weren't used again. 0.9% NaCl injection1000 ml was taken with one tube together with Dexamethasone 5mg intravenous push and adrenaline 1mg intravenous push. After one minute, cardio-respiratory arrest was noted. Rescue measurements were taken for more times, but the patient was not responding to the rescue. At 21:55 pm, on [redacted], the patient died from the event of anaphylactic shock (consciousness loss, pale face, dyspnea). The reporter assessed the event of anaphylactic shock (consciousness loss, pale face, dyspnea) to be serious with the following serious criterias: death, life threatening and important medical event.

The Applicant also submitted the results of a scientific literature search for the period 1 January 2010 to 11 September 2012. The Applicant identified 3 articles considered to be the most relevant for assessment of safety in this patient population. No new safety concerns were identified from these publications.

Table 28. Post-marketing Safety Literature Search Results, IV Nexium, January 2010 to September 2012

den Hoed CM and Kuipers EJ. Esomeprazole for the treatment of peptic ulcer bleeding. Expert Rev. Gastroenterol Hepatol 2010;4(6):679-95.
Kuipers EJ, Sung JJY, Barkun A, Mössner J, Jensen D, Stuart R et al. Safety and Tolerability of High-Dose Intravenous Esomeprazole for Prevention of Peptic Ulcer Rebleeding. Adv Ther 2011;28(2):150-9.
Lin P-C, Chang C-H, Hsu P-I, Tseng P-L, Huang Y-B. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: A meta-analysis. Crit Care Med 2010;38(4):1197-1205.

There was no new information from clinical studies relevant to this patient population during the same period.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

See Final label.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this Application.

9.4 Regulatory Briefing

On April 19, 2013, DGIEP presented this Application at a CDER Regulatory Briefing. The purpose of the briefing was to discuss the adequacy of evidence provided to support approval of Nexium® for this new indication, for which PPIs have become standard of care.

The following questions were posed to the panel:

1. Do the data presented (from Study 01, the Lau et al. study, Study 840, Study 841, and PK/PD studies) represent substantial evidence of efficacy for the proposed indication (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers")?

Brief Answer: Yes, the data represent substantial evidence of efficacy for the proposed indication.

2. Given the overall safety database (including Study 01, the Lau et al. study, Study 840, and Study 841), is it reasonable to conclude that the mortality difference observed in Study 841 does not preclude approval?

Summary answer: The mortality difference observed in Study 841 does not preclude approval.

See the official Regulatory Briefing Slides[6], Meeting Minutes[7], and Transcripts[8] for further information.

6 http://inside.fda.gov:9003/downloads/CDER/OfficeoftheCenterDirector/RegulatoryBriefings/UCM348981.pdf
7 http://inside.fda.gov:9003/downloads/CDER/OfficeoftheCenterDirector/RegulatoryBriefings/UCM352972.pdf
8 http://inside.fda.gov:9003/downloads/CDER/OfficeoftheCenterDirector/RegulatoryBriefings/UCM348791.pdf

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/s/

AISHA P JOHNSON
07/11/2013

ROBERT FIORENTINO
07/15/2013

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	NDA 21-689/S-014
Priority or Standard	Priority
Submit Date(s)	09/15/2010
Received Date(s)	09/16/2010
PDUFA Goal Date	06/16/2011
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism
Reviewer Name(s)	Erica Wynn, MD MPH through Lynne P. Yao, MD
Review Completion Date	June 7, 2011
Established Name	Esomeprazole Sodium
Trade Name	NEXIUM® I.V.
Therapeutic Class	Proton Pump Inhibitor
Applicant	AstraZeneca LP
Formulation(s)	Powder for Injection Solution, Lypophilized
Dosing Regimen	80mg I.V. infusion over 30 minutes followed by continuous I.V. infusion of 8mg/hr for 71.5 hours.
Indication(s)	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.
Intended Population(s)	Patients with Peptic Ulcer Bleeding

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is the second review cycle for this application. During the first review cycle, the applicant submitted a single trial that failed to provide evidence of a highly statistically significant effect for the primary outcome, (b)(4) .

In this second submission, the applicant submitted five types of data:

- Pharmacokinetic/pharmacodynamic (PK/PD) bridging data between intravenous Omeprazole and Esomeprazole
- Data from the literature and trials conducted with intravenous Omeprazole
- Observational data from use of intravenous Esomeprazole in patients with peptic ulcer bleed
- A systematic review of available trials from any proton pump inhibitor
- Additional observational data from other data sources including healthcare and administrative databases, and hospital networks with field-based studies.

The applicant has demonstrated a bridge in the PK/PD parameters for Omeprazole and Esomeprazole. The clinical pharmacology reviewer concluded that the extent of differences between the Esomeprazole and Omeprazole PK/PD parameters is dependent on the route of administration. When the drug products are administered according to the applicant's proposed dosing regimen, there are no major differences in the PK and PD parameters. In light of this bridge, successful trials conducted with intravenous Omeprazole could support an indication for Esomeprazole.

However, based on the information provided, the randomized controlled studies conducted with Omeprazole fail to meet the regulatory standard required for approval. Under Section 314.125 of the Federal Food and Drug Cosmetic Act, the FDA may refuse to approve an application if there is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Usually it has been the position of the FDA to require at least two clinical trials, each convincing on its own, to establish efficacy. However, the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products states that, "In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a

single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact multiple studies supporting the new use and expert judgment could conclude that the studies together present substantial evidence of effectiveness. In other cases, FDA has relied only on a single adequate and well controlled efficacy study to support approval – generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as effect on survival, and a confirmatory study would be difficult to conduct on ethical grounds."

Two of the randomized controlled trials with Omeprazole were omitted from the efficacy analysis due to marked differences in the designs of the trials with regards to treatment regimen, patient population, and primary endpoint relative to the originally submitted pivotal trial. When the reviewer selected a subset of patients from these trials that would allow comparison to the pivotal trial, the sample size was too small to permit meaningful statistical analysis. Furthermore, there were marked differences in the baseline characteristics of the placebo and treatment groups for this subset of patients. Therefore, support of the pivotal study must be based solely on the trial conducted by Lau, et al. Reliance on a single study requires a high degree of scientific rigor. This trial was a single center study conducted in Hong Kong between 1998 and 1999. It has been documented in the literature that Asians have a lower parietal cell mass; a higher prevalence of *H. pylori* infection; and a higher prevalence of cytochrome 2C19 genetic polymorphism, all of which may explain why PPI therapy has been demonstrated to be more efficacious in this population. [1] The Lau trial population more than likely does not reflect the more diverse population of the United States. Given this information, one could argue that drug will not have the effect it purports "under the conditions of use prescribed", i.e. the treatment effect seen in China may not reflect that which would occur in the United States due to differences in the population. In support of this argument, consider that the treatment effect in the Lau trial was 15.8%. However, in the pivotal trial which included more study centers cross different countries, the treatment affect was only 4.4%. In addition, the Lau study fails to show a statistically significant effect on mortality, an important clinical benefit.

The applicant has argued that conducting an additional trial would be difficult on ethical grounds. There may be some validity to the applicant's argument especially in light of consensus clinical guidelines that recommend the administration of proton pump inhibitors following therapeutic endoscopy. However, it may be reasonable for the applicant to conduct a multicenter, active treatment concurrent control trial. This may be in the form of a dose comparison trial. There is some data in the literature to suggest that a lower bolus dose of the intravenous proton pump inhibitor may also be efficacious at preventing the recurrence of rebleeding.[2]

In support of their resubmission, the applicant provided a summary of available literature, a metaanalysis, and outcomes from an observational study of treatment in

clinical practice. An independent search of the literature was performed by this reviewer. The data presented in the literature is conflicting. Although some clinical trials have shown positive outcomes in preventing rebleeding in peptic ulcer patients, most of these studies were conducted in Asia. Trials that were conducted in Europe and North America were less favorable. More importantly, there is little evidence in the literature that preventing the recurrence of rebleeding in patients with peptic ulcer bleeds, has a significant impact on improving mortality. In fact, the results of the observational study submitted with this application, also concluded that with the exception of Asians and patients with high-risk stigmata for rebleeding at therapeutic endoscopy, use of high-dose intravenous proton pump inhibitor therapy failed to improve survival.

There were no additional safety signals detected in the Lau trial. However, this reviewer can not ignore the imbalance in mortality that was seen in trial I-841, which was excluded from the efficacy analysis. This trial enrolled patients who may have been considered to have high-risk stigmata for recurrent bleeding following endoscopy. The fact that there were more deaths in the treatment group for this population is concerning and worth mentioning.

Given all the information presented, it is the recommendation of the Division that a complete response be issued for NDA 21689 Supplement 14.

1.2 Risk Benefit Assessment

The applicant seeks approval of intravenous Esomeprazole for the proposed indication. Intravenous Esomeprazole is currently approved and marketed in the United States, although not at the proposed doses. During the first review cycle of trial D961DC00001, the reviewer concluded that the safety profile of intravenous Esomeprazole was similar to that of placebo and that there were no new safety concerns. There were no new data presented in this submission to the contrary. However, a risk:benefit analysis must also take into consideration efficacy. In the absence of established efficacy for the patient population, the risks of treatment do not outweigh the benefits.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This section is not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

To comply with regulations under the Pediatric Research Equity Act (PREA), the applicant submitted a request for waiver of pediatric trials. In support of their waiver, the applicant submitted data on the occurrence of peptic ulcer bleeding in children and an analysis of two US pediatric databases exploring the incidence of pediatric peptic ulcer bleeding. Consults were obtained from the Pediatric Maternal Health Staff (PMHS) and

the Office of Surveillance and Epidemiology (OSE). Both consultants concluded that the incidence of peptic ulcer bleeding in pediatric patients was uncommon. The reader is referred to the finalized PMHS consult by Dr. Amy Taylor dated March 2, 2011, and the OSE consult by Dr. Jing Ju dated February 1, 2011. Based on the information provided, this reviewer concurs with the PMHS consult, the OSE consult, and the applicant in that the number of pediatric PUB patients who are eligible to participate in a study is very limited and it may not be feasible to conduct trials in pediatric patients. In the opinion of this reviewer, the applicant's waiver request seems reasonable and should be granted for future trials. This issue was taken before the Pediatric Review Committee on February 16, 2011, and the committee concurred.

2 Introduction and Regulatory Background

Upper gastrointestinal bleeding is a complication of peptic ulcer disease. Eighty percent of bleeding from peptic ulcers or nonvariceal causes stops spontaneously.[3,4] For the other 20% of patients that will require endoscopy, morbidity and mortality usually result from either continuous active bleeding or episodes of recurrent bleeding.[3] There are data to suggest that death associated with peptic ulcer bleeding is related to other co-morbidities rather than a direct consequence of the bleeding ulcer itself.

Certain clinical features have been associated with an increased risk of rebleeding and poor outcomes. These include: age > 65 years, poor overall health status, comorbid illnesses, ulcer size and hemodynamic instability (i.e. shock, low initial hemoglobin level, requirement for blood transfusions).[5] The Forrest Classification scheme is used to predict the risk of rebleeding in peptic ulcer disease.[6] The following is a modified version of the Forrest classification.[6,7,8,9]:

Table 1 Forrest Classification of Gastric Ulcer Hemorrhage with Prognosis

	Forrest Classification	Rebleeding Incidence if untreated
Type I Active Bleeding	Type Ia: Spurting bleeding Type Ib: Oozing bleeding	100% 55% (17 -100%)
Type II Recent Bleeding	Type IIa: Non-bleeding visible vessel Type IIb: Adherent Sentinel Clot Type IIc: Black base vessel (Hematin covered flat spot)	43% (8 – 81%) 22% (14 -36%) 10% (0 -13%)
Type III No bleeding	Type III: No stigma	5% (0 – 10%)

Current medical therapy for peptic ulcer bleeding includes initial hemodynamic stabilization, volume replacement, and correction of any known coagulopathies. Most patients should undergo upper endoscopy within 6 to 24 hours of arriving in the hospital.[24] In clinical practice, the goal for treatment of peptic ulcer bleeding is to prevent the recurrence of rebleeding after achieving initial hemostasis and hemodynamic stability.[10] Most mechanical hemostatic techniques are equally effective when used alone. According to the most recently published clinical guidelines, injection therapy with

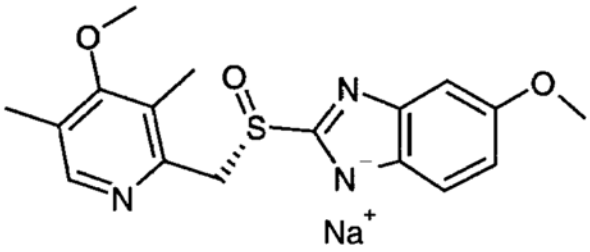
epinephrine is useful only as adjunct therapy in combination with other modalities (e.g. thermocautery, hemoclips).[11]

Use of proton pump inhibitors in the treatment of peptic ulcer bleeding is based on previous in-vitro and animal studies which have shown that the ability to form clots is sensitive to alterations in hydrogen ion concentration.[12,13] "Platelet aggregation decreased significantly at pH ≥ 6.8 and gastric mucosal bleeding time fell significantly at pH ≥ 6.4."[13] Additionally, under acidic conditions pepsinogen is converted to pepsin which lyses blood clots.[13] Thus the theory behind the use of intravenous proton pump inhibitors in this setting is that proton pump inhibitors may decrease peptic ulcer bleeding by maintaining gastric pH above 6. This is believed to be the pH at which platelet aggregation is optimized and fibrinolysis is relatively inhibited, potentially improving the likelihood of clot stability at the ulcer site.[3] Previous studies have shown that H_2-receptor antagonists provide no clinical benefit in the management of peptic ulcer bleeding.[14] Studies that have evaluated the use of intravenous proton pump inhibitors have been confounded by heterogeneity in terms of patient populations studied, the specific regimen of PPI used, and the timing and/or type of endoscopic intervention employed.[7] Despite this, current guidelines recommend that intravenous proton pump inhibitor therapy be used in all patients with high-risk lesions after endoscopic therapy.[11]

2.1 Product Information

Intravenous Esomeprazole (NEXIUM® I.V.) was approved in the United States in 2005 for use in adults for short-term treatment (up to 10 days) of gastroesophageal reflux disease (GERD) in patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with NEXIUM® Delayed-Release Capsules is not possible or appropriate. Based on current labeling, when oral therapy is possible or appropriate, intravenous therapy with NEXIUM® I.V. for injection should be discontinued and the therapy should be continued orally.

Product Name:	Esomeprazole Sodium
Proposed Trade Name:	NEXIUM® I.V.
Pharmacological Class:	Proton Pump Inhibitor
Chemical formula:	$C_{17}H_{18}N_3O_3SNa$
Molecular weight:	367.4 g/mol



Structural formula:

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

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no other approved treatments for this indication: (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers (aka PUB).

2.3 Availability of Proposed Active Ingredient in the United States

Currently the active ingredient, Esomeprazole, is available in the U.S. by prescription in oral and intravenous forms for a number of indications including: treatment of gastroesophageal reflux disease (GERD); risk reduction of NSAID-associated gastric ulcer; *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; and pathological hypersecretory conditions including Zollinger-Ellison syndrome. The intravenous form is only approved for the treatment of gastroesophageal reflux disease (GERD) with erosive esophagitis (EE) when oral therapy is not possible or appropriate. There are also generics approved for marketing in the U.S. Esomeprazole is marketed by AstraZeneca as NEXIUM®. Esomeprazole has also been combined with NAPROSYN®, a non-steroidal anti-inflammatory drug (NSAID), in VIMOVO® which is also marketed by AstraZeneca.

2.4 Important Safety Issues With Consideration to Related Drugs

As with all medications, proton pump inhibitors should be used at the lowest dose for the shortest duration necessary to treat the condition. Although current labeling for the six proton pump inhibitors (PPIs) approved for use in the US acknowledge common adverse reactions (i.e. headache, abdominal pain, nausea, vomiting, flatulence and diarrhea), the class of drugs is generally well tolerated. Current labeling of Esomeprazole states that the PPI may increase INR and prothrombin time when

administered concomitantly with warfarin. Additionally Esomeprazole may interfere with the absorption of drugs for which gastric pH is an important determinant of their bioavailability and those drugs metabolized by the cytochrome P450 pathways. The labeling of Esomeprazole recommends that a dose of 20mg should not be exceeded for patients with severe liver impairment.

There are a number of potential issues concerning the prolonged use of proton pump inhibitors. Some studies have suggested that PPI therapy, particularly when given long-term and/or in high doses, is associated with several potential adverse effects, including enteric infections (e.g. *Clostridium difficile*) and community acquired pneumonia due to bacterial overgrowth.[15] Other potential areas of concern regarding long-term proton pump inhibitor use have included carcinoid formation; development of gastric adenocarcinoma, and malabsorption of fats, minerals, and vitamins, especially vitamin B_{12}.[16] There have also been concerns about rebound acid secretion following PPI discontinuation leading to dependency on the drug.[17] Recently the labeling of Omeprazole has been updated to reflect the diminished anti-platelet activity of PLAVIX® when administered concomitantly with Omeprazole.[18]

Reflex-mediated elevations in serum gastrin levels occurs secondary to acid suppressive therapy. The increased gastrin levels cause both enterochromaffin-like cell hyperplasia and increased chromogranin A levels.[19] Because gastrin is a trophic hormone, there have been concerns about whether high-doses can affect the onset and development of conditions such as colon cancer in people who are genetically predisposed.[20]

Under the Food and Drug Administration Amendments Act (FDAAA), the full prescribing information for each drug in the PPI class was revised to include language regarding the increased risk of hypomagnesemia and increased risk of fractures of the hip, wrist, and spine in patients taking proton pump inhibitors for prolonged periods of time. The greatest risk of fractures was reported in those taking high doses of proton pump inhibitors or those treated for more than 12 months.[21] Likewise low serum magnesium levels were seen most often in patients taking the medication for longer than one year.[22]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

May 29, 2008 – Original efficacy supplement submitted for the new proposed indication

November 26, 2008 – Complete Response Action for Clinical and Statistical deficiencies. The primary efficacy results in the single non-U.S. study (D961DC00001) do not provide substantial evidence of efficacy. Recommendations to address the deficiencies were:

- Conduct at least one additional adequate and well-controlled study to demonstrate the proposed benefit of NEXIUM I.V. for (b) (4)

(b) (4)

- Consider if the dose evaluated in the pivotal trial was adequate to achieve the desired efficacy. Conduct an additional dose finding study in the target population to evaluate dose optimization.
- Study site 0102 in the Netherlands, which reported the greatest treatment effect will need to be inspected by the Division of Scientific Investigations (DSI).
- Conduct a pharmacokinetic study in sufficient number of patients with hepatic impairment and include matching healthy subjects as controls.
- Submit a pediatric plan
- Submit Safety update as described in 21CFR 314.50(d)(5)(vi)(b) to include data from all nonclinical and clinical data trials of the drug under consideration regardless of indication, dosage form, or dose level

March 26, 2009 – The applicant requested a meeting to discuss issues conveyed in the complete response letter.

June 11, 2009 – Type C meeting held between the Division and applicant to discuss a path forward for the application. The Division rejected (b) (4) The Division also stated that the study data from a published study by Lau, et al could be included but would be considered as supportive only because it was a single center trial and was not conducted using Esomeprazole. The Division proposed that one path forward would be for the applicant to review and reanalyze the data from previously conducted well-controlled trials using Esomeprazole. The applicant agreed to propose and submit a preliminary response to the CR letter for FDA review.

July 14, 2009 – The applicant submitted an outline of their proposal for the response to the Complete Response Package

December 03, 2009 – An advice letter was issued to the applicant regarding their proposed complete response proposal.

- Provide supportive data, including clinical study reports (CSRs) for each trial included in the new submission. Submit justification describing how the supportive evidence is similar to that of trial D961DC00001 (the pivotal trial reviewed with the original efficacy supplement submission). Present a summary of a head to head comparison between the submitted trials and D961DC00001 evaluating the patient population, therapeutic endoscopic procedures, dosing of drug, endpoints criteria, and efficacy results.
- Provide criteria used to define a clinically significant rebleeding event in each trial and the timing of all clinically significant rebleeding events

- Provide information on rebleeding events during the first 72 hours post-endoscopy using Forrest's classification criteria. Also provide separate tables for the percent of patients with clinically significant rebleeding events by age, race, gender for each trial.
- Provide additional supportive evidence of efficacy for specified variables:
  - Proportion % (n) of mortalities within 72 hours and 30 days
  - Proportion % (n) who had surgery due to a rebleeding event within 72 hours and 30 days
  - Proportion % (n) who had endoscopic re-treatment due to a rebleeding event within 72 hours and 30 days
  - Number of blood units transfused within 72 hours and 30 days
- Provide complete case report forms (CRFs) for patients who died, sustained a serious adverse event (SAE) and/or rebleeding event at any time during the trial.
- Provide datasets in a format similar to those in the original submission.

September 16, 2010 – Applicant's resubmission following the complete response is received.

2.6 Other Relevant Background Information

This section is not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the current submission is adequate for review. During the process of the review, there were 4 information requests and one teleconference with the applicant to clarify information presented in the resubmission package.

3.2 Compliance with Good Clinical Practices

A single pivotal study was submitted in support of the original NDA application. Study D961DC00001 was an international randomized, double-blind, placebo-controlled trial and only foreign data were submitted. The study was conducted in 16 countries and 91 centers randomized patients. A DSI inspection of the site with the largest treatment effect (Site 102) in the Netherlands was requested by the Division. No significant deficiencies were observed during the DSI inspection and according to the DSI consult, the study data appear reliable.

3.3 Financial Disclosures

There were no additional financial disclosures with the current submission. During the last review cycle one investigator, Dr. Ernst J. Kuipers, reported receiving significant financial payments. This investigator site was the subject of a DSI inspection in the current cycle. Reference is made to section 3.2.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no new data related to CMC presented in the current application. No CMC labeling changes were provided. During the first review cycle, CMC recommended approval of the application.

4.1.1 Product Quality Microbiology

Please refer to the Product Quality Microbiology reviews of Dr. Bryan S. Riley dated March 23, 2011, and May 4, 2011, for additional details.

The labeling for this product allows this product to be stored at room temperature for extended periods. However there were no microbiology stability data provided to support the proposed holding conditions. The microbiology reviewer concluded that this application was approvable pending resolution of the following product quality microbiology deficiencies:

- The applicant should provide microbiological data that shows that the reconstituted product solution will not support microbial growth during the proposed storage periods (6 or 12 hours).
- The applicant should provide a risk assessment summarizing studies that show that adventitious microbial contamination does not grow under the proposed storage conditions.
- Tests should be run at the recommended storage conditions proposed in the label. If this data is not provided, the labeling should recommend that the admixture storage period is not more than 4 hours at room temperature.

Following review of the sponsor's reply to a solicited information request, the microbiology reviewer recommended approval of the submission.

4.2 Clinical Microbiology

Other clinical microbiology considerations do not apply because this product is not intended for use as an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

There were no new preclinical pharmacology/toxicology data presented in this resubmission. During the prior review cycle, the application was recommended for approval from a preclinical standpoint.

4.4 Clinical Pharmacology

The reader is referred to the clinical pharmacology review by Dr. Dilara Jappar, dated May 28, 2011 for additional details.

During the first review cycle for this application, the clinical pharmacology reviewer, Dr. Tien Mien Chen, noted several deficiencies that needed to be addressed by the applicant. The initial clinical pharmacology reviewer noted limitations in the dose ranging study (D9615C00015). Most notably, results of the dose ranging study showed that the dosing regimen chosen for the Phase 3 trials did not result in a desirable gastric pH range. The reviewer suggested that the applicant conduct a new dose ranging study in the target population for better dose selection and that the applicant evaluate pharmacokinetics, pharmacodynamics, and clinical outcomes in both the intravenous and oral treatment phases. The reviewer noted that patients with moderate and severe hepatic impairment were excluded from the pivotal trial. It was recommended that the applicant either conduct a PK trial in patients with various degrees of hepatic impairment against matching healthy control or revise the labeling with restrictions for use of intravenous Esomeprazole in patients with hepatic impairment. The clinical pharmacology reviewer also noted that because of the higher dose being administered, there was a higher potential for interactions with co-administered drugs that are metabolized by CYP2C19. There was also the potential for interaction with a different set of drugs whose absorption are affected by gastric pH. The clinical pharmacology reviewer recommended that the labeling be revised to reflect the lack of a drug-drug interaction study for the new dosing regimen.

In the complete response letter, the applicant was asked to provide bridging data between intravenous Omeprazole and intravenous Esomeprazole to demonstrate that the two drugs have comparable PK and PD profiles. Establishing the comparability of the two products would justify the use of trials conducted with Omeprazole in support of the efficacy of Esomeprazole for the proposed indication. The clinical pharmacology reviewer for this resubmission concluded that the C_{max} and AUC_{τ} of Esomeprazole were 14% higher compared to Omeprazole when administered as the continuous infusion proposed by the sponsor. Both drugs reduced intragastric acidity and there were no

statistically significant differences between the treatments administered. The clinical pharmacology reviewer also concluded that there was less inter-individual variability in percentage of time with intragastric pH>4 and AUCτ for Esomeprazole compared to Omeprazole. The reader is referred to the clinical pharmacology review for additional details.

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

The reader is referred to the clinical pharmacology review for additional details.

In the complete response letter the applicant was asked to consider whether the dose evaluated was adequate to achieve the desired efficacy. In the original submission, the desired pH was not achieved by a substantial proportion of patients in the first 24 hours of treatment and was not sustained for a prolonged duration of time.

The applicant acknowledged that the level of intragastric pH observed in the two PK/PD studies may have contributed to the lack of robustness of the treatment effect. However, the applicant asserts that studies were conducted in *H. pylori* negative patients in whom it would be more difficult to suppress intragastric acidity. The applicant states that the acid suppressive effect of the proposed dosing regimen for Esomeprazole can be expected to be more pronounced when given to patients with peptic ulcer bleeding. However, this argument appears to assume that the majority of patients with peptic ulcer bleeding will be H. pylori negative. This is not necessarily the case, especially with the high prevalence of NSAID induced gastric ulcers.[23] The applicant also argues that treatment with intravenous Omeprazole (80mg bolus, followed by 8mg/hr as a continuous intravenous infusion) given to patients with bleeding gastric and duodenal ulcers resulted in a rapid increase to intragastric pH>6 and was maintained throughout the remainder of the 24-hour treatment period. The applicant argues that in the current submission, the comparative PK/PD study showed that intravenous Esomeprazole 80mg bolus followed by 8mg/hr resulted in at least as pronounced effect on intragastric pH as the corresponding dosage regimen of intravenous Omeprazole. Consequently the applicant maintains that intravenous Esomeprazole will result in a level of acid suppression sufficient to achieve the desired efficacy. The clinical pharmacology reviewer concluded that the percentage of time that intragastric pH>4, pH>5, and pH>6 was slightly longer for Esomeprazole and the difference increased with higher pH cut-off levels. However, the differences between the treatments were not statistically significant. Additionally the 24-hour median intragastric pH was similar for both

Esomeprazole and Omeprazole. Overall there were no major differences between intravenous Esomeprazole and intravenous Omeprazole given as an 80mg bolus over 30 minutes and followed by continuous infusion of 8mg/hr for 23.5 hours.

Of note, *in vitro* studies conducted by Green, et al, showed that "at pH 6.4, assays of the intrinsic and extrinsic coagulation systems, the polymerization of fibrinogen, and assay of the availability of platelet factor 3 were twice prolonged over control values."[12] Theoretically, even if the proposed regimen is able to achieve a significant proportion of time with intragastric pH above 6, the target pH level may still be below that which is necessary to definitively alter hemostasis

4.4.3 Pharmacokinetics

The reader is referred to the clinical pharmacology review for additional details. The applicant was asked to conduct a pharmacokinetic study in a sufficient number of patients with hepatic impairment and include matching healthy subjects as controls. The applicant states that they have not performed any study with intravenous Esomeprazole in patients with hepatic impairment. However, a study with the oral preparation has been conducted in the population and was submitted in the original NDA. (b) (4) The data from this study showed a 70% higher AUC and a 30% higher Cmax than that seen in healthy patients. (b) (4)

Previous studies have shown that low dose Omeprazole at 4mg/hr after an initial 80mg bolus is effective at maintaining a pH consistent pH between 4 and 6.[10] However, there was a relative amount of inter-subject variability in AUC. (b) (4) Given the lack of PD data to demonstrate efficacy of the proposed dose and the fact that there is no evidence to suggest that this dose would achieve the desired outcomes, additional safety and efficacy data with the intravenous preparation in hepatically impaired patients may be required.

The reader is again referred to the clinical pharmacology review for additional details. The clinical pharmacology reviewer concluded that the proposed loading dose of 80mg over 30 minutes for all degrees of hepatic impairment appeared acceptable (b) (4) (b) (4) However, the clinical pharmacology reviewer still maintained concerns regarding the proposed constant intravenous infusion rate of (b) (4) in patients with moderate impairment and 4mg/hr in patients with severe hepatic impairment. The clinical pharmacology reviewer

recommends that the applicant use PK and PD modeling and simulation to estimate the proper constant infusion rate for patients with moderate and severe hepatic impairment.

5 Sources of Clinical Data

The reviewer's table below summarizes the randomized controlled studies using intravenous Esomeprazole and intravenous Omeprazole submitted in support of this application. The first study D961DC00001 was submitted during the first review cycle and will not be reanalyzed. It was presented here to allow the reader to compare study designs for the trial conducted with intravenous Esomeprazole and those conducted with intravenous Omeprazole.

5.1 Tables of Studies/Clinical Trials

Trial Name	Trial Type	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population
D961DC00001 (TRIAL 01)	Safety and Efficacy	Multicenter International Prospective Randomized Double-blind, Parallel Group, Placebo-controlled	Esomeprazole (a bolus 80mg over 30 min followed by a continuous infusion of 8mg/hr for 71.5 hours) or Placebo Follow-up treatment after I.V. Esomeprazole with Oral Esomeprazole 40mg once daily for 27 days	767 Randomized 764 Treated	Patients who had undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer classified as Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment modalities varied.)
Lau, et. al.	Safety and Efficacy	Single Center (Hong Kong) Randomized Double-blind, Parallel Group Placebo-controlled	Omeprazole (a bolus intravenous injection of 80mg over 30 min followed by a continuous 8mg/hr infusion for 71.5 hours) or Placebo Follow-up therapy after I.V. Omeprazole infusion with oral 20mg Omeprazole once daily for 8 weeks	320 Planned 240 Randomized	Hospitalized Patients who had undergone successful endoscopic treatment of a bleeding peptic ulcer. Forrest Class Ia, Ib, IIa, or IIb (Endoscopic treatment was injection epinephrine followed by thermocoagulation)
Trial I-840	Safety and Efficacy	Multicenter International Double Blind Parallel Group Placebo Control	Omeprazole 80mg given intravenously as a bolus dose over 30 minutes followed by 8mg/hr for 71.5 hours or Placebo Follow-up therapy after I.V. Omeprazole infusion with oral 20mg Omeprazole once daily for 21 days. (Oral therapy started at 48hours)	350 Planned 274 Randomized	Hemodynamic ally unstable outpatients and inpatients with PUB endoscopically classified as Forrest Ia, Ib, IIa, or IIb. (Endoscopic treatments varied. Pre-entry endoscopic treatment only in patients classified as Forrest Ia or IIa)
Trial I-841 (study stopped prematurely due to safety monitoring)	Safety and Efficacy	Multicenter International Randomized Double-Blind Parallel Group Placebo-Controlled	Omeprazole 80mg given intravenously as a bolus over 30 minutes followed by continuous infusion of 8mg/hr for 3 to 5 days. (If there were signs of bleeding during day 2 or 3 the infusion was given for 120 hours) Follow-up therapy after I.V. Omeprazole with Omeprazole 20mg daily for 21 days	400 Planned 333 Randomized	Patients ≥ 60 years old with endoscopic signs of peptic ulcer bleeding and clinical symptoms of upper gastrointestinal bleeding. (Forrest Ia, Ib, IIa, IIb) (Endoscopic treatments varied. Pre-entry endoscopic intervention was only to be used in patients with bleeding classified as Forrest Ia)

5.2 Review Strategy

The current submission consisted of two components:

- the applicant's responses to address deficiencies outlined in the original CR letter dated November 26, 2008
- the supporting documentation from related compounds and epidemiologic data

The supporting documentation contained the following:

- Data bridging Omeprazole I.V. and Esomeprazole I.V.
- Supporting data from randomized controlled clinical trials with Omeprazole I.V.
- Observational studies with Omeprazole I.V.
- A systematic review and metaanalysis of available clinical studies with Omeprazole I.V. in peptic ulcer bleeding
- Supporting Esomeprazole I.V. data including outcomes of PUB treatment in routine clinical practice
- A summary of published systematic reviews of available literature on clinical studies with PPIs

The strategy for this second review cycle consisted primarily of reviewing the applicant's responses to the original CR letter and the supporting documentation, after consideration of the clinical pharmacology reviewer's assessment of the data bridging I.V. Omeprazole and Esomeprazole. Reference is made to the clinical pharmacology review of Dr. Dilara Jappar. Reference is also made to the statistical review of Dr. Lisa Kammerman.

During a Type C meeting with the Agency, the Agency suggested that the applicant review and analyze data from previously conducted well controlled trials using Esomeprazole. Omeprazole trials would be considered supportive only. The Agency stated that the data should come from trials designed to minimize bias and include a similar target population, inclusion criteria, exclusion criteria, primary efficacy measures and drug dose administration as used in study D961DC00001. This was also communicated to the applicant in an advice letter. In addition, the applicant was asked to provide criteria used to define a clinically significant rebleed in each trial and the time when a clinically significant rebleeding event happened for all occurrences.

In the supporting document, the applicant included the clinical study reports for three previously conducted trials using Omeprazole I.V. as treatment. The trial conducted by Lau et al, hereafter referred to as the Lau trial, will be reviewed in detail in section 5.3.

Two of the trials (Trial I-840 and Trial I-841) were excluded from the efficacy analysis. The clinical reviewer examined the trial protocol synopsis and the clinical study reports for these studies. (Refer to Section 5.1 above for summary information.) In the opinion of this reviewer, the designs of these trials were substantially different from the original

pivotal study (D961DC00001) with regards to treatment regimen, patient population, and primary endpoint. Therefore trials I-840 and I-841 did not appear to provide supportive evidence for the indication sought. In the pivotal trial, treatment consisted of either I.V. Esomeprazole or placebo administered over 72 hours followed by oral Omeprazole therapy for 27 days. In trial I-840, oral therapy with 20mg of Omeprazole was started after 48 hours of the 72 hour intravenous infusion. In study I-841, intravenous infusion therapy was permitted up to day 5 if a patient bled within the first 3 days. In addition, because both trials were conducted in the 1990s, there were no standardized endoscopic treatment regimens for these trials.

(b)(4) The pivotal trial was designed to include patients with and without high-risk stigmata for rebleeding at time of endoscopy. Patients enrolled in trials I-840 and I-841 do not reflect the patient population for which the sponsor is seeking an indication. In the literature, all Forrest classifications carry some risk of rebleeding. In the pivotal trial, all patients classified as Forrest Ia, IIa, Ib, and IIb underwent diagnostic and interventional endoscopy to achieve hemostasis prior to initiation of the infusion therapy. In trial I-840, only patients classified as Forrest Class Ia and IIa underwent intervention to achieve hemostasis. In trial I-841, only patients classified as Forrest Class Ia, underwent intervention to achieve successful hemostasis and received treatment. Additionally, all patients enrolled in trial I-841 were over the age of 60 years. As stated previously, increased age is associated with a higher risk of rebleeding and complications from peptic ulcer bleeds. If the drug demonstrated efficacy, the older patient population may confound outcomes resulting in a larger treatment effect favoring the treatment group because all patients would be at higher risk for rebleeding events..

Information requests were generated to address the differences in the endoscopic treatment regimens and differences noted in the patient population. The applicant's responses dated February 14, 2011, February 18, 2011, and April 6, 2011, provided additional clarity for the reviewer. The applicant asserted that 137 patients randomized in trials I-840 and I-841 were treated with endoscopic modalities comparable to those in the original pivotal trial (Trial D961DC00001). In some cases, a patient who had received an injection agent not used in the original trial was included The applicant stated these patients fulfilled the inclusion criteria of Trial D961DC00001 and there were no exclusion criterion in the trial that would exclude patients who, in addition to receiving endoscopic therapy as specified in the clinical study protocol for D961DC00001, also received other endoscopic therapy. However, in the original protocol of trial D961DC00001, there were restrictions concerning endoscopy. Specifically, the protocol stated that "Endoscopic treatment with modalities not mentioned in Section 3.3.2 (of the protocol), inclusion criterion no. 5, e.g. Argon plasma coagulation, injection of water, thrombin, fibrin glue or sclerosing agents (lipidocanol, ethanol), is not allowed."

In order for Trials I-840 and I-841 to be supportive of the pivotal trial, the endoscopic treatment regimens should be comparable to those submitted in the original trial.

Following review of the applicant's responses to the solicited information requests, it was determined that of those patients enrolled in I-840 and I-841 combined, only 52 of the 137 patients suggested for inclusion by the applicant, received an endoscopic treatment that was allowed in D961DC00001. Of these 52 patients, 38 received epinephrine injection only which is not consistent with past or present standard of care guidelines for endoscopic treatment of peptic ulcer bleeds. The applicant acknowledged that endoscopic injection therapy was not standardized during the conduct of these trials and cited a study by Park, et al, to support their argument that different endoscopic therapies appear to have similar efficacy.[3] However, the Park, et al, article concluded that there are differences in endoscopic treatment modalities. Specifically, the authors concluded that 1) the addition of a second modality to epinephrine is superior to epinephrine alone 2) mechanical therapy alone with either hemoclips or thermal therapy using a heater probe is similar to combination therapy with epinephrine and 3) combination therapy with injection therapy is superior to cautery using bipolar coagulation alone.[3] The applicant also included 9 patients in this group, for whom the agent used during the injection therapy was not known. After excluding the 38 patients who received epinephrine injection therapy only, 14 patients remained that clearly matched the enrollment and treatment criteria of trial D961DC00001.

Despite the inconsistencies in treatment provided, the reviewer reviewed the efficacy and safety of the 52 patients from trials I-840 and I-841. The results demonstrated that 13.6% (3/22) patients in the omeprazole group experienced a clinically significant rebleeding event as opposed to 23.3%(7/30) in the placebo group. These findings represents a fraction of the patients from the original studies and are not statistically significant (p=0.49) based on the analysis provided by the statistical reviewer. Baseline demographics for those 52 patients are provided below. The reviewer notes that there were baseline discrepancies in these groups. Patients in the omeprazole group had a higher mean age and a higher percentage were over the age of 65 years. There were also marked differences in the proportion of patients classified in each of the Forrest groups and more patients in the placebo group presented in shock.

Table 2 Baseline Demographics for 52 patients in Trials I-840 and I-841 who received the same endoscopic treatment as Pivotal Trial

Characteristic	Omeprazole Group (n = 22)	Placebo Group (n = 30)
Male Sex – no. (%)	10 (45.5%)	18/30 (60%)
Female Sex – no. (%)	12 (54.5%)	12/30 (40%)
Mean Age – (years)	70.5	68.3
Patients ≥ 65 years – no. (%) < 65 years – no. (%)	17/22 (77.3%) 5/22 (22.7%)	19/30 (63.3%) 11/30 (36.7%)
Mean Hemoglobin (g/L) (Standard Deviation)	82.9 (32.3)	95.8 (32.4)
Number of Patients with Shock at Presentation	18/22 (81.8%)	26/30 (87%)
Number of Patients with Endoscopic Signs of Rebleeding Spurting Hemorrhage (Forrest Class Ia) Oozing Hemorrhage (Forrest Class Ib) Nonbleeding Visible Vessel (Forrest Class IIa) Clot with underlying vessel (Forrest Class IIb)	 2/22 (9.1%) 8/22 (36.4%) 1/22 (4.5%) 11/22 (50%)	 5/30 (16.7%) 9/30 (30.0%) 7/30 (23.3%) 9/30 (30.0%)
Number of Patient with Duodenal ulcer Gastric ulcer	 13/22 (59%) 9/22 (41%)	 15/30 (50%) 15/30 (50%)
Number of Patients with A Previous Ulcer	10/22 (45.4%)	17/30 (56.7%)
Number of Patients with A Previous Ulcer Complication	3/22 (13.6%)	3/30 (10%)
Number of Patients with Each Risk Factor for Bleeding Peptic Ulcer (%) Use of Cox-2 NSAID Use of Aspirin Use of Warfarin	 2/22 (9.1%) 5/22 (22.7%) 1/22 (4.5%)	 1/30 (3.3%) 6/30 (20%) 1/30 (3.3%)

Finally the clinical reviewer examined the primary outcomes for each of the trials. The primary outcome measures for I-840 and I-841 were markedly different from that of the original pivotal study. In trial I-840, the primary endpoint was overall outcome of treatment. Each patient was ranked for his/her worst outcome according to a predefined graded scale which included death, operation, additional endoscopic treatment, more than 3 units of blood transfused after initial endoscopic treatment, and 0 to 3 units of blood transfused after initial endoscopic treatment. The time to endoscopy was not standardized in this trial. In the literature, patients with bleeding more than 48 hours prior to presentation have a lower risk of recurrent bleeding.[24] Finally in trial I-840, clinically significant rebleeding was defined as slight, moderate, or severe and no objective definitions were provided for markers of hypotension. In trial I-841, the primary objective was achieved through assessment of the total number of blood transfusions and overall outcome of treatment (including death, operation, endoscopic treatment, and number of blood transfusions). The objective measures for hemodynamic instability were vaguely defined with a different threshold for hemoglobin drop as that used in trial D961DC00001.

Trial I-841 was omitted from the review because of differences in the trial design as described above. Furthermore, the applicant stated that trial was terminated prematurely after 333 patients had been randomized due to a substantial imbalance between treatment groups in the number of deaths. The mortality rate was 6.9% in the omeprazole group and 0.6% in the placebo group. This trial does not provide additional support for the applicant's efficacy claim and the increase in mortality may also be concerning for a potential safety signal. (Refer to Section 7 below.)

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Overview of Protocols Submitted Under Supplement 14

The applicant submitted clinical data from a trial conducted in Hong Kong in 2000 by Lau. et al, using Omeprazole I.V. in support of the current application. The clinical trial was conducted at a single center at the Chinese University of Hong Kong, Prince Wales Hospital and was funded by an academic research grant. The exact study protocol was not available for review. Following a solicited information request, the applicant provided the academic research application for this trial which included information on the clinical study protocol. This study will be referred to as the "Lau trial" hereafter. The results of this study were published in the New England Journal of Medicine and will also be referred to during this review.

The following tables provide a summary of the original trial submitted during the first review cycle and the clinical criteria used to define rebleeding. This is provided for comparison purposes only. Tables 5 and 6 provide summary information on the Lau trial. Additional efficacy data are provided in Section 6 along with the applicant's responses to the complete response letter.

Table 3 Summary of the Pivotal Trial D961DC00001 contained in the Original NDA submission dated May 29, 2008

Study # and Period	**D961DC00001 (October 30, 2005 – December 14, 2007)**
Design	International, randomized, multicenter, prospective, double-blind, parallel group, placebo controlled
Primary Objectives	To compare, in subjects with Peptic Ulcer Bleeding (PUB) after successful endoscopic hemostasis, the efficacy of 72 hours continuous intravenous infusion of either Esomeprazole or placebo at preventing rebleeding by assessment of the rate of clinically significant rebleeding during the intravenous treatment period.
Key Secondary Objectives	To compare, in subjects with PUB after successful endoscopic hemastasis, 72 hours continuous I.V. infusion of either Esomeprazole or placebo with regard to the following, where time period begins at start of I.V. treatment: • Rate of clinically significant rebleeding within 7 days and 30 days • Proportion of mortalities within 72 hours and 30 days • Proportion of "bleed-related" mortalities within 30 days, based on assessments by the Endpoint Committee • Proportion of subjects who, within 72 hours and 30 days, had surgery (except endoscopic treatment) due to rebleeding • Number of blood units transfused within 72 hours and 30 days • Number of days hospitalized due to rebleeding within 30days • Safety and tolerability
Treatments	(AFTER successful endoscopy) Intravenous Esomeprazole 80mg (0.5hr)+ 8mg/hr (71.5hr) or Placebo I.V. 80mg (0.5hr)+8mg/hr (71.5 hr) followed by Esomeprazole Oral 40mg once daily (27days)
**Endoscopic Treatment*	Endoscopic treatment administered for the PUB of all enrolled subjects having Forrest classification Ia, Ib, IIa, and IIb. Successful hemostasis required for study inclusion. Successful hemostasis (considered to have been established if bleeding was stopped and, if applicable, formerly bleeding vessels were flat or cavitated and must be achieved by endoscopic treatment with injection therapy (epinephrine, dilution 1:10000) and/or one of the following: coagulation with heater probe, electrocautery, hemoclips. Endoscopic treatment with modalities not mentioned (e.g. argon plasma coagulation, injection of water, thrombin, fibrin glue or sclerosing agents (lipidocanol, ethanol) is not allowed. Routine "second look" endoscopy without clinical signs of rebleeding is not allowed.
Number of Enrollees Planned (Number Enrolled)	Planned: 760-800 of both sexes (10 – 25 per center) Randomized: 767 Treated: 764
Primary Efficacy Parameters	Clinically significant rebleeding within 72 hours of continuous infusion of Esomeprazole or placebo (yes or no).
Key Secondary Efficacy Parameters	Clinically significant rebleeding within 7 days and 30 days Death within 72 hours and 30 days Death related to rebleeding within 30 days as judged by the Endpoint Committee Requirement for surgery within 72 hours and 30 days Requirement for endoscopic re-treatment within 72 hours and 30 days Number of blood units transfused within 72 hours and 30 days Number of days hospitalized due to rebleeding during the 30-day treatment phase
Key Tolerability Parameters	Adverse events, clinical laboratory findings, physical examination, vital signs including blood pressure and pulse.
Sample Patient Population	Patients who have undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer Key Inclusion Criteria / Key Exclusion Criteria

Study # and Period	**D961DC00001 (October 30, 2005 – December 14, 2007)**	
	Upper gastrointestinal bleeding (hematemesis, melena, or hematochezia) or with such sign within the last 24 hours as judged by the investigator	Malignancy or advanced disease with a life expectancy of <6months as judged by the investigator
	One endoscopically confirmed bleeding gastric or duodenal peptic ulcer, at least 5mm in diameter, classified as Forrest Ia, Ib, IIa, or IIb. Photo documentation of the source of bleeding is required. In the case of Forrest class IIb, all efforts should be made to remove the clot. If the clot cannot be removed, it is to be handled as follows: • If the clot can be removed with 5min of high-pressure water irrigation or by cold snare, the ulcer should be reclassified and only Forrest Ia, Ib, and IIa should be included • If the clot cannot be removed despite these measures, the subject should be included as Forrest IIb	American Society of Anesthesiology Classification of Physical Status of physical status > 3 as judged by the investigator
	Successful hemostasis (which is considered to have been established if bleeding has stopped and, if applicable, formerly bleeding vessels are flattened or cavitated) achieved by endoscopic treatment with injection therapy (epinephrine, dilution 1:10000) and/or coagulation with heater probe, electrocautery, or hemoclips	Severe hepatic disease defined as Child-Pugh B or C
		Major cardiovascular event at enrollment or within 3 months prior to study start, such as stroke, myocardial infarction, or hospitalization for treatment of unstable angina pectoris as judged by the investigator
		Hemorrhagic disorder, platelets <100X10^{9}/L, INR.1.5, APTT>1.5XULN, treatment with low-molecular weight heparin
		Endoscopic suspicion of gastric malignancy or juxta pyloric stenosis as judged by the investigator.
		Sign of multiple bleeding peptic ulcers or concomitant other gastrointestinal bleeding from esophageal varices, reflux esophagitis, gastritis, Mallory Weiss tears, ulcus implex, Dieulafoy's lesions, colon, small bowel, or ulcer distal to the stoma in Billroth-resected subjects
		Need for treatment during the first 7 days of the study with NSAIDS, COX-2 inhibitors, ASA (including low dose) and clopidogrel
		Chemotherapy within two weeks prior to study start or planned during the course of the study
Key Changes in Protocol Amendment 1	• Overall study time table changed and estimation of study date completion extended to 2007. • The number of patient enrolled increased from 2000 to 2500. • Section 3.3 "Exclusion criteria" modified to include statement that "Intravenous administration of a PPI (Esomeprazole, Omeprazole, lansoprazole, rabeprazole, or pantoprazole) exceeding a total dose of 40mg within 24 hours prior to enrollment" • Section 3.6 "Pre-study, concomitant and post-study treatments" section modified to state that intravenous administration of a PPI exceeding a total of 40mg within 24 hours prior to enrollment is not allowed	

Source: Reviewer's Table

As stated above in the table above, the primary objective was determined by assessing the rate of clinically significant rebleeding during the intravenous treatment period (i.e. the first 72 hours after achieving hemostasis). The table below outlines the diagnostic criteria for clinically significant rebleeding used in the trial.

Table 4 Diagnostic criteria for clinically significant rebleeding for Study D961DC00001

Rebleeding Diagnosed by:	Criteria for diagnosis
A. Endoscopy Endoscopy: initiated by clinical signs of rebleeding defined as: a. one of B1 or B2 or B3 AND Endoscopic verification, i.e. one of A1 or A2 (It is the result of the endoscopy that defines if there is rebleeding or not.)	A1: Blood in stomach (this criterion cannot be used during the first 6 hours after primary endoscopic hemostasis). A2: A verified active bleeding from a peptic ulcer (Forrest Ia, Ib).
B. Clinically A true clinically based definition, at least two of B1 and/or B2 and/or B3	B1: Vomiting of fresh blood or fresh blood in a gastric tube or hematochezia or melena after a normal stool. B2: Decrease in Hgb>20g/L (or Hct >6%) during 24 hours or an increase in Hgb <10g/L (or Hct <3%) despite ≥ 2 units of blood has been transfused during 24 hours. B3: Unstable circulation systolic blood pressure ≤ 90 mmHg or pulse ≥ 110/min (after having had a stable circulation)
C. Hematemesis	C: Vomiting significant amounts (>200 mL) of fresh blood as estimated by the investigator.

Table 5 Summary of the Lau Trial

Study # and Period	**Lau, et al May 1998 – July 1999**
Design	Double-blind, placebo-controlled, randomized
Study Centers	Prince of Wales Hospital
Primary Objectives	To examine whether maximal acid suppression, i.e. 72 hours of continuous intravenous (I.V.) infusion of Omeprazole followed by Omeprazole oral 20mg daily reduced the incidence of rebleeding after endoscopic hemostasis within 30 days after endoscopy compared to placebo for 72 hours followed by Omeprazole 20mg oral daily for 8 weeks.
Treatments	(AFTER successful endoscope) Either 80mg bolus injection of Omeprazole OR equivalent placebo followed by continuous infusion of Omeprazole 8mg/hr for 72 hours. After 72 hours H. pylori positive patients receive oral Omeprazole 20mg b.i.d, clarithromycin 500mg b.i.d, and amoxicillin 1gm bid for 1 week. H. pylori negative patients receive oral Omeprazole 20mg daily for 4 weeks.
**Endoscopic Treatment*	(Performed within 24 hours of admission) Endoscopes: Dual channel scopes XQ-2T200 or 2T10. Dual therapy of epinephrine injection AND heater probe coaptive thermocogulation: Epinephrine injection (1:10,000) in 0.5 to 1mL aliquots using a 21 or 23 gauge injection needle around and into bleeding point, followed by 3.2 mm heat probe tamponade (30 Joules 3-4 continuous pulses onto bleeding vessel). Successful endoscopic treatment defined by the cessation of bleeding and flattening or cavitation of bleeding vessel.
Number of Enrollees Planned/Enrolled/Completed	320 (160 patients in each arm) planned 240 (120 patients in each arm) enrolled 239 Completed the trial.
Primary Efficacy Parameters	Recurrent bleeding within 30 day after endoscopy.
Key Secondary Efficacy Parameters	Late rebleeding; i.e. beyond 72 hours and day 28 / Number of blood units transfused within 30 days Early rebleeding, i.e. by 72 hours / Hospital stay (Duration of hospitalization within 30 days) Rebleeding requiring surgery within 30 days / Death (of any cause including rebleeding) within 30 days Ulcer healing at 4-week / In-hospital and 30-day mortality Rebleeding defined as • fresh hematemesis, • hypotension (SBP <90, tachycardia PR>110) and melena • drop of Hemoglobin by 2gm/dl in 24hours and melena (documentation required by repeat endoscopy showing coffee ground materials or fresh blood in the stomach and the presence of stigmata in ulcer floor)
Sample Patient Population	Patients who have undergone successful endoscopic treatment of a bleeding gastric or duodenal ulcer **Key Inclusion Criteria** / **Key Exclusion Criteria** Patients with bleeding peptic ulcers; ulcer actively bleeding or with major stigmata of visible vessels (protuberant discolorations in ulcer bases) and clots (Forrest I, IIa, and IIb ulcers) seen at endoscopy within 24 hours of their admissions. / Presence of an inter-current ulcer complication precluding endoscopic treatment such as gastric outlet obstruction or ulcer perforation mandating surgical intervention Age ≥ 16 years / Mor bound patients e.g. patients with terminal illnesses or malignancy Endoscopic hemostasis achieved /

Clinical criteria were used in the Lau trial to initially diagnose patients who had recurrent bleeding. Those criteria are outlined in the table below and similar to those used in trial D961DC00001. Like trial D961DC00001, patients suspected of having recurrent bleeding underwent urgent endoscopy. "Recurrent bleeding was confirmed if the ulcer was actively bleeding (spurting or oozing hemorrhage) or if there was either coffee ground material or flesh blood in the stomach near a vessel."[25]

Table 6 Clinical Criteria used to define rebleeding in the Lau Trial,

Vomiting of fresh blood
Drop in hemoglobin of more than 2 grams/dL within 24 hours after transfusion to a level of 10grams/dL.
Shock: defined as SBP≤90mm Hg or Pulse ≥110beats/min with melena after stabilization

5.3.2 Clinical Overview of The Lau Trial

There were 240 patients enrolled in the Lau trial (120 in the Omeprazole arm and 120 in the Placebo arm). Summaries of demographic and baseline characteristics are provided below. These data were confirmed by the reviewer using the applicant's submitted dataset. Baseline characteristics were similar between the treatment groups and provided in the table below. Patients within the placebo group were slightly older and there were more patients in the placebo group who had coexisting illnesses. As stated previously, an increased risk of rebleeding and poor outcomes is associated with increasing age, comorbid illnesses, ulcer size, hemodynamic instability (i.e. shock, low initial hemoglobin level, requirement for blood transfusions), and poor overall health status. The older and sicker population in the placebo group could result in more favorable outcomes for Omeprazole. However, in the opinion of this reviewer, it is unlikely that the outcomes were influenced by these factors because the differences were small. In addition, baseline hemoglobin levels and ulcer size were roughly the same for both groups. There were actually more patients in the treatment arm who would be classified as Forrest Class 1a (which carries the highest risk of rebleeding). This would actually favor the placebo. The treatment arm also contained more patients that were *H. pylori* positive and used aspirin. These imbalances would favor the placebo group. In summary, although the baseline risk factors for rebleeding were not completely balanced, it appears that the overall baseline risk of rebleeding is not substantially different between the treatment groups.

Table 7 Baseline Characteristics of the Patients enrolled in the Lau Trial.

Characteristic	Omeprazole Group (n = 120)	Placebo Group (n = 120)
Male Sex – no. (%)	80 (66.7%)	80 (66.7%)
Female Sex – no. (%)	40 (33.3%)	40 (33.3%)
Mean Age – (years)	64 ±17.2	67 ± 15.9
Patients ≥ 65 years – no. (%)	76 (63.3%)	80 (66.7%)
Mean Hemoglobin (g/L)	9.4 ± 2.7	9.5 ± 2.6
Number of Patients with Shock at Presentation (defined as SBP ≤ 90mm HG or pulse ≥110 beats per minute) (%)	16 (13.3%)	14 (11.7%)
Number of Patients with Endoscopic Signs of Rebleeding		
Spurting Hemorrhage (Forrest Class Ia)	14 (11.7%)	9 (7.5%)
Oozing Hemorrhage (Forrest Class Ib)	50 (41.7%)	49 (40.8%)
Nonbleeding Visible Vessel (Forrest Class IIa)	38 (31.7%)	36 (30.0%)
Clot with underlying vessel (Forrest Class IIb)	18 (15.0%)	26 (21.7%)
Number of Patients with High-risk ulcers		
Posterior duodenal ulcer	17 (14.2%)	15 (12.5%)
Lesser curvature gastric ulcer	12 (10%)	5 (4.2%)
Angular incisura ulcer	11 (9.2%)	11 (9.2%)
Size of ulcer (cm)	1.2 ± 1.1	1.1 ± 0.8
Number of Patients with Ulcers ≥ 2cm	21 (17.5%)	25 (20.8%)
Number of Patients with A Previous Ulcer	38 (31.7%)	45 (37.5%)
Number of Patients with A Previous Bleeding Ulcer	36 (30%)	36 (30%)
Number of Patients with Each Risk Factor for Bleeding Peptic Ulcer (%)		
Helicobacter Pylori Infection	78 (65%)	64 (53%)
Use of NSAID	39 (32.5%)	40 (33.3%)
Use of Aspirin	23 (19.2%)	18 (15.0%)
Use of Warfarin	5 (4.2%)	5 (4.2%)
Number of Patients with Coexisting Illnesses (%)	30 (25%)	40 (33.3%)
Cerebrovascular disease	8 (6.7%)	13 (10.8%)
Chronic renal failure	8 (6.7%)	4 (3.3%)
Cardiovascular disease	3 (2.5%)	9 (7.5%)
Cancer	11 (9.2%)	14 (11.7%)
Endoscopic treatment		
Dose of epinephrine (ml)	11 ± 4	11.8 ± 5
Median number of probe pulses	8	7

Source: Lau JYW, Sung JJY, Lee K, Yung , et al "Effect of intravenous Omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers" *New England Journal of Medicine*.2000;343(5) 310-316.

In trial D961DC00001, the primary efficacy variable was "clinically significant rebleeding within 72 hours of continuous infusion of Esomeprazole or placebo (yes or no)". However, the primary outcome in the Lau trial was recurrent bleeding within 30 days following endoscopy. The proportion of patients having clinically significant rebleeding within the first 72 hours was measured as a secondary outcome. A summary of the primary and secondary efficacy results from the Lau trial have been provided in the table below. More patients in the placebo group relative to the Omeprazole group experienced recurrent bleeding by days 3, 7, and 30. Most of the enrolled study

participants who experienced clinically significant rebleeding did so within the first 72 hours. All of the results were statistically significant. (Please refer to the statistical review of Dr. Lisa Kammerman. The p-values listed in this table were reported from information requested from the statistical reviewer or reproduced from the publication of the Lau trial results.[25])

The Lau publication reported the primary efficacy outcomes stratified by those patients who had active bleeding ulcers and those who had ulcers with nonbleeding visible vessels. The results were statistically significant for both groups. The applicant's current analyses combines Forrest Class Ia and Ib in one group and Forrest Class IIa and IIb in a second group. When the results were stratified by each of the Forrest categories individually, the treatment effect was fairly consistent across categories; however, the results were only statistically significant for Forrest Class Ib. (Refer to the reviewer's Table 8 below.) The small treatment effect (7.9%) observed in Forrest Class Ia may be secondary to the small number of study participants in that group.

This reviewer conducted exploratory analyses examining the percentage of patients with clinically significant rebleeding within the first 72 hours by age and gender. An analysis based on race was not applicable given that the racial and ethic background of this trial was uniform. While gender did not seem to have an impact on the rate of rebleeding, it appears that patients 65 years of age and older experienced more clinically significant bleeding within the first 3 days following endoscopy compared to patients less than 65 years of age. This is consistent with literature reports. Notably, the three patients in the treatment group who died within the first 72 hours were also over the age of 65 years.

Although more patients in the placebo arm compared to the Omeprazole arm died within 30 days, this difference was not statistically significant. Again this is consistent with reports in the literature that have concluded that reducing the risk of rebleeding after endoscopic therapy does not significantly affect mortality.

Table 8 Efficacy Results for the Lau Trial.

Efficacy Outcome		Omeprazole (N = 120)	Placebo (N = 120)	P Value
Number of patients with recurrent bleeding (%)				
By Day 3 (72 hours)		5 (4.2%)	24 (20.0%)	<0.001
By Day 7		7 (5.8%)	26 (21.7%)	<0.001
By Day 30*		8 (6.7%)	27 (22.5%)	<0.001
Recurrent Bleeding Within 30 days by Forrest Class (# patients/total #)				
Active bleeding ulcers (Forrest Ia + Ib)		3/64 (4.7%)	10/58 (17.2%)	0.04
Forrest Class Ia		2/14 (14.3%)	2/9 (22.2%)	1.00
Forrest Class Ib		1/50 (2.0%)	8/49 (16.3%)	0.02
Ulcers with nonbleeding visible vessels (Forrest IIa + IIb)		5/56 (8.9%)	17/62 (27.4%)	0.02
Forrest Class IIa		3/38 (7.9%)	9/36 (25.0%)	0.06
Forrest Class IIb		2/18 (11.1%)	8/26 (30.8%)	0.17
Recurrent Bleeding Within 3 days by Sex (#patients/total #)				
Male		2/80 (2.5%)	14/80 (17.5%)	
Female		3/40 (7.5%)	10/40 (25%)	
Recurrent Bleeding Within 3 days by Age (#patients/total#)				
≥ 65 years old		5/76 (6.6%)	21/80 (26.3%)	
< 65 years old		0/44	3/40 (7.5%)	
Recurrent Bleeding Within 30 days by Sex (#patients/total #)				
Male		5/80 (6.3%)	17/80 (21.3%)	<0.001
Female		3/40 (7.5%)	10/40(25.0%)	0.06
Recurrent Bleeding Within 30 days by Age(#patients/total#)				
≥ 65 years old		6/76 (7.9%)	24/80 (30.0%)	<0.001
< 65 years old		2/44 (4.6%)	3/40 (7.5%)	
Mean number of units of blood transfused within 30 days after endoscopic therapy (Standard Deviation)		1.7 (1.9)	2.4 (3.2)	0.03
Number of patients who died (%)				
Within 3 days		3/120 (2.5%)	0/120	
Within 30 days		5/120 (4.2%)	12/120 (10.0%)	0.13
Number of patients who had surgery due to rebleeding (%)				
Within 3 days		1/120 (0.8%)	5/120 (4.2%)	
Within 30 days		3/120 (2.5%)	8/120(6.7%)	
Number of patients who had endoscopic retreatment for rebleeding (%)				
Within 3 days		4/120(3.3%)	21/120 (17.5%)	
Within 30 days±		6/120 (5%)	23/120 (19.1%)	<0.001
Total Number of hospitalization days from date of endoscopy until the date of discharge		757	859	

Sources: Reviewer's Table Derived from Applicant's Table 2 Supporting Documentation p. 16 – 17 and Lau Table 2 p.313 - Lau JYW, Sung JJY, Lee K, Yung , et al "Effect of intravenous Omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers" *New England Journal of Medicine*.2000;343(5):310-316.

*This number is the total number of patients in the group who had recurrent rebleeding within 30 days after treatment

±In the applicants analysis, there were 2 additional patients included n the placebo group for whom initial hemostasis was never achieved. The p-value remained statistically significant.

The applicant was asked to provide case report forms for the patients in the trials who died or had serious adverse events and/or rebleeding at any time while on the study. While the case report forms for the Lau trial were provided in the complete response resubmission, the treatment group assignments for patients were not provided.

Although intravenous Esomeprazole is currently approved and marketed for use in the U.S., the sponsor's proposed dosing regimen is not a part of the current labeling. An assessment of safety would reveal if administering the proton pump inhibitor as an 80mg I.V. bolus followed by a continuous infusion of 8mg/hour for 71.5 hours would result in new adverse events not currently in the approved labeling. Like trial D961DC00001 conducted with Esomeprazole, the total dose PPI (omeprazole) in the Lau trial was 652 mg over a 72-hour period (268mg in the first 24 hours and 384mg over the following 48 hours).

The applicant noted that the pharmacokinetic properties of Esomeprazole are different from those of Omeprazole, resulting in higher exposures (AUC) for Esomeprazole compared to Omeprazole following repeated oral administration. The applicant also stated that the PK differences between Esomeprazole and Omeprazole are less pronounced when the drugs are administered as once daily I.V. doses compared to oral administration (40% to 70%). The PK differences, although still statistically significant, are further decreased when the drugs are administered intravenously as an 80mg bolus followed by continuous infusion of 8mg/h (14% for AUC and C_{max}). Although one would have to factor in the formulation used, because Esomeprazole exposures are higher than Omeprazole exposures, there would be no reason to anticipate a new safety signal would have arisen in the Lau trial that was not evident in trial D961DC00001. In addition, during the follow-up period of trial D961DC00001 a higher dose of oral Esomeprazole was administered (40mg/day) for 27 days. (The Lau trial administered 20 mg/day of oral Omeprazole for 8 weeks.)

An adverse event dataset was not provided with the Lau trial for review.
In the original review of D961DC001, the reviewer noted the most common adverse events in both treatment groups (placebo and Esomeprazole) were related to rebleeding, the primary efficacy outcome. The reviewer also noted that infusion site reactions were more common in the Esomeprazole treatment group compared to the placebo group. However, the events were mild, of short duration, and did not cause discontinuation of study drug. The original reviewer noted that although the alkaline phosphatase values increased to a slightly higher degree in the Esomeprazole treatment group, overall the adverse event profile for intravenous Esomeprazole did not differ from that expected in acutely ill patients with peptic ulcer bleeding. Given the similarities in dosing administration and anticipating that exposures would be higher for Esomeprazole relative to Omeprazole, it is likely that the adverse event profile in the Lau trial would not have been substantially different (if not better) than that which was demonstrated in trial D961DC00001. In summary, given the information available to this reviewer, one may assume that there would not be any additional safety signals from

the data in this resubmission package, that are not currently part of labeling. However, the reader must bear in mind that the majority of the trial data is from randomized trials conducted with Omeprazole. There is still a small possibility that a new safety signal could arise with Esomeprazole in this study population. There are no controlled trials to confirm or refute this assumption.

In the publication by Lau et. al., they state that "no side effect related to the infusion was reported in either group."[25] There were five patients in the Omeprazole group who died within 30 days after the initial endoscopy. Twelve patients in the placebo group died within 30 days of the initial endoscopy to achieve hemostasis. None of the five deaths in the Omeprazole group were caused by recurrent bleeding.[25] Four of the patients in the placebo group died after surgery (three following gastrectomy for recurrent bleeding and one after excision of a perforated ulcer). Two patients in the placebo group who were deemed unfit for surgery, died from recurrent bleeding. The remaining six patients died from complications related to the concurrent illnesses. All but two patients in the Omeprazole group and four patients in the placebo group completed follow-up assessments at 8 weeks. Biopsies of the ulcers from three patients revealed cancer (two in the Omeprazole group and one in the placebo group).

Case report forms from the Lau trial were reviewed. However, the absence of accompanying narratives and treatment groups limits the utility of the information provided. A sampling of the data from the case report forms is presented in the table below.

Table 9 Reviewers Summary of Deaths and Serious Adverse Events in the Lau Trial

Patient Number	Treatment	Verbatim Terms for SAE	Reviewers Summary Narrative
(b) (6)	??	Recurrent GI bleeding Pneumonia Death	Patient was an 84 year old male with a past medical history of bladder cancer (s/p surgery). There was no prior history of UGI bleed and he was H. pylori negative. Patient was had been on Voltaren but no aspirin use. Presented to ED on (b) (6) with melena and a hemoglobin of 4. He was admitted for GI bleeding, transfused with 4 units of blood, and underwent emergent endoscopy which revealed a small amount of coffee ground debris in the stomach, mild reflux esophagitis and a 1.5 cm duodenal ulcer with a visible vessel. Hemostasis was achieved with 8cc of adrenaline and thermocoagulation. On hospital Day 2, patient developed melena, chest pain, and a drop in his hemoglobin (14.3 to 10.7). Interestingly the patient did not undergo repeat endoscopy until hospital day 3 after his hemoglobin dropped to 8.8 and SBP 90/50. After repeat endoscopic intervention failed to result in hemostasis, the patient underwent emergent surgery to control bleeding. Patient died on Hospital day 13 of pneumonia.
(b) (6)	??	Acute Myocardial Infarction Pulmonary Tuberculosis Urinary Tract Infection Death	Patient was a 76 year old male with a past medical history of complete heart block (s/p pacemaker placement in 1993), congestive heart failure, dementia, diabetes mellitus, and primary tuberculosis. He was H. pylori negative and did not have a previous ulcer history however he was taking aspirin regularly. Patient initially presented on (b) (6) with melena and hypotension. He was admitted to the hospital for heart failure but underwent endoscopy on the day of admission which revealed a stomach full of coffee ground/food debris, several non-bleeding pre-pyloric ulcers, extensive ulceration of the duodenum and active bleeding of a 2cm ulcer on the posterior wall of the D1/D2. Hemostasis was achieved after injection of 9mls of adrenaline and thermocoagulation. On hospital Day 2, patient developed fresh melena and hypotension and underwent repeat endoscopy but did not require additional intervention. The patient was discharged from the hospital on (b) (6) He subsequently died on (b) (6) The causes of death were noted to be recurrent acute myocardial infarction, urinary tract infection, and pulmonary tuberculosis. However, there were no details provided on the interim time period between time of discharge and time of death.
(b) (6)	??	Lymphoma Possible LGI Bleed Cerebrovascular Accident Death	Patient was a 68 year old male with a history of lymphoma and coagulopathy. Patient was H. pylori positive and had a history of NSAID use. During inpatient hospitalization for treatment of his lymphoma, he developed melena and hypotension. He was transfused with 6 units of blood and underwent endoscopy where fresh blood and clots were seen in the stomach. Bleeding of a 3cm ulcer was

			controlled with injection of 20ml of epinephrine and thermocautery. The course is unclear. However, it appeared as if the patient had persistent GI bleeding. A repeat endoscopy on hospital Day 3 was showed revealed no UGI bleeding. The endoscopist questioned if the patient has mucosal bleeding due to thrombocytopenia from a lower GI source. The patient died on hospital day 4. The cause of death was malignant lymphoma, cerebrovascular accident, and gastrointestinal bleeding.
(b) (6)	??	Cerebrovascular Accident Bronchopneumonia Death	Patient was an 82 year old male with a history of gallstones, gastric ulcers (with bleeding), myeloproliferative disorder, thrombocytopenia, "chest infection", and fracture of right femur. He was admitted for a viral gastroenteritis, diarrhea, and severe dehydration. Four days later he developed melena. An endoscopy revealed a 0.1 – 0.4cm gastric ulcer with an adherent clot. After injection with epinephrine, the clot was removed and hemostasis of the bleeding vessel was achieved with a heater probe. On hospital Day 8, patient had an ischemic stroke. During the hospitalization, the patient also developed a bronchopneumonia and was treated with ciprofloxacin for 7 days. The patient died on hospital day 12. The cause of death was bronchopneumonia.
(b) (6)	??	Death	Patient was an 84 year old male with a past medical history of hypertension, emphysema, renal impairment, and stroke. The patient was an aspirin user but had no prior history of ulcers or NSAID use. The patient was admitted up UGI bleeding. Initial endoscopy revealed light "coffee ground stain" in the stomach and a 0.3cm duodenal ulcer showing a visible vessel. Hemostasis was achieved with 10cc of epinephrine and thermocoagulation. The patient was discharged on hospital Day 5. He died approximately 23 days later prior to the follow-up visit. The cause of death was listed as pneumonia, however no additional details were provided.
(b) (6)	??	Death	Patient was a 76 year old female with a history of hypothyroidism (s/p thyroidectomy), community acquired pneumonia, left knee pain (on NSAID), and coagulopathy. Patient was admitted for fever, cough, complicated by upper GI bleed. Endoscopy revealed moderate amount of coffee ground debris in the stomach. There were multiple 0.5cm – 1cm ulcers in the gastric antrum with old clots. There was also a 1 cm gastric ulcer showing visible vessel with adherent clot. Hemostasis was achieved with 8 ml of epinephrine and thermocoagulation. Multiple duodenal ulcers were noted but none showed signs of hemorrhage. Later the patient developed hypotension, respiratory failure, multiorgan dysfunction and appeared to be in septic shock. She was started on antibiotics but continued to deteriorate and died 3 days after admission. The cause of death was sepsis from unknown cause.
(b) (6)	??	Recurrent UGI bleed	Patient was a 62 year old male with a past medical history of I.V. drug use and ulcer. He was admitted for gastrointestinal bleeding after presenting with melena and

			hypotension. Initial endoscopy revealed coffee ground clots in the stomach and a 1.5 cm ulcer with a visible vessel in the first part of the duodenum. Hemostasis was achieved with 8ml of epinephrine and thermocautery. On hospital Day 4 patient developed hypotension (SBP<80) and a drop in hemoglobin. A repeat endoscopy revealed large amount of fresh clots in the fundus of the stomach, a bleeding 2cm duodenal ulcers (Forrest Class IIa). Hemostasis was again achieved with epinephrine and thermocoagulation. Patient was able to complete the follow-up visit at 8 weeks. There were no additional details available
(b) (6)		Recurrent UGI bleeding Recurrent UGI bleeding	Patient was a 73 year old male with a history of Hepatitis C, cirrhosis, ascites, and coagulopathy. He also had a previous history of ulcer disease but was H. pylori negative. Patient was admitted for gastrointestinal bleeding after he presented with melena and hypotension. Initial endoscopy revealed blood clots in the stomach; a 0.1-0.4 cm ulcer in the first part of the duodenum with no signs of hemorrhage; grade 1 esophageal varices with no signs of hemorrhage; and a pseudodIverticulum in the first part of the duodenum. The endoscopy also revealed a 1.5 cm duodenal ulcer showing with a blood clot and visible vessel. Hemostasis was achieved with adrenaline and thermocautery. The CRF is unclear and there were several corrected errors. However, it appears that the patient experienced persistent hypotension and a drop in hemoglobin which lead to a repeat endoscopy on the following 2 days. The endoscopy on hospital Day 2 revealed a 2 cm duodenal ulcer with “brisk” spurting blood. Hemostasis was achieved with epinephrine, thermocautery, and hemoclips. Repeat endoscopy on Day 3 showed a large duodenal ulcer with a large vessel traversing along the ulcer floor with a hemoclip. The ulcer appeared to be healing over the hemoclip. There was slight oozing of the ulcer on pretreatment with epinephrine. Heat was reapplied to the ulcer. This episode was not considered as a rebleed, but it’s unclear why. Patient again bled on hospital Day 12. Endoscopy revealed coffee ground blood in the stomach and a 1 cm bleeding duodenal ulcer. Hemostasis was achieved with 9ml of epinephrine and thermocautery. The patient was discharged 7 days later. At the 8 week follow up visit, repeat endoscopy showed healed ulcers.
(b) (6)	??	Recurrent UGI bleeding Dieulafoy's lesion	Patient was a 69 year old with a past medical history of anemia, dehydration, functional tachycardia, and influenza pneumonia. There was no prior history of ulcers, coagulopathy, NSAID or aspirin use. The patient was initially hospitalized for dizziness but subsequently developed hematemesis. Endoscopy revealed coffee ground blood in the stomach and a 1 cm gastric ulcer showing a visible vessel. Hemostasis was achieved with 8cc of epinephrine and heater probe. On day 3 following the initial endoscopy, the patient developed hematemesis and tachycardia.

			Repeat endoscopy revealed large amounts of blood clots in the stomach. After failed attempts to achieve hemostasis, an urgent laparotomy with excision of Dieulafoys lesion was performed. It appears as if the patient was discharged 9 days later on (b) (6) However, there is no follow up information available. It also appears that that the patient was still hospitalized as of (b) (6)
(b) (6)	??	Recurrent UGI bleeding Recurrent UGI bleeding	Patient was a 76 year old male with a history of smoking, emphysema (on steroids). There is no mention of a history of cardiovascular disease, however, the patient has reported aspirin use. Patient was H. pylori positive. He was admitted for UGI bleeding after presenting with melena. Endoscopy revealed a 1.5cm gastric ulcer with a visible vessel. Hemostasis was achieved with 6 mls of epinephrine and thermocoagulation. The patient rebled the following day. Repeat endoscopy revealed a large amount of blood clots in the stomach with a 3 cm bleeding ulcer. Hemostasis was again achieved with 13 ml of epinephrine and heat. The following day, the patient experienced another episode of recurrent bleeding and underwent surgery to achieve hemostasis. He was discharged on hospital day 24. No follow-up information was available.
(b) (6)	??	Recurrent UGI bleeding Death	Patient was a 68 year old male with a history of non-insulin dependent diabetes mellitus, sinus tachycardia admitted for pneumonia. There was no prior history of ulcer, coagulopahty, NSAID use, or aspirin use. During the hospitalization he developed melena, hypotension. Endoscopy revealed multiple duodenal ulcers. The CRF reports a “huge DU in the posterior wall of the stomach from D1 down to D2” covered with “black slough”. This was more likely a duodenal ulcer. Notwithstanding, one visible vessel was identified. Hemostasis was achieved with 11mls of epinephrine and thermocautery. The CRF is somewhat unclear. It appears that the initial endoscopy on (b) (6) was negative. It then appears that the patient experienced bleeding (as evidenced by a drop in hemoglobin) on July 1, within the first 24 hours of the initial endoscope. However, there are two endoscopy reports dated (b) (6) It is also documented on the CRF that neither early or late rebleeding occurred. A third endoscopy report dated (b) (6) was significant only for scarring at the D1/D2 junction with a circumferential ulcer. The hospital course is unclear but it appears as if the patient developed an aspiration pneumonia, was transferred to the I.V.U and started on antibiotics, but subsequently died on (b) (6) (b) (6) The cause of death is listed as septicemia of uncertain etiology.
(b) (6)	??	Recurrent UGI bleeding	Patient was a 76 year old male with a history of hypertension, arthritis (on allopurinol), and cerebrovascular accident. There are several errors and correction in the case report form. There was no history of a coagulopathy. It appears as if the patient was on aspirin and concurrent H2 blocker and PPI therapy. From the CRF, it

			appears that the patient was admitted for loss of consciousness on April 20. He later developed melena and underwent endoscopy on (b) (6) The endoscopist noted coffee grounds in the stomach. There was a 1.5 cm ulcer at the anterior wall of the antrum with a visible vessel. Hemostasis was achieved with epinephrine and theromocautery. There was no recurrence of rebleeding with the first 72 hours of endoscopy. Later the patient vomited large amounts of blood and underwent an anterior gastrotomy and excision of the gastric ulcer to control bleeding. The patient was discharged on (b) (6) and there was no follow-up visit noted.
(b) (6)		Recurrent UGI bleeding Death	Patient was a 54 year old male with a history of hypertension and liver disease (? Hepatocellular carcinoma s/p right lobectomy and cholescystectomy). Patient also had a previous history of ulcer disease and GI bleeds. He was not taking warfarin, aspirin, or NSAIDs. Patient was admitted on (b) (6) for evaluation of a gastrointestinal bleed after he presented with melena. He was noted to have a coagulopathy on admission. Initial endoscopy on (b) (6) revealed coffee ground debris in the stomach and a >2.0 cm duodenal ulcer with a spurting blood vessel. Hemostasis was achieved with 11cc of epinephrine and thermocoagulation. It appears as if the patient did well and was discharged on (b) (6) He was readmitted on (b) (6) for melena. Endoscopy revealed a small clot in the stomach and fresh blood in the duodenum. There was an oozing duodenal ulcer. Hemostasis was achieved with heat and injection of 8mls of epinephrine. There are no additional details on the 2nd hospitalization. The patient subsequently died on (b) (6) at a separate facility. The cause of death was listed at hepatocellular carcinoma.
(b) (6)	??	Recurrent UGI bleeding Peritonitis Death	The age of this female patient was not provided. She had a history of COAD, cor pulmonale and congestive heart failure. Additionally the patients had a previous history of ulcer disease, active pulmonary tuberculosis, respiratory failure, and drug-induced hepatitis. She was admitted on (b) (6) with melena. Initial endoscopy showed 2 1.5cm duodenal ulcers. Hemostasis was achieved with 19cc of epinephrine and heater probe. The following day the patient developed hypotension after vomiting coffee ground debris. Repeat endoscopy was performed showing a oozing 1.5 cm ulcer in the second part of the duodenum and hemostasis was again achieved with epinephrine and thermocoagulation. According to the autopsy report, following the procedure, the patient had increasing abdominal pain with an X-ray showing surgical emphysema. The patient was diagnosed clinically with peritonitis secondary to heater probe perforation of her intestine. She was managed conservatively and (b) (6)
(b) (6)	??	Death	80 year old male with a history of a stroke, gout, and hypertension. He was admitted for melena and evaluation of GI bleeding. Initial endoscopy revealed 0.1 – 0.4 cm

			ulcer with no signs of hemorrhage. Additionally, there as a 1.0cm gastric ulcer with an oozing visible vessel. Bleeding was controlled with 12 cc of adrenaline and heat. The patient died the following day of respiratory failure but no additional information is provided.
(b) (6)	??	Recurrent GI bleeding	Patient was a 68 year old male admitted with hypotension and melena. Past medical history was remarkable only for nocturnal headaches and convulsions. Initial endoscopy showed several blood clots in the stomach along with a 1.0cm ulcer at the lesser curve of the stomach with a spurting vessel. Hemostasis was achieved with 28cc of epinephrine and heat. The patient had fresh hematemesis the following day. Repeat endoscopy showed fresh blood and clots in the stomach, a 1 cm gastric ulcer with a fresh clot covering an exposed vessel. Hemostasis was achieved with epinephrine and heat. The patient was discharged 3 days later. On repeat endoscopy at the follow-up 8 weeks later, the ulcer had healed and only antral gastritis was noted.
(b) (6)	??	Multiple Myeloma Death Recurrent Bleeding	77 year old female with a previous history of ulcer disease, hypertension, chronic renal failure and NSAID use. She was admitted for evaluation of melena and gastrointestinal bleeding on (b) (6) Endoscopy revealed blood clots in the stomach; a 5 cm gastric ulcer showing “black sough”; a 5 cm antral ulcer with a blood clot. When the blood clot was removed a spurting vessel was identified. Bleeding was controlled with 25cc of epinephrine and heat. The patient apparently did well and was discharged on hospital Day 5. Prior to the 8 week follow-up visit, the patient was readmitted with hypercalcemia, abdominal pain, and multiple joint pain. She was diagnosed with multiple myeloma. It appears that following discharge from this second hospitalization, she was readmitted a 3rd time for evaluation of a GI bleed. Endoscopy during the 3rd hospitalization showed coffee ground debris in the stomach and gastric and duodenal ulcers without signs of hemorrhage. Biopsies were taken for history but no other intervention was document. The patient subsequently died 2 weeks later. The cause of death was end-stage multiple myeloma.
(b) (6)	??	Recurrent Bleeding	This was a 67 year old female with a past medical history of multiple joint pain (on NSAIDs), congestive heart failure (on digoxin), cerebrovascular accident (on warfarin), and CRHD. She was admitted with melena and GI bleeding. Initial endoscopy revealed fresh and coffee ground blood in the stomach. There was a 1.0 cm ulcer at the anterior wall of the antrum with an adherent clot. The clot could not be removed with washing. Hemostasis of another 1.0 cm ulcer on the posterior wall of the antrum showing an adherent clot and fresh oozing, was achieved with 5mls of epinephrine and heat. The patient’s hemoglobin dropped 2 days later and repeat

			endoscopy was performed. Coffee ground debris mixed with food was noted on endoscopy. Additionally two prepyloric ulcers with oozing were noted. Bleeding was controlled with epinephrine and heat. The patient was discharged 6 days later. At the 8 week follow-up the ulcers had healed and the patient was put on lifelong acid suppressive therapy to prevent ulcer relapse.
(b) (6)	??	Recurrent GI bleeding Abdominal Sepsis Enterocutaneous fistula Death	95 year old female with a possible fall and left shoulder pain (on NSAIDs) prior to admission for melena and GI bleeding. The patient also had a previous history of ulcer disease and bleeding, but there was no additional information available on past medical history. On examination of the CRF, it is unclear if the patient was discharged in May after the initial workup and then readmitted in June for rebleeding. However, it appears that the initial endoscopy on (b) (6) showed a clean stomach and a >2.0cm duodenal ulcer. Bleeding was controlled with epinephrine and heat. The following day, the patient had fresh melena and a drop in hemoglobin. A 5.0 cm ulcer in the first part of the duodenum was noted on repeat endoscopy with a spurting blood vessel. Epinephrine injection was attempted but the patient developed desaturation and shock. The procedure was aborted, the patient resuscitated and rushed to the operating room where a partial gastrectomy was performed to control bleeding. It is unclear if the patient was discharge. However, in June she again developed melena and a drop in her hemoglobin. Endoscopy in June revealed multiple linear erosions and superficial ulcers. There were no stomach ulcers. One "erosion" was oozing and bleeding was controlled with epinephrine only. The patient died in July. The cause of death was uncontrolled abdominal sepsis and enterocutaneous fistula.
(b) (6)	??	Recurrent GI bleeding	This was a 90 year old male with a past medical history of a cerebellar stroke and aspirin use. There was no previous history of chronic NSAID use, coagulopathy, or ulcer disease. He was admitted with melena and anemia. Initial endoscopy showed blood clots in the stomach and a 1.5 cm duodenal ulcer with a visible vessel. Hemostasis was achieved with 8ml of adrenaline and heat. The following day the patient again had melena and hypotension. On repeat endoscopy, coffee ground fluid was noted in the stomach along with fresh clots at the pylorus and in the duodenum. A 1.5cm duodenal ulcer was noted. Thirteen cc's of epinephrine were injected at the site of the previous visible vessel and heat was applied with further flattening and cavitation of the vessel. The patient was discharged 3 days later. The follow-up visit was not completed as the patient's further management was done in China.

Source: Reviewer's Table

6 Review of Efficacy

Efficacy Summary

The applicant submitted five types of data in this resubmission:

- Clinical Pharmacology bridging data between intravenous Omeprazole and Esomeprazole
- Data from the literature and trials conducted with intravenous Omeprazole
- Observational data from use of intravenous Esomeprazole in patients with peptic ulcer bleed
- A systematic review of available trials from any proton pump inhibitor
- Additional observational data from other data sources including healthcare and administrative databases and hospital networks with field-based studies.

In order to support the proposed efficacy claim, the applicant presented bridging data to support the PK/PD comparability between Esomeprazole and Omeprazole. The applicant also submitted supportive data from three randomized controlled clinical trials with Omeprazole I.V. Two of the trials were omitted because of marked differences in study population, design, and outcome. (See Section 5.2 above). The third trial, the Lau trial, demonstrated superiority of Omeprazole over placebo at reducing the rate of recurrent bleeding within 30 days following initial endoscopic treatment for peptic ulcer bleeding. (The treatment effect in the Lau trial was 15.8%. vs. 4.4% in the pivotal trial DC96100001). However, this trial was a single center study conducted in Hong Kong and the results of this trial may not be applicable to populations outside of China. While the standardized endoscopic treatment in the Lau trial may contribute to the robustness of the results and the larger treatment effect seen (compared to that in the pivotal trial), it may limit the generalizability of the trial outcomes. The preferred endoscopic treatment modality may vary between countries as well as within different regions of the same country. In example of this, some have reported that injection of dilute epinephrine has been the main method of achieving hemostasis in Europe, while the application of heat appears to be the preferred strategy in the United States.[7] Furthermore, Asians reportedly have a lower parietal cell mass and there is a higher prevalence of *H. pylori* infection and the cytochrome 2C19 genetic polymorphism, all of which may explain why PPI therapy has been demonstrated to be more efficacious at reducing ulcer bleeding in the population. [26]

In the original complete response, the Division cited issues with the results obtained from the single pivotal trial D961DC00001. The Division stated that highly statistically significant results were not demonstrated and the observed outcomes were not robust when subjected to sensitivity analyses. The Division also cited that there was marked variability in the incidence of rebleeding and treatment effect observed in different

countries and among leading centers. Finally the Agency stated that the pivotal trial lacked internal consistency in demonstrating treatment effect in important secondary efficacy outcomes evaluated in the first 72 hours. The applicant acknowledged the efficacy results in trial D961DC00001 did not reach the level of significance required for a single pivotal study to support approval. However, they maintain that this lack of statistical significance does not suggest a lack of clinically meaningful treatment effect but rather a lack of adequate powering of the trial. The applicant states that they have re-examined the data across subgroups and secondary endpoints and found that the results are consistent and that the variation in treatment effect is consistent with what would be expected by chance alone. The applicant also examined the homogeneity among centers and for patients aged 65 years and older using a Breslow-Day test. The applicant asserts that this analysis demonstrates that the observed variation is due to chance because of the limited sample size. The applicant acknowledged that some of the secondary outcome variables did not show statistically significant results in favor of the treatment group. However, the applicant asserts that because the primary outcome was statistically significant, the null hypothesis could not be rejected nor the efficacy of their product denied. It was the position of the applicant that secondary endpoints should be regarded as supportive only especially in light of all the evidence that showed a positive effect favoring the treatment group.

This reviewer can not comment on the applicant's position on the aforementioned issues as they are statistical in nature. However, the statistical reviewer during the first cycle of this review concluded that no significant country-by-treatment interactions were found based on the Breslow-Day test. The supportive trials conducted with Omeprazole seem to provide little additional information to address the aforementioned statistical issues. The Lau trial was a single center trial in Hong Kong. These results may not be generalizable to the more diverse population of the United States. Additionally there were no analyses done across subgroups. Exploratory analyses were conducted by this reviewer however no definitive conclusions can made on the basis of exploratory analyses. With the exception of Forrest Class Ia, it appears that the results from the Lau trial are consistent across Forrest classes. It also appears that the results are consistent for age and gender. However, there is no information reported in the Lau trial related to outcomes for patients at high-risk for rebleeding at baseline. Like the pivotal trial, there was no mention of how adjusting for multiplicity would occur as it relates to the secondary endpoints. Trials I-840 and I-841 were excluded from the analyses because of differences in study design and conduct which resulted in a limited number of evaluable patients who met enrollment criteria and received similar treatments provided in the pivotal trial. The applicant did provided information on the primary outcomes by study site for these trials. On quick review of the primary outcome results by study site, it appears that the outcomes would have again varied by study sites within the countries.

In the complete response letter, the Division identified additional study design and concerns that limited the ability of the pivotal trial to provide persuasive evidence that Esomeprazole was effective for the proposed indication. The issues were:

- Endoscopic epinephrine injection is not currently an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers.
- Although the inclusion criteria excluded patients with more than a single ulcer, a substantial proportion of the randomized patients had multiple ulcers and there was an imbalance between study arms in prognostic factors favoring the Esomeprazole arm.
- Despite randomization, small imbalances in important prognostic factors were observed between the 2 study arms favoring Esomeprazole treatment arm.
- The lack of exclusion criteria from intravenous administration of proton pump inhibitor within 24 hours prior to enrollment is a potential confounding factor for the observed efficacy outcome.
-

The applicant acknowledged the Division's concerns However, they contend that the pivotal trial demonstrates efficacy and the results are supported in the evidence presented in the supporting documentation. It is the applicant's position that the study protocol did not impose restrictions on the method of endoscopic hemostasis in order to make the results more generalizable across academic as well as community based centers. They report that therapy with epinephrine injection only was administered to 17 to 23% of patients with active bleeding and that post-hoc analysis of the results in the pivotal trial showed that the reduction in rebleeding was similar for single and combination therapy. (The applicant's post-hoc analyses are provided in the figure below.) Finally the applicant stated that the imbalances in baseline demographics only had a marginal effect on the p-values and that even after stratifying on all imbalances, the p-values remain significant. This reviewer can not comment on the appropriateness or validity of the statistical tests performed. However, the reader must be aware that the value of stand-alone injection epinephrine therapy to achieve hemostasis following therapeutic endoscopy has been highly debated. Despite this controversy, neither the 2003 nor the updated 2010 International Guidelines recommend the use of injection only therapy for control of upper GI bleeding.[5,11]

Table 10 Analysis of clinically significant rebleeding within 72 hours with various stratifications, ITT population Trial D961DC00001

Time	Rebleed status	Eso[a] (n=375)	Placebo[b] (n=389)	p-value[c]	p-value[d]	p-value[e]	p-value[f]
72 hours	No rebleed	353(94.1%)	349(89.7%)				
	Rebleed	22(5.9%)	40(10.3%)	0.0260	0.0238	0.0358	0.0376

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Cochran-Mantel-Haenszel test stratified by ulcers size (>2 cm/≤2 cm) (post-hoc analysis)
[d] Cochran-Mantel-Haenszel test stratified by multiple ulcers (single incl. missing/multiple) (post-hoc analysis)
[e] Cochran-Mantel-Haenszel test stratified by Forrest class (Ia/all other classes) (post-hoc analysis)
[f] Cochran-Mantel-Haenszel test stratified by Forrest class (Ia/all other classes), multiple ulcers (single incl. missing/multiple) and ulcer size (>2 cm/≤2 cm), note 15 pts are not included in computing the logit estimator (post-hoc analysis)

Source: Table 1 Applicants Complete Response Document dated June 29, 2010.

The reviewer considered the applicant's analysis across various stratifications. It is not entirely clear why the applicant chose a 2 cm cut-off for the ulcer size. The medical reviewer performed a literature review of the definition of ulcers used in clinical trials. A review of the literature was also conducted to determine the relationship between ulcer formation and clinical outcomes. One metaanalysis reviewing 45 publications, found that in 25 publications an ulcer was defined using a diameter of ≥ 3mm with depth.[27] Some studies have used a diameter of 5mm. The medical reviewer was unable to find any studies assessing the relationship between the risk of developing ulcer-related complications and ulcer diameter. However, it may be reasonable to assume that any true ulcer (an excavation that penetrates through the muscularis mucosa into the submucosa) regardless of size may carry some risk of complication and clinically significant bleeding, even if the severity of the complication can not be predicted.

The applicant states that the protocol required only one bleeding ulcer be present at endoscopy and therefore it was not a protocol violation to include patients with more than one ulcer (non-bleeding) at baseline. Indeed, most endoscopically diagnosed ulcers are asymptomatic. The appearance of the ulcer on endoscopy helps to determine the risk of rebleeding. Allowing patients with multiple ulcers to be included in the trial may render the outcome results uninterpretable. Consider the following; a patient has one ulcer that is Forrest Class Ib on initial endoscopy. There is also an ulcer that may be classified as a Forrest Class IIa and several small ulcers that are Forrest Class IIb. All carry a risk of rebleeding, but only the first two required intervention on initial endoscopy. On clinical presentation alone, the investigator could not assure that a rebleed event was caused by the same ulcer initially requiring intervention unless a repeat endoscopy were performed.

In the applicant's resubmission, they state that the reason for allowing inclusion of patients exposed to standard doses of proton pump inhibitor was based on study operational aspects and concerns over generalizability. They assert that excluding all patients receiving even single doses of an I.V. proton pump inhibitor before enrollment would have complicated recruitment and reduced external validity. This reviewer agrees that not allowing patients who had been on standard doses of oral PPIs prior to study entry may have limited the practicality and feasibility of the study. However, the only approved indication for intravenous Esomeprazole is for the treatment of GERD with erosive esophagitis when oral therapy is not possible. Therefore there would be limited reasons for patients to have received an intravenous PPI therapy prior to study entry. For those patients who had received an intravenous PPI, it would most likely be patients that have received the drug for stress ulcer prophylaxis, a study population which should not be included in a trial of this nature. Furthermore, Dr. Lau and his colleagues published another study in 2007 on the use of Omeprazole before endoscopy in patients with gastrointestinal bleeding. In that trial the authors concluded that infusion of-high dose Omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy.[28] This supports the Division's position that enrolling patients who had received an intravenous PPI could confound the interpretation of the study results.

6.1 Indication

The applicant is seeking the following indication: (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. There are currently no proton pump inhibitors that are approved for this indication.

6.1.1 Methods

This is the second review cycle for this application. During a Type C between the Division and the application to discuss the contents the resubmission package, the Division suggested that the applicant review and analyze data from previously conducted well controlled trials using Esomeprazole. Omeprazole trials would be considered supportive only. The Division also stated that the data should come from trials designed to minimize bias which included similar study populations, inclusion criteria, exclusion criteria, primary efficacy measures and drug dose administration as used in study D961DC00001. The applicant submitted three (3) randomized, control clinical studies with intravenous Omeprazole. The following table, reproduced from the applicant's submission illustrates all of the trials submitted with the current application.

As stated previously in Section 5, trials I-840 and I-841 were omitted from the analysis of this reviewer due to marked differences in the study design. The statistical reviewer also noted her review that studies I-840 and I-841 only contained 52 patients that could

reasonably be compared with patients enrolled in the original trial D961DC00001 based on inclusion criteria and treatments administered. Although the treatment effect favored Omeprazole for the primary endpoint of rebleeding within 72 hours, this difference was not statistically significant (p = 0.49)

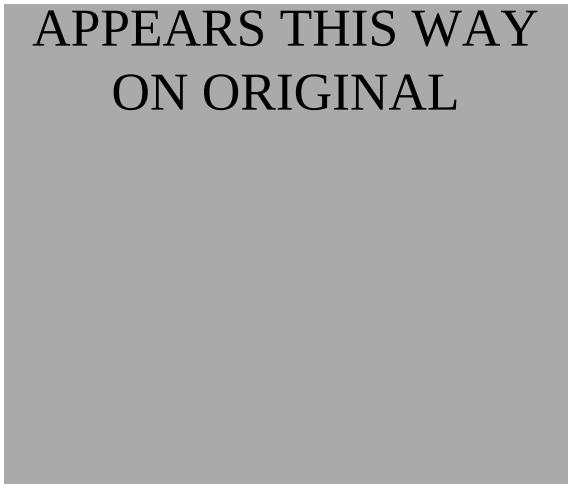


Table 11 Comparisons of Trials Submitted (The Lau trial, I-840, I-841, and trial D961DC00001)

	Lau, et. al. 2000	I-840	I-841	D961DC00001
Definition of endpoint criterion	Fresh hematemesis Hypotension: Systolic Blood Pressure<90 Tachycardia PR>110 and Melena Drop in hemoglobin by 20g/l in 24 hours and melena	Moderate: • Hematemesis • Significant amount of coffee grounds or red blood in the nasogastric tube • Hemoglobin falling 16g/l or more • Neither tachycardia or hypertension Severe: • Voluminous hematemesis, red blood in the nasogastric tube or in stools • Unstable circulation or rapid transfusions required to prevent it.	Hemodynamic ally unstable and/or Hb fall>10g/l over 12 hours Fresh Blood (macroscopic in the nasogastric tube or fresh hematemesis) Blood transfusion was necessary to maintain the hemoglobin level.	Blood in the stomach or a verified active bleeding from a peptic ulcer (Forrest class Ia, Ib) **Or** At least 2 of the following: • Vomiting of fresh blood or fresh blood in a gastric tube or hematochezia or melena after a normal stool • Decrease in hemoglobin >20g/l or (hematocrit >6%) despite ≥ 2 units of blood has been transfused during 24 hours • Unstable circulation systolic blood pressure ≤90mm Hg or pulse≥110/min (after having had a stable circulation) **Or** Hematemesis (vomiting of significant amount of (>200ml) of fresh blood)
Therapeutic endoscopic procedures	Injection therapy (epinephrine) followed by captive thermocoagulation with heater probe	Preferably injection technique but thermal coagulation or electrocoagulation allowed	E.g.: sclerotherapy, heater probe	Injection therapy (epinephrine) and/or one of the following: coagulation with heater probe, electrocautery, hemoclips.
Drug and dosing	Placebo or Omeprazole (a bolus I.V. injection of 80mg followed by a continuous infusion of 8mg/hr for 72 hours)	Placebo or Omeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)	Placebo or Omeprazole (a bolus infusion of 80mg over 30mg followed by a continuous infusion of 8mg/hr for 71.5 hours). If signs of rebleeding occurred within 48 hours the continuous infusion was given for 120 hours	Placebo or Esomeprazole (a bolus infusion of 80mg over 30 minutes followed by a continuous infusion of 8mg/hr for 71.5 hours)
Oral Follow-Up Treatment After I.V. treatment	Omeprazole (20mg once daily for 8 weeks)	After 48 hr I.V. therapy, all patients received Omeprazole (20mg once daily until F/U visit Day21)	Omeprazole (20mg once daily until follow-up visit, day 21)	Esomeprazole (40mg once daily for 27 days)

	Lau, et. al. 2000	I-840	I-841	D961DC00001
Inclusion criteria Age (years)	≥ 16 years	>18 years	>60 years	≥18 years
Signs of Gastrointestinal Bleeding	Within 24 hours after admission endoscopy performed	Within 12 hours prior to endoscopy	Within 48 hours prior to admission	Within 24 hours prior to endoscopy
Forrest Classification of Bleeding Ulcers	Ia, Ib, IIa, or IIb	Ia, Ib, IIa, or IIb	Ia, Ib, IIa, or IIb	Ia, Ib, IIa, or IIb
Successful endoscopic hemostasis	Yes	Only Forrest Ia, IIa	Only Forrest Ia	Yes

Sources: Table 9 "Comparisons of the study by Lau et al (Lau et al 2000), studies I-840, I-841 and D961DC00001)" Applicants Supporting Document page 32.
Study Synopsis Trials I-840 and I-841.

Please refer to section 5.3 above for additional details on the Lau trial using Omeprazole I.V. In the complete response letter issued after the first review cycle, the Division recommended that the applicant conduct an additional adequate and well-controlled trial to demonstrate the proposed benefit of Esomeprazole I.V. for the proposed indication. In the complete response resubmission, the applicant cited "substantial practical and ethical challenges" to conducting an additional trial, especially taking into account the existing data that suggest a possible positive effect of high-dose PPI treatment in patients with peptic ulcer bleeding. Current clinical guidelines recommend that an intravenous bolus followed by continuous infusion of PPI therapy be used to decrease rebleeding and mortality in patients that have undergone successful endoscopic therapy.[11]

6.1.2 Demographics

Baseline characteristics for the Lau trial have been presented in detail in Section 5. The following table is a comparison of the baseline characteristics for the Lau trial and trial D961DC00001. Both of the trials enrolled a higher percentage of male study participants. The Lau trial enrolled more patients over the age of 65 years in both treatment groups. In addition, both treatment groups in the Lau trial contained more patients who were hospitalized at the time of upper GI bleeding prior to endoscopy; were in shock at presentation; or on concomitant anticoagulation therapy. The older and sicker population may explain why the Lau trial demonstrated a larger treatment effect in the primary outcome compared to the pivotal trial. It may also account for the differences between trials in mortality within 72 hours and within 30 days.

Differences in treatment effect may be attributable to differences in the pharmacokinetics of the drugs used, baseline demographics, or in the conduct of the trial itself. Interestingly there were more patients classified as Forrest Class Ia in the treatment arm of the Lau trial compared to placebo arm. Forrest Class Ia carries the highest risk of rebleeding. Consequently, this difference may favor the placebo group with respect to outcomes and decrease the treatment effect. (The treatment effect observed in the Lau trial was 15.8%.) In contrast the pivotal trial D961DC00001 enrolled more patients in the placebo arm classified as Forrest Class Ia. This would favor the results for the treatment group. However, the treatment effect in this trial was only 4.4%.

Table 12 Comparison Baseline Characteristics trials D96DC00001 and Lau Trial

Characteristic	Lau Trial		Trial D961DC00001	
	Omeprazole (N = 120)	Placebo (N = 120)	Esomeprazole (N = 375)	Placebo (N = 389)
Gender, n (%)				
Male	80 (66.7%)	80 (66.7%)	254 (67.7%)	268 (68.9%)
Female	40 (33.3%)	40 (33.3%)	121 (32.3%)	121 (31.1%)
Age, years				
Mean (SD)	64 (17.2)	67 (15.9)	62.1 (17.1)	60.2 (17.6)
Min – Max	18 – 99	22 - 95	18 - 95	18 – 98
Patients per age category, n (%)				
< 65 years	44 (36.7%)	40 (33.3%)	182 (48.5%)	210 (54.0%)
≥ 65 years	76 (63.3%)	80 (66.7%)	193 (51.5%)	179 (46.0%)
Shock at Presentation, n (%)				
No	104 (86.7%)	106 (88.3%)	356 (94.9%)	370 (95.1%)
Yes	16 (13.3%)	14 (11.7%)	19 (5.1%)	19 (4.9%)
H. pylori status, n (%)				
Negative	42 (35.0%)	56 (46.7%)	92 (24.5%)	119 (30.6%)
Positive	78 (65.0%)	64 (53.3%)	246 (65.6%)	226 (58.1%)
Trace			18 (4.8%)	26 (6.7%)
Missing			19 (5.1%)	18 (4.6%)
Forrest Class, n (%)				
Ia	14 (11.7%)	9 (7.7%)	28 (7.5%)	40 (10.3%)
Ib	50 (41.7%)	49 (40.8%)	166 (44.3%)	163 (41.9%)
IIa	38 (31.7%)	36 (30.0%)	136 (36.3%)	151 (38.8%)
IIb	18 (15.0%)	26 (21.7%)	42 (11.2%)	34 (8.7%)
Missing	0	0	3 (0.8%)	1 (0.3%)
Ulcer location, n (%)				
Gastric	53 (44.2%)	48 (40.0%)	157 (41.9%)	155 (39.8%)
Duodenal	67 (55.8%)	72 (60.0%)	216 (57.6%)	233 (59.9%)
Missing	0	0	2 (0.5%)	1 (0.3%)
Hemoglobin, g/L				
Mean (SD)	94.5 (27.2)	95 (25.7)	97.7 (24.9)	97.4 (25.9)
Hospitalized at time of UGI bleeding prior to enrollment, n(%)				
Not hospitalized	98 (81.7%)	97 (80.8%)	338 (90.1%)	354 (91.0%)
Hospitalized	22 (18.3%)	23 (19.2%)	37 (9.9%)	35 (9.0%)
Previous history of gastric or duodenal ulcer, n (%)	38 (31.7%)	45 (37.5%)	112 (29.9%)	118 (30.3%)
Previous ulcer bleeding, n (%)	36 (30.0%)	36 (30%)	---	--
Previous complications related to gastric or duodenal ulcer, n (%)	---	---	44 (11.7%)	41 (10.5%)
Medication use prior to enrollment, n(%)				
NSAIDs	39 (32.5%)	40 (33.3%)	151 (40.3%)	157 (40.4%)
Acetylsalicylic acid (dose unknown)	23 (19.2%)	18 (15.0%)	103 (27.5%)	103 (26.5%)
Warfarin	5 (4.2%)	5 (4.2%)	9 (2.4%)	13 (3.3%)

Source: Applicant's Table 10 "Comparison of baseline characteristics at baseline, studies Lau et al, I-840 + I-841 (only endoscopically treated patients), and D961DC00001" p. 36 Supporting Document

6.1.3 Subject Disposition

According the Lau publication, 739 patients were admitted with bleeding peptic ulcers.[25] Of these, 267 patients received endoscopic treatment. "Endoscopic treatment was not required in 472 patients who had ulcers with clean bases or flat pigments."[25] Surgery was required for five patients in whom endoscopic treatment was unsuccessful. There were 22 patients not included in the trial; 10 had terminal cancer, 9 were moribound as a result of concomitant illnesses, and 3 did not provide consent.[25] Two hundred forty were randomized to treatment (120 Omeprazole and 120 placebo). With the exception of one patient in the placebo group, all patients completed their assigned infusion treatment according to the protocol. The eight week follow-up visit was completed for all but two patients in the Omeprazole group and four in the placebo group. According to the article, 85 patients in the Omeprazole group and 83 patients in the placebo group underwent follow-up endoscopy at 8 weeks. The percentage of patients who had ulcer healing at 8 weeks was not significantly different between the two groups (84.7% Omeprazole and 92.8% placebo). Among those who did not undergo follow-up endoscopy, no further bleeding was documented.[25]

6.1.4 Analysis of Primary Endpoint(s)

Peptic ulcer bleeding is a common cause of hospitalization in the United States.[29] Recurrence of bleeding from a peptic ulcer is most likely to occur in the first week following initial endoscopy to achieve hemostasis. The primary endpoint chosen appears adequate. Some articles have held that rebleeding is an independent predictor of mortality.[30]

The primary endpoint in trial D961DC00001 was the presence of clinically significant rebleeding within 72 hours of continuous infusion of Esomeprazole or placebo (yes or no). Likewise the Lau trial also measured clinically significant rebleeding. However the primary efficacy variable was recurrent bleeding within 30 days after endoscopy. Early rebleeding (within the first 72 hours) was measured as a secondary endpoint in the Lau trial as opposed to a primary endpoint in the original trial D961DC00001.

Diagnostic criteria to define clinically significant rebleeding for trial D961DC00001 and the Lau trial were provided in tabular form in Section 5 and in Section 6.1.1. Both trials used similar definitions of hypotension and similar thresholds for decreases in hemoglobin. In both trials, a follow-up endoscopy was performed to confirm the occurrence of rebleeding. However, in the original trial, it was only recommended that confirmatory endoscopy be performed. Clinically significant rebleeding may have also been diagnosed solely on the basis of a predefined clinical definition or hematemesis >200ml. The fact that the Lau trial required repeat confirmatory endoscopy provides additional robustness to the outcome. However, it is unclear whether patients were

required to have fresh hematemesis OR hypotension and melena OR a drop in hemoglobin and melena prior to endoscopy because the full protocol for the Lau trial was not available for review. Notwithstanding, it appears from examining the case report forms from the Lau trial, that patients were not required to have the presence of all 3 criteria prior to repeat endoscopy.

Hematemesis was included in the outcome definition of both trials; however, the Lau trial did not quantify the amount of hematemesis required. It is possible that a patient may have vomited residual blood from the procedure itself or from the placement of the NG tube. However, as stated above, repeat endoscopy was required to confirm recurrence of bleeding and therefore quantification of the amount of hematemesis was not necessary.

The proportion of patients with clinically significant rebleeding within 72 hours (the primary endpoint for D961DC00001) and within 30 days (the primary endpoint for the Lau trial) are presented below for comparison. The reader is referred for Section 5 for additional information on the statistical analysis of outcome results for the Lau trial.

Table 13 Proportion of patients with clinically significant rebleeding within 72 hours and 30 days, Trial D961DC00001 and the Lau Trial

Outcome Variable	Trial by Lau et al		Trial D961DC00001	
	Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)	Placebo (n = 389)
Patients with clinically significant rebleeding within 72 hours, n (%)	5 (4.2%)	24 (20%)	22 (5.9%)	40 (10.3%)
Patients with clinically significant rebleeding within 30 days	8 (6.7%)	27 (22.5%)	29 (7.7%)	53 (13.6%)

6.1.5 Analysis of Secondary Endpoints(s)

There were a number of secondary endpoints in the Lau trial. Secondary endpoints were outlined in Section 5 of this review and are as follows:

- Early rebleeding, i.e. within the PPI infusion period of 72 hours
- Late rebleeding; i.e. beyond 72 hours and day 28
- Blood transfusion
- Hospital stay
- Rebleeding requiring surgery
- Death (of any cause including rebleeding) within 30 days
- In-hospital and 30-day mortality
- Ulcer healing at 4 weeks

The choice of secondary endpoints appears reasonable. In the research application grant (provided in lieu of the protocol), guidelines for the definition of rebleeding are provided. Outcome parameters were monitored daily along with adverse events, concomitant illnesses, concomitant medications, laboratory variables and vital signs.

Guidance related to the secondary endpoints was provided for the investigators in the Lau research grant. This adds some degree of uniformity to the outcomes. Indications for surgical intervention were:

- failed endoscopic hemostasis in spurting hemorrhage
- rebleeding after two attempts at endoscopic hemostasis.

The research grant states that transfusion would be required to maintain a hemoglobin of around 9gm/dl. Furthermore, patients were discharged on the 4th day if they had a stable hemoglobin and return of bowel function. However, there were no objective criteria outlined for “return of bowel function”. In clinical practice, “return of bowel function” may be demonstrated by presence of bowel sounds, passing of flatus or tolerance of oral feeding.

Acceptable forms of endoscopic intervention allowed during the second endoscopy were not outlined. The experience level of the endoscopist and the choice of intervention (e.g. combination therapy with hemoclips and injection vs. thermocautery) may also affect secondary outcome. The number of days hospitalized, transfusion requirements, and need for surgery may be affected by the technique used during the endoscopy.

There was no formal statistical analysis plan provided for how secondary endpoints were analyzed. The reader is referred to Section 5 for additional details on the Lau trial. A comparison of the some of the secondary endpoints is provided in the table below. With the exception of death within the first 72 hours, secondary outcomes favored the treatment arm. This reviewer can not comment on the statistical significance of these results as these analyses were not powered sufficiently to demonstrate statistical significance. Therefore, it is difficult to draw clear conclusions based on these results.
.

Table 14 Secondary Outcomes in the Lau Trial

Outcome Variable	Lau Trial		Trial D961DC00001	
	Omeprazole (n = 120)	Placebo (n = 120)	Esomeprazole (n = 375)	Placebo (n = 389)
Proportion of patients who died within 72 hours, n (%)	3 (2.5%)	0 (0%)	1 (0.3%)	0 (0%)
Proportion of patients who died within 30 days, n (%)	5 (4.2%)	12 (10.0%)	3 (0.8%)	8 (2.1%)
Proportion of patients who had surgery due to rebleeding within 72 hours, n (%)	1 (0.8%)	5 (4.2%)	5 (1.3%)	9 (2.3%)
Proportion of patients who had surgery due to rebleeding within 30 days, n (%)	3 (2.5%)	8 (6.7%)	10 (2.7%)	21 (5.4%)
Number of blood units transfused within 30 days, Mean (SD)	1.7 (1.9)	2.4 (3.2)	1.6 (2.5)	2.4 (4.5)
Proportion of patients who had endoscopic retreatment within 72 hours, n (%)	4 (3.3%)	21 (17.5%0	16 (4.3%)	32 (8.2%)
Proportion of patients who had endoscopic retreatment within 30 days, n (%)	6 (5.0%)	25 (20.8%)	24 (6.4%)	45 (11.6%)

6.1.6 Other Endpoints

This section is not applicable.

6.1.7 Subpopulations

The research grant application states that additional analyses were to be done on the rates of recurrent bleeding in different strata, actively bleeding ulcers and ulcers with major stigmata. This information was not provided in the publication but may have been useful for demonstrating internal consistency across subpopulations. In the Lau trial, there were no analyses done for subpopulations. An analysis of the efficacy results based on the presence (or absence) of high risk stigmata for recurrence of bleeding at initial endoscopy would have been useful. Because the Lau trial was conducted at a single center in Hong Kong, it may have also been useful to stratify the analyses based on H. pylori status and by CYP 2C19 phenotype. Both of these characteristics are reportedly higher in Asian populations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose of the intravenous proton pump inhibitor was studied in both trial D961DC00001and the Lau trial. There is some data to suggest that low-dose intravenous PPI therapy can result in similar efficacy outcomes as high dose intravenous PPI therapy following endoscopic hemostasis.[31]

In the original complete response letter, it was stated that there was inadequate information to permit proper dosing in patients with hepatic impairment. The applicant stated that although, a study with I.V. Esomeprazole had not been done in hepatically impaired patients, a study with oral Esomeprazole had conducted and was submitted in the original NDA file for NEXIUM Delayed-Release Capsules. Additionally the applicant stated that there was a study with intravenous Omeprazole in hepatically impaired patients. The data from that study demonstrated a 70% higher AUC and a 30% higher C_{max} than in healthy adults. The applicant proposed [redacted] (b) (4) Reference is made to the clinical pharmacology review by Dr. D. Jappar. It is recommended that the applicant conduct a modeling and simulation to estimate the proper infusion rates in patients with moderate and severe hepatic impairment.

During the first review cycle, the Agency also recommended that the applicant consider and additional dose finding study in the target population. The applicant asserted that prior PK/PD studies were conducted in *H. pylori* negative patients in whom it would be more difficult to suppress intragastric acidity, therefore it was expected that a more pronounced effect would be seen in those patients that had peptic ulcer bleeding. The clinical pharmacology reviewer concurred with the applicant's explanation and agreed that no further dose finding study in the target population is necessary.

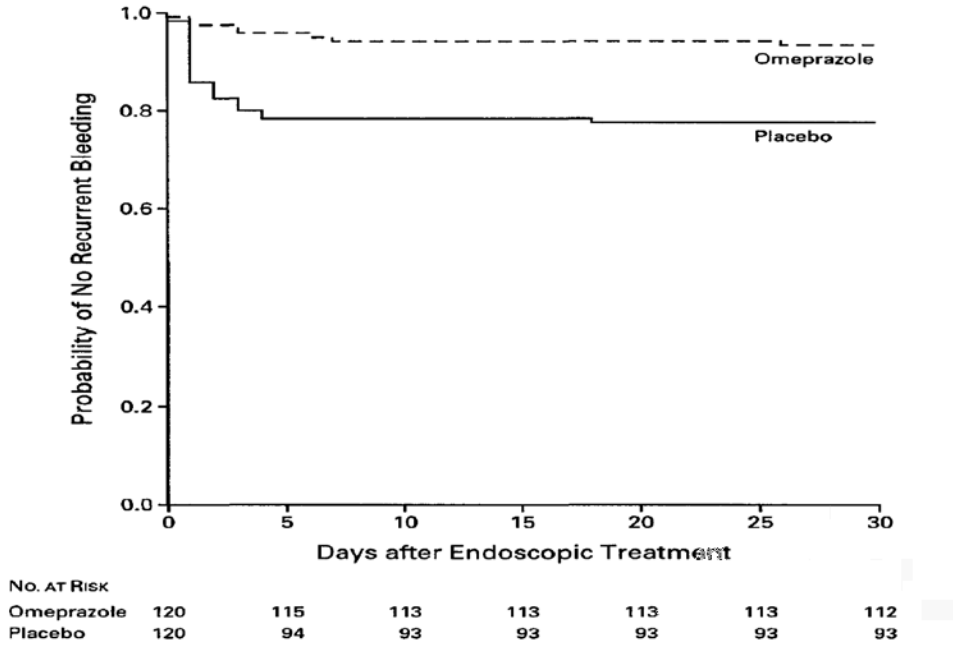
In the opinion of this reviewer, the applicant seems to imply that most patients with peptic ulcer bleeding will be *H. pylori* positive. This may not necessarily be true, especially given the high prevalence of NSAID-induced gastric ulcers. Additionally, in the invitro studies conducted by Green, et al, "at pH 6.4, assays of the intrinsic and extrinsic coagulation systems, the polymerization of fibrinogen, and assay of the availability of platelet factor 3 were twice prolonged over control values."[12] It may be possible that even if the proposed regimen is able to achieve a significant proportion of time with intragastric pH above 6, the target pH level may still be below that which is necessary to definitively alter hemostasis. The addition of a PD parameter to an efficacy trial may provide useful information.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the context of this indication, the administration of high-dose intravenous proton pump inhibitor therapy is considered short-term. The effect of intravenous proton pump

inhibitor therapy on the recurrence of rebleeding seems to plateau after the first 3 – 5 days. There is no data to indicate if this therapeutic effect would diminish over time. This is consistent with the Kaplan-Meier plot presented in the Lau article that estimates the likelihood that rebleeding would occur within 30 days after endoscopic treatment. It is also consistent with the clinical pharmacology conclusion that the PD effect appears to plateau.

Figure 1 Kaplan-Meier Estimates of the Likelihood that Bleeding Would Not Recur within 30 days after Endoscopic Treatment



Source: Lau JYW, Sung JJY, Lee K, Yung , et al "Effect of intravenous Omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers" *New England Journal of Medicine.*2000;343(5):310-316.

6.1.10 Additional Efficacy Issues/Analyses

The applicant included information from an observational cohort study performed in seven European countries at 123 centers. The purpose of the study, which included patients admitted to the hospital between October 1, 2008, and November 30, 2008, was to describe clinical outcomes of current management strategies for non-variceal upper gastrointestinal bleeding. The primary endpoints were continuation of bleeding, rebleeding, surgery, and in-hospital mortality. Patients fulfilling the following criteria were included:

- Adult patients (≥ 18 years) admitted to the hospital, or inpatients admitted for another reason, presenting with overt non-variceal upper gastrointestinal bleeding manifested as hematemesis/coffee ground vomiting, melena, hematochezia and other clinical or laboratory evidence of acute blood loss from the upper gastrointestinal tract over the selection period.

- Evidence that an upper gastrointestinal endoscopy was performed
- Complete medical records related to hospitalizations were available.

The observational nature of the study may overcome many of the issues that make conducting an experimental trial less feasible. However, the results may be difficult to interpret because of lack of a control group. The observational nature of the may also be confounded by selection bias and missing data. In the absence of randomization, there may be differences in the distribution of baseline patient characteristics that affect the outcome. In this observational trial, complete information on the dose of the intravenous PPI administered was not always available. This limits the utility of these results, especially in light of data that suggest that low-dose intravenous PPI therapy may be as effective as high-dose.[31]

Medical records from 2660 enrolled patients were evaluable, of which approximately 374 were reported to have fulfilled inclusion criteria of the pivotal trial, D961DC00001. Of these 374, 142 were on Omeprazole, 107 were on Esomeprazole, and 125 used another PPI. Treatment groups were somewhat similar for baseline demographics. However the Omeprazole group may have been a sicker population at baseline, as more of these patients presented in shock. This may also account for the higher percentage of patients that died in the Omeprazole group. Interestingly, more patients taking Esomeprazole continued bleeding after first endoscopy; continued bleeding or rebleeding within 30 days; and required additional endoscopy. The pharmacokinetic profile (AUC and C_{max}) of intravenous Esomeprazole were noted to be similar to Omeprazole by the clinical pharmacology reviewer, but the outcomes for Esomeprazole were worse in this observational study.

Figure 2 Demographic and baseline characteristics of subsample of patients from Observational Cohort Study NCT00797641 who approximately fulfilled the inclusion criteria in Trial D961DC00001 and were treated with PPI after initial endoscopy

Characteristic	Omeprazole n=142	Esomeprazole n=107	Other PPIs[a] n=125
Gender, n(%)			
Male	95(66.9%)	70(65.4%)	86(68.8%)
Female	47(33.1%)	37(34.6%)	39(31.2%)
Race, n(%)			
Caucasians	142(100%)	99(92.5%)	122(97.6%)
Age, years			
Mean(SD)	65.2(18.9)	66.3(17.8)	65.7(17.2)
Smoker, n(%)			
Non-smoker	118(83.1%)	83(77.6%)	108(86.4%)
Smoker	24(16.9%)	24(22.4%)	17(13.6%)
NVUGIB symptoms, n(%)			
Fresh blood hematemesis	53(37.3%)	36(34.0%)	35(28.0%)
Melena	110(77.5%)	78(73.6%)	91(72.8%)
Shock/syncope	21(14.8%)	10(9.4%)	12(9.6%)
Coffee ground vomiting	17(12.0%)	11(10.4%)	13(10.4%)
Blood up NG tube	4(2.8%)	2(1.9%)	2(1.6%)
Other	8(5.6%)	10(9.4%)	13(10.4%)
Hospitalized at time of upper GI bleeding prior to enrolment, n(%)			
Not hospitalized	119(83.8%)	89(83.2%)	108(86.4%)
Hospitalized	20(14.1%)	14(13.1%)	15(12.0%)
Do not know	1(0.7%)	1(0.9%)	1(0.8%)
Other	2(1.4%)	2(1.9%)	1(0.8%)
Missing	0(0%)	1(0.9%)	0(0%)
Medication at enrollment, n(%)			
NSAIDs	31(21.8%)	24(22.6%)	31(24.8%)
COX-2 selective	2(1.4%)	2(1.9%)	1(0.8%)
Acetyl salicylic acid	46(32.4%)	36(33.6%)	42(33.6%)
Warfarin	10(7.0%)	11(10.4%)	17(13.6%)
SSRI	3(2.1%	2(1.9%)	4(3.2%)

NVUGIB nonvariceal upper gastrointestinal bleeding; NG nasogastric; PPI proton pump inhibitor; NSAID non-steroidal anti-inflammatory drug

a Other PPIs include 124 patients on pantoprazole

Source: Table 12 Applicants Supporting Document "Demographic and baseline characteristics of the sub-sample of PUB patients in study NCT000797641 who approximately fulfilled the inclusion criteria in study D961DC00001 and were treated with PPI after initial endoscopy

The results of the observational cohort are presented in the table below.

Table 15 Results from Subsample of Patients in Observational Cohort study NCT00797641 who approximately fulfilled inclusion criteria for pivotal trial D961DC00001 and were treated with PPI after initial endoscopy

Variable	Omeprazole n=142	Esomeprazole n=107	Other PPIs[a] n=125
Description of continued bleeding/re-bleeding, n(%)			
Continued bleeding after first endoscopy	15(10.6%)	14(13.2%)	10(8.0%)
Re-bleeding during hospitalization	21(14.9%)	15(14.2%)	21(16.8%)
Re-bleeding after discharge	2(1.4%)	2(1.9%)	4(3.2%)
Continued bleeding or re-bleeding within 30 days	26(18.4%)	23(21.7%)	27(21.6%)
Death within 30 days, n(%)	8(5.6%)	5(4.7%)	6(4.8%)
Surgery within 30 days, n(%)	7(4.9%)	5(4.7%)	8(6.4%)
Additional endoscopies, n(%)	74(52.1%)	67(62.6%)	56(44.8%)
Number of blood units transfused within 12 hours			
Mean (SD)	1.3(1.2)	1.9(2.9)	1.6(1.8)
Number of blood units transfused within 30 days			
Mean (SD)	2.8(3.7)	2.7(3.3)	2.9(3.7)

Source: Table 13 Applicants Supporting Document "Results from the sub-sample of patients in study NCT00797641 who approximately fulfilled the inclusion criteria in study D961DC00001 and were treated with PPI after initial endoscopy.

The applicant submitted a systematic review and metaanalysis of randomized controlled trials investigating intravenous Omeprazole for the prevention of rebleeding in patients with peptic ulcer bleeding. This review was conducted by an external consultant. These analyses were not verified. However, the results appeared to indicate that high dose intravenous Omeprazole reduced rebleeding, surgery, and further endoscopic retreatment. With the exception of trials conducted in Asia or in trials that only included patients at high-risk for rebleeding, high dose intravenous Omeprazole did not significantly affect mortality rates. Geographical location of the trials was reportedly the only characteristic shown to be significantly associated with treatment effect.

Finally the applicant stated that they have not conducted any additional randomized controlled trials with intravenous Esomeprazole for this particular indication. The applicant submitted data from a multicenter retrospective observational study conducted by an external consultant using the Hospital Network in Spain. Patients in this study were ≥ 18 years old; hospitalized due to peptic ulcer bleeding; fulfilled criteria for endoscopic high risk stigmata; received standard endoscopic therapy; and were treated with an intravenous PPI (either Esomeprazole or Pantoprazole) after endoscopy. Patients were recruited from selected hospitals that almost exclusively used one type of PPI when managing patients with at high risk for rebleeding following therapeutic endoscopy. Data were collected from medical records using a common case report form. The primary outcome variables were continuation of bleeding within 72 hours and recurrent bleeding; need for surgery to control bleeding; and mortality within 72 hours, 7 days, and 30 days. In addition the number of blood units transfused and re-endoscopy were also evaluated. Again, the results of the trial may be difficult to interpret because this trial was not controlled. In the absence of adequate randomization and control there may be differences in baseline patient characteristics that may affect outcomes. The observational nature of the trial also introduces the possibility of selection bias. Some may argue that the results of observational trials are more generalizable to a much broader population. However, this trial was conducted outside the United States, and extrapolation of the results may not account for differences in clinical practice and social norms. Finally outcomes from use of intravenous Pantoprazole would not support the approval of intravenous Esomeprazole for the proposed indication because the efficacy of pantoprazole for the proposed indication has not been established.

There were 594 patients recruited by participating study centers between January 2006 and December 2009. Fifty-five (55) were excluded because they did not fulfill the eligibility criteria or had incomplete information in their medical records. Of the remaining 539 patients, 268 were treated with intravenous Esomeprazole and 271 were treated with intravenous Pantoprazole after initial therapeutic endoscopy. Baseline demographics and characteristics are provided in the table below.

Table 16 Baseline Characteristics from Observational Study (Using Pantoprazole and Esomeprazole) for patients with PUB and high-risk stigmata at endoscopy in routine clinical practice

Characteristic	All patients n=539	Pantoprazole n=271	Esomeprazole n=268
Gender, n(%)			
Male	380(70.5%)	197(72.7%)	183(68.3%)
Age, years			
Mean(SD)	65.4(16.3)	66.8(15.3)	63.9(17.2)
Any comorbidity, n(%)	413(76.6%)	217(80.1)	196(73.1)
Any medication before admission, n(%)	380(70.5%)	180(66.4%)	200(74.6%)
Medication before admission, n(%)			
NSAID	158(29.3%)	69(25.5%)	89(33.2%)
ASA	126(23.4%)	58(21.5%)	68(25.4%)
Clopidogrel	41(7.6%)	28(10.3%)	13(4.9%)
Anticoagulants	61(11.3)	36(13.3)	25(9.3)
Shock at presentation, n(%)	36(6.7%)	16(5.9%)	20(7.5%)
Forrest class, n(%)			
Ia	41(7.6%)	19(7.0%)	22(8.2%)
Ib	173(32.1%)	91(33.6%)	82(30.6%)
IIa	192(35.6%)	91(33.6%)	101(37.7%)
IIb	133(24.7%)	70(25.8%)	63(23.5%)
Endoscopic treatment, n(%)			
Injection (Adrenalin/polidocanol)	462(85.7%)	215(79.3%)	247(92.2%)
Clips/Adrenaline	43(8.0%)	32(11.8%)	11(4.1%)
Other/Unknown	34(6.3%)	24(8.9%)	10 (3.7%)
Ulcer location, n(%)			
Stomach	236(43.8%)	110(40.6%)	126(47.0%)
Duodenal	324(60.1%)	172(63.5%)	152(56.7%)

NSAID non-steroidal anti-inflammatory drugs; ASA acetylsalicylic acid

Source: Applicants Supporting Document. pp 47- 48. Table 14 "Baseline characteristics for patients with PUB and high-risk stigmata at endoscopy by PPI treatment after endoscopy in routine clinical practice.

There were baseline differences in the characteristics that may impact the outcomes. Most importantly, single injection therapy was used during the initial endoscopic treatment in the majority of patients (79.3% in the pantoprazole group and 92.2% in the Esomeprazole group). As mentioned previously, single injection therapy is not recommended standard of care for achieving endoscopic hemostasis.

The outcome results are presented in the table below.

Table 17 Outcomes: Observational study for patients with PUB and high-risk stigmata at endoscopy by PPI treatment after endoscopy in routine clinical practice

Clinical outcome	All patients (n=539)	Pantoprazole (n=271)	Esomeprazole (n=268)
Bleeding continuation, n (%)			
within 72 h	19 (3.5%)	10 (3.7%)	9 (3.4%)
Recurrent bleeding, n (%)			
within 72 h	30 (5.6%)	18 (6.6%)	12 (4.5%)
within 7 days	51 (9.5%)	32 (11.8%)	19 (7.1%)
within 30 days	58 (10.8%)	36 (13.3%)	22 (8.2%)
Bleeding continuation + recurrent bleeding, n(%)			
Within 72 hours	49(9.1%)	28(10.3%)	21(7.8%)
Within 7 days	70(13.0%)	42(15.5%)	28(10.4%)
Within 30 days	77(14.3%)	46(17.0%)	31(11.6%)
Surgery, n (%)			
within 72 h	11 (2.0%)	7 (2.6%)	4 (1.5%)
within 7 days	16 (3.0%)	9 (3.3%)	7 (2.6%)
within 30 days	19 (3.5%)	11 (4.1%)	8 (3.0%)
All-cause mortality, n (%)			
within 72 h	5 (0.9%)	4 (1.5%)	1 (0.4%)
within 7 days	10 (1.9%)	8 (3.0%)	2 (0.7%)
within 30 days	18 (3.3%)	13 (4.8%)	5 (1.9%)
Bleeding-related mortality, n (%)			
within 72 h	3 (0.6%)	2 (0.7%)	1 (0.4%)
within 7 days	4 (0.7%)	3 (1.1%)	1 (0.4%)
within 30 days	7 (1.3%)	6 (2.2%)	1 (0.4%)

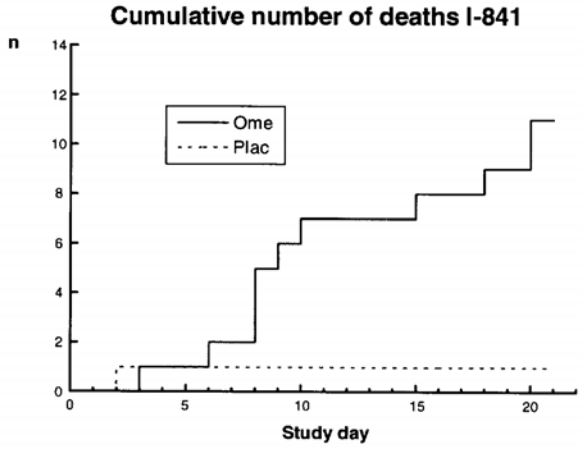
7 Review of Safety

Safety Summary

The applicant submitted supporting data from the trials conducted with intravenous Omeprazole. As described above, there were limitations precluding a full safety analysis of the Lau trial data. Notwithstanding, given the similarities in dosing administration and anticipating that exposures would be higher for Esomeprazole compared to Omeprazole, it appears unlikely that a new safety signal would have arisen in these trials that was not evident in pivotal trial D961DC00001. The most common adverse events in both treatment groups (placebo and Esomeprazole) of the pivotal trial were related to rebleeding, the primary efficacy outcome. Infusion site reactions were more common in the Esomeprazole treatment group compared to the placebo group. However, the events were mild, of short duration, and did not cause discontinuation of study drug. Although the alkaline phosphatase values increased to a slightly higher degree in the Esomeprazole treatment group, overall the adverse event profile for intravenous Esomeprazole did not differ from that expected in acutely ill patients with peptic ulcer bleeding.

Trials I-840 and I-841 were omitted from the efficacy analysis. It is important to note that both trials were terminated prematurely after an imbalance in mortality was detected in study I-841. Per the applicant, an independent expert group, the primary investigators, and personnel from the company examined the data and determined that the difference in mortality was secondary to chance. However, no new patients were enrolled in the trials and the Steering Committee decided not to resume enrollment. This is concerning. Trial I-841was terminated prematurely after 333 patients had been randomized. The mortality rate was 6.9% in the omeprazole group and 0.6% in the placebo group.
A graphic depicting the cumulative number of deaths in trial I-841 is presented below.

Table 18 Cumulative Number of Death by Study Treatment and Day Trial I-841



Source: Clinical Study Report Trial I841, p.34

The authors of an article published on data from the Lau trial state that "no side effect related to the infusion was reported in either group."[25] There were five patients in the Omeprazole group who died within 30 days after the initial endoscopy. Twelve patients in the placebo group died within 30 days of the initial endoscopy to achieve hemostasis. According to the publication, none of the five deaths in the Omeprazole group were caused by recurrent bleeding.[25] Four of the patients in the placebo group died after surgery (three following gastrectomy for recurrent bleeding and one after excision of a perforated ulcer). Two patients in the placebo group, who were deemed unfit for surgery, died from recurrent bleeding. The remaining six patients died from complications related to the concurrent illnesses. All but two patients in the Omeprazole group and four patients in the placebo group completed follow-up assessments at 8 weeks. Biopsies of the ulcers from three patients revealed cancer (two in the Omeprazole group and one in the placebo group).

The applicant also submitted a safety update summarizing data from September 1, 2008, to April 30, 2010. According to the applicant there were no new data from clinical studies relevant to this patient population. No safety concerns were identified for intravenous Esomeprazole.

The reader is referred to Section 5 for additional information.

7.1 Methods

There was limited data from clinical trials to assess the safety of intravenous Esomeprazole for this indication. The safety data from the Lau trial was presented in Section 5. In the original submission, the applicant submitted a safety update report that summarized safety data received between January 1, 2008 and August 31, 2008 for this indication. The current submission contains complementary data covering the period from September 1, 2008 to April 30, 2010.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data source was derived from the trial conducted with intravenous Omeprazole by Lau, et al. Reference is made to Section 5 of review for this safety information. It is important to note that while case report forms from this trial were provided by the applicant, the patients' treatment group assignments were not included on the case report forms. This limits the ability of the reviewer to conduct a full safety assessment. The applicant states in the resubmission that studies included in the original supplemental NDA were finalized at the time of submission.

Secondary sources of safety data included post-marketing data in the safety update report and two case reports from clinical studies in other indications where intravenous

Esomeprazole treatment was given. No other studies relevant to this indication were performed during the period covered by the safety update.

7.1.2 Categorization of Adverse Events

There was no information provided in the Lau article on the dictionary used to categorize adverse events.

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

Please refer to section 5 for individual trial safety data. This section is not applicable as there was only one new randomized controlled trial included in the analysis. Data from the observational cohorts and metaanalyses could not be pooled for this safety assessment.

7.2 Adequacy of Safety Assessments

Assessments of safety were included in the efficacy analyses, as the sponsor measured death as a secondary outcome. Apart from the reported hemoglobins and assessments for hypotension, there were no data provided on clinical laboratory evaluations and physical examination findings.

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

Given the short-term nature of the indication, exposure guidelines from ICH E1 would not be applicable. Intravenous Esomeprazole is currently approved and marketed but not at the doses proposed for the indication sought.

7.2.2 Explorations for Dose Response

Please refer to the clinical pharmacology review and section 4 for additional details. Only one dose of the intravenous Omeprazole was studied. Previous studies have shown that low dose Omeprazole at 4mg/hr after an initial 80mg bolus is effective at maintaining a pH consistent pH between 4 and 6.[10] However, there was a relative amount of inter-subject variability in AUC.

7.2.3 Special Animal and/or In Vitro Testing

This section is not applicable

7.2.4 Routine Clinical Testing

There were no data provided on clinical laboratory evaluations.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see the clinical pharmacology review for details and refer to Section 4 of this review. There were no additional data provided on drug-drug interactions.

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

There are no other proton pump inhibitors approved for this indication.

7.3 Major Safety Results

Please refer to section 5 of this review and section 8

7.4 Supportive Safety Results

This section does not apply. Please refer to section 5.

7.4.1 Common Adverse Events

Please refer to Section 5.

7.4.2 Laboratory Findings

There were no data on laboratory findings presented in the current submission.

7.4.3 Vital Signs

Vital signs were recorded and included as part of the definition of clinically significant rebleeding. However no additional data were provided.

7.4.4 Electrocardiograms (ECGs)

There were no new ECG data provided

7.4.5 Special Safety Studies/Clinical Trials

This section is not applicable.

7.4.6 Immunogenicity

There were no new immunogenicity data provided.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose was studied, therefore this section is not applicable

7.5.2 Time Dependency for Adverse Events

This section is not applicable

7.5.3 Drug-Demographic Interactions

New data was presented was from a single center trial in one country. Please refer to Section 5

7.5.4 Drug-Disease Interactions

This section is not applicable.

7.5.5 Drug-Drug Interactions

Please refer to the clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No additional carcinogenicity data were submitted. While, there is an increased incidence of treatment related enterochromaffin cell hyperplasia associated with proton pump inhibitor use, the data are inconclusive.

7.6.2 Human Reproduction and Pregnancy Data

According to the label, Omeprazole is a Pregnancy Category C, while Esomeprazole is a Pregnancy Category B.

7.6.3 Pediatrics and Assessment of Effects on Growth

This section is not applicable. No assessment of growth effects was provided. The proposed intravenous regimen is designed to be used short-term and would unlikely have an effect on child growth. Furthermore, there is limited data specific to pediatric peptic ulcer bleeding in the literature and it appears that peptic ulcer bleeding is uncommon in children.

Consults were obtained from the Pediatric and Material Health Staff (PMHS) and the Officer of Surveillance and Epidemiology (OSE). Per OSE, "The projected annual number of hospitalized pediatric patients with a diagnosis of PUB in the U.S. during 2004 through 2008 (based on the SDI inpatient data) ranged from (b) (4) when only the primary discharge diagnosis was used, and from (b) (4) when all discharge diagnoses were used. These numbers are slightly higher then the numbers provided by the applicant in their request for waiver of pediatric trials (b) (4) when only the primary discharge diagnosis was used; (b) (4) when all discharge diagnoses were used).When both peptic ulcer bleeding codes and upper GI bleeding codes were used to obtain more conservative estimates of pediatric patients who may have peptic ulcer bleeding on the SDI inpatient data, the annual numbers ranged from (b) (4) when only the primary discharge diagnosis was used and from (b) (4) when all discharge diagnoses were used. The PMHS consult also concurred that the condition was unlikely to occur in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose were reported during the Lau clinical trial. In general, there is limited experience with proton pump inhibitor overdose. Symptoms are transient and manifestations may vary. The drug abuse potential is small. As stated previously, proton-pump inhibitor therapy in healthy volunteers may induce acid-related symptoms after withdrawal, a phenomenon referred to as rebound acid hypersecretion.

8 Postmarketing Experience

The applicant searched the Astra Zeneca Global Patient Safety Database using the following criteria:

- Events of peptic ulcer or any type of gastrointestinal bleeding reporting on NEXIUM I.V.
- Any event reported on NEXIUM I.V. with a daily dosage of 80mg or an infusion rate of 8mg/hour.

According to the applicant, a total of 41 case reports describing 45 serious adverse events (SAEs) and 20 non-serious adverse events were identified. In nearly a quarter (10 of 41) of the case reports, the indication for use was gastrointestinal bleeding. Two

of the reports were from clinical trials where Esomeprazole had been given either as a concomitant drug or the indication was for used in pediatric patients. Three of the case reports involved a death (one case of agranulocytosis, hematoma, and acute hepatitis respectively). Doses were provided in 35 of the case reports and ranged from 20mg to 200mg daily. When the information was provided, the time from initiation of the intravenous Esomeprazole therapy to the onset of the adverse event ranged from 0 days to 61 days. A review of the case reports did not identify any new safety concerns regarding the use of intravenous NEXIUM. The applicant provided narratives for the serious adverse events. A sampling of those narratives is provided in the table below.

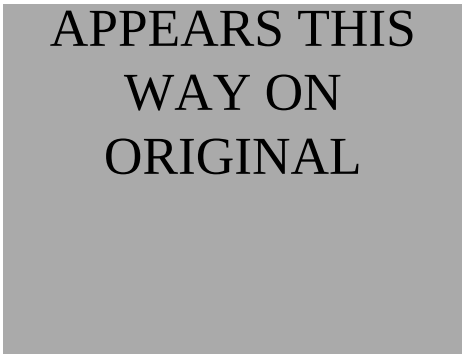


Table 19 Narrative Summaries of Adverse Events from the Applicants Postmarketing Database September 1, 2008 through April 30, 2010

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
2009UW07589 Mexico / HCP Unknown / Male	40 mg / Daily Intravenous / 15 days Gastric ulcer	Galactorrhea 0 days Recovered	A report has been received from a Physician concerning an Adult , Male subject, who had been receiving intravenous (not otherwise specified) NEXIUM 40 Milligrams, daily for gastric ulcer The drug was started during (b) (6) or gastric ulcer. The patient experienced galactorrhea which started during (b) (6) 10 days after NEXIUM treatment began. The drug was discontinued. The patient recovered from the event of during (b) (6) 15 days after the NEXIUM end date. The report was considered to be nonserious.
2008PK02076 Germany / Regulatory Authority 71 years / Male	40 mg / twice daily Intravenous / 2 days Unknown Indication	Acute Hepatitis 28 days Died	A report has been received from a physician concerning a male patient whose medical history included cor pulmonale. The patient's concurrent diseases included pulmonary embolus, lung adenocarcinoma, hypertensive heart disease, chronic atrial fibrillation and type II diabetes mellitus with neurological manifestations. Concomitant medications included prednisolone and bisoprolol hemifumarate. The patient received treatment with oral Avalox (moxifloxacin hydrochloride) 400 mg daily between (b) (6) for pneumonia following pulmonary infarction; intravenous (Avalox Amp (moxifloxacin hydrochloride) 1x 1 infusion on (b) (6) for pneumonia following pulmonary infarction; oral Diflucan single dose different for candida esophagitis between (b) (6) (b) (6) oral Nexium (Esomeprazole magnesium) 40 mg; number of single dose different per day, between (b) (6) (b) (6) intravenous (not otherwise specified) Nexium Amp 40 mg two times a day between (b) (6) oral Novonorm (b) (6) (repaglinide) from single dose different (b) (6) for type II diabetes mellitus with neurological manifestations. (b) (6) the patient was hospitalized. The reason was right-sided central pulmonary artery embolism and diffuse embolism oft he left upper and lower lobe. Transaminases were inconspicuous. Due to the extended pulmonary embolism the patient developed

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
			infarction pneumonia, which was treated with Avalox (moxifloxacin hydrochloride), 1x 1 infusion from (b) (6) Under this treatment, the patient's general condition was worsened with icterus and massive pruritus. Laboratory investigations showed considerable increase of hepatic function parameters and of bilirubin (values on (b) (6) ALT 735 U/l (normal range: 0-50 U/l), AST 242 U/l (normal range: 0-50 U/l), bilirubin 7.2 mg/dl (normal range: 0-1 mg/dl)). Serologically exclusion of viral hepatitis. Maximum values were reached (b) (6) ALAT 1283 U/l, ASAT 648 U/l, bilirubin on (b) (6) 26.2 mg/dl. In the further course normalization of transaminases with continuing massively increased bilirubin values (laboratory values: ALAT 44 U/l (b) (6), ASAT 45 U/l (b) (6) , bilirubin 20.9 mg/dl (b) (6). The adverse drug reaction developed in hospital.
2008CG01403 France / Regulatory Authority 71 years / Male	8mg/every hour intravenous drip/4 days/Unknown	Agranulocytosis 3 days Died	A report has been received from the French Medicine Agency concerning a 71-year-old male patient. His medical history included ischemic cerebrovascular accident, prostate cancer and multiple bone metastases. At the time of event, the patient was being treated with propacetamol chlorolhydrate. Three weeks before event, the patient had received Taxotere (docetaxel). On 0 (b) (6), the patient was hospitalized for hemorrhagic shock on bulb ulcer. He urgently underwent surgery with gastro-duodenal artery suture at bulb ulcer and pyloroplasty. After operation, he was transferred to a surgical intensive care unit where he was intubated, ventilated and sedated. Intravenous Nexium 8 mg every hour, Acupan (nefopam hydrochloride) and propacetamol were started. On (b) (6), sedation was stopped and intubation was removed without any particular problem. Biological work-up showed thrombocytopenia (56000 cells/mm3) associated to prothrombin activity at 51 percent. Hemodynamic values remained stable. On (b) (6), the patient's respiratory function deteriorated. He

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
			presented with tachypnea but physical auscultation only evidenced symmetric vesicular murmurs. White blood cell count was decreased to 0.5 G/L and neutrophil count to 0.41 G/L. On that day, intravenous Nexium, Acupan and propacetamol were discontinued. On (b) (6), the leukopenia worsened again. On that day, Neupogen (filgrastim) was started. Pulmonary fibroscopy with bronchoalveolar lavage were performed and showed "dirty secretions". White blood cell count was at 0.9 G/L and neutrophil count at 0.66 G/L. On (b) (6), the patient presented with febrile symptoms and was started on Claforan (cefotaxime), gentamicin and vancomycin intravenously. Respiratory distress worsened leading to oral tracheal intubation. Bronchoalveolar lavage showed Gram-positive diplococci. White blood cell count was at 0.5 G/L and neutrophil count at 0.37 G/L. Global cardiac failure occurred requiring vascular filling and treatment with dobutamine and adrenalin. Myelogram disclosed absence of extra-hemopoietic cells, decreased total cellularity and partial blockade of granulocytic series maturation without anomaly of other series. On (b) (6), septic shock and pneumopathy worsened. White blood cell count was at 4.3 G/L. On 1 (b) (6), neutrophil count was at 3.66 G/L. The patient died. The French Medicine Agency reported agranulocytosis as serious adverse event due to hospitalization and as the cause of death and suspected intravenous Nexium, Acupan, propacetamol and Taxotere in its occurrence. The French Medicine Agency stated that two hypothesis were evoked for agranulocytosis - post-chemotherapy bone marrow aplasia occurring three weeks after the latest course of Taxotere with retardation of cell regeneration. leukocytic medullar toxicity related to high dose of intravenous Nexium.
2009AP02894 Philippines / HCP 81 years / Female	40 mg / UNK Intravenous / 3 days Peptic ulcer hemorrhage	Hematoma* 0 days Died	A report has been received from a Physician concerning an 81 year old, Female subject, who had been receiving intravenous Nexium, 40 mg (frequency not reported), for peptic ulcer bleed. The patient was

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
			hospitalized for peptic ulcer bleeding. She was given Nexium I.V. for three days. An intraluminal hematoma developed in the duodenum. The size was big enough to occupy almost the entire lumen. It eventually ruptured, thus required surgery. The patient was referred to a surgeon from the same institution. The patient expired due to complication of surgery on (b) (6). The patient had been hospitalized for a peptic ulcer bleed (no further details obtained).
2009SE03936 France / Regulatory Authority 60 years / Female	20mg/daily/intravenous/ 2months/gastric ulcer	Alanine aminotransferase increased, Aspartate aminotransferase increased, cytolytic hepatitis, 61days/Recovered	A report was received from the French Medicine Agency Regulatory Authority concerning a 60 year old female patient, who had been receiving intravenous Nexium, 20mg, daily for gastric ulcer, intravenous voriconazole 150mg twice a day for pulmonary aspergillosis and intravenous paracetamol 1 gram four times a day for pain. The patient's medical history included intestinal occlusion (started on (b) (6), and required operation) The patient's concurrent diseases included obesity and right mammary ductal intraepithelial neoplasia. No concomitant medications were mentioned in the report. Nexium was started on (b) (6) for gastric ulcer, Voriconazole started on (b) (6), for pulmonary aspergillosis and Paracetamol started on (b) (6), for pain. The patient experienced hepatic cytolysis, increased aspartate aminotransferase and increased alanine aminotransferase which started on (b) (6). The first control of blood voriconazole was at the upper limit of normal leading voriconazole dose decreased. On (b) (6). blood voriconazole was at 4.40mg/L. Voriconazole, Nexium and paracetomol were stopped on (b) (6) Voriconazole was switched to Ambisome (amphotericin B) at 225 mg/24hours. The second day after stopping the voriconazole hepatic cytolysis regressed and became normal after one week. The patient recovered from the event of hepatic cytolysis, aspartate aminotransferase increased and alanine aminotransferase increased. Nexium and paracetomol were re-introduced without recurrence of symptoms

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
2009SE04550 France / HCP 93 years / Female	40 mg / twice daily Intravenous / 3 days Gastroesophageal reflux disease	Neutrophil count decreased*, White blood cell count decreased* 2 days Not recovered	A report has been received from a pharmacist concerning a 93 year old, female subject, who had been receiving intravenous Nexium, 40 milligrams, two times a day for gastroesophageal reflux. The patient was treated with lansoprazole since an unspecified date. Concomitant medications included zolpidem, oxazepam, furosemide and enoxaparin sodium. On (b) (6), the patient was emergently hospitalized for an unspecified cause and Esomeprazole sodium 40 mg intravenous twice a day was started on the same day for gastroesophageal reflux. The patient experienced white blood cell decreased and neutrophil decreased on (b) (6). (white blood cell count at 1.5 G/L and neutrophil count at 0.43 G/L.) Esomeprazole was discontinued on (b) (6). At the time of reporting, the event of white blood cell decreased and neutrophils decreased was ongoing.
2010SE09660 France / Regulatory Authority 54 years / Female	40 mg / twice daily Intravenous / 3 days Gastritis erosive	Dermatitis bullous*, Eczema*, Pruritus*, Rash macular* 2/5 days Recovered	A report has been received from French health authority concerning 54 year old, female patient, who had been receiving intravenous Nexium 40mg, two times a day for gastric mucous membrane erosion and subcutaneous Lovenox (enoxaparin sodium), 0.6ml, two times a day. The patient's medical history included pulmonary embolism, phlebitis and cholecystectomy. The patient's concurrent diseases included protein S deficiency, hypertension arterial and the patient was allergy to iodine, fraxiparin, and heparin. Concomitant medication included ibuprofen. On (b) (6), the patient received Esomeprazole magnesium for gastric mucous membrane erosion and On (b) (6), the patient had upper limbs pruritis. On (b) (6) (b) (6) the patient had bullous eruption and edema appeared on upper limbs. The patient presented also with squamous lesions and generalized pruritus. Urticarial lesions were found on the back. Dermatologists diagnosed hand bullous eczema with maculopapullar rash (probable drug eruption). Bullae were aseptic and regressed within 48 hours under dermocorticoids and after Nexium and Lovenox were

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
			discontinuation on (b) (6). At the time of reporting, the urticarial lesions on the back were still persistent. The patient recovered from the event of eczema, bullous eruption, pruritis and rash macular under corticoids and left the hospital after 8 days.
2009UW04521 US / HCP 11 years / Female	Unknown/unknown Intravenous / <1 year Peptic ulcer	Urticaria 0 days Recovered	A report has been received from a Physician via Takeda Global Research and Development concerning an 11 year old, Female subject, who had been receiving intravenous Esomeprazole for peptic ulcers. Intravenous Nexium was started in (b) (6) (b) (6)The patient experienced hives. The Nexium was discontinued and the patient recovered from the event. The report was considered to be non-serious
2009UW03896 US / SI 15 years / Female	40 mg / Four times a day Intravenous / 4 days Unknown	Abdominal abscess, Psoas abscess, 28 days Recovered with sequelae	A report has been received from a Study Investigator concerning a 15 year old Caucasian, Female enrolled in study D9615C00021; A Randomized, Open-Label, Multi-National Study to Evaluate the Pharmacokinetics of Repeated Once- Daily Intravenous Doses of Esomeprazole in Pediatric Patients 0 to 17 years Old, Inclusive with Gastroesophageal Reflux Disease (GERD). Intravenous Nexium was started on (b) (6). Nexium was discontinued on (b) (6) (b) (6).The patient experienced an abdominal abscess and an illiopsoas abscess which started on (b) (6), The event of became serious on (b) (6).The patient recovered with sequelae from the event on (b) (6). The investigator considered that there was no causal relationship between the event and the Nexium
2009SE19277 France / HCP UNK / Female	Unknown / Unknown Intravenous / Unknown Gastrointestinal hemorrhage	Thrombocytopenia 3 days Not recovered	A report has been received from a physician via a sales representative concerning a female patient. The patient's medical history included renal failure, ulcer and anemia. Concomitant medication included anticoagulation drug. In (b) (6), the patient started on oral Nexium (Esomeprazole magnesium) 20 mg for prophylaxis of NSAID gastric ulceration. On (b) (6), she was hospitalized in the intensive care unit

Report ID#/Country Patient Age/Gender	Dose/Schedule Route/Duration/Indication	Preferred Term for Adverse Event Time to Onset Outcome	Narrative
			for gastrointestinal hemorrhage of an ulcer. Nexium intravenous 80 mg daily was started. The patient received O (-) type blood transfusion. On that day, platelet count was normal. On (b) (6) (b) (6), the patient was diagnosed thrombocytopenia with platelet count of 60000/mm3. There were no symptoms related to the event. Nexium oral was discontinued on (b) (6). At the time of reporting, the event was ongoing
2009SE32897 France / HCP UNK / Female	40mg/ twice daily/ intravenous/unknown/ unknown	Confusional state, Hallucination, Unknown Unknown	A report was received from a pharmacist concerning a female who had been receiving intravenous Nexium (Esomeprazole sodium), 40 mg two times a day. The patient's concurrent diseases included cephalic pancreatectomy. Nexium was started on an unknown date when the patient was hospitalized in digestive surgery ward after cephalic pancreatectomy. The patient had one episode of confusional state and hallucination during the night of (b) (6) after the second injection of Nexium 40 mg on that day. The dose of Nexium was reduced to 40 mg daily. The outcome of the events was unknown.

9 Appendices

9.1 Labeling Recommendations

Intravenous esomeprazole is not recommended for Approval during this review cycle. Labeling changes will be addressed during subsequent review cycles.

9.2 Advisory Committee Meeting

This section is not applicable.

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/s/

ERICA L WYNN
06/09/2011

LYNNE P YAO
06/14/2011

CLINICAL REVIEW

Application Type	NDA (Efficacy Supplement)
Submission Number	21-689
Submission Code	SE1-014
Letter Date	May 29, 2008
Stamp Date	May 29, 2008
PDUFA Goal Date	November 29, 2008
Reviewer Name	Anil Nayyar, MD
Review Completion Date	November 17, 2008
Established Name	Esomeprazole-sodium
(Proposed) Trade Name	NEXIUM Injection
Therapeutic Class	Proton-pump inhibitor
Applicant	Astra-Zeneca
Priority Designation	P (Priority)
Formulation	Parenteral
Dosing Regimen	80 mg I.V. infusion in 30 minutes followed by continuous I.V. infusion of 8 mg/hour for 71.5 hours.
Indication	(b) (4)
Intended Population	Patients with Peptic ulcer bleeding

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewer recommends that NEXIUM Intravenous formulation in the dose of 80 mg in 30 minutes followed by continuous infusion at the rate of 8 mg per hour for next 71.5 hours for the indication of (b) (4) be not approved. The primary efficacy result in this non-US, single study is weak, has not been replicated and does not provide substantial evidence to support the proposed indication.

1.2 Recommendation on Post-marketing Actions

1.2.1. Risk Management Activity

N.A.

1.2.2. Required Phase 4 Commitments

N.A.

1.2.3. Other Phase 4 Requests

N.A.

1.3 Summary of Clinical Findings

1.3.1. Brief Overview of Clinical Program

NEXIUM intravenous formulation (Esomeprazole-sodium) is S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole and shares the same mechanism of action. It works through an inhibition of the final step in gastric acid production (the H+/K+-ATPase, located in the secretory membranes of the parietal cells in the gastric oxyntic mucosa), resulting in a profound inhibition of gastric acid secretion.

The intravenous (I.V.) formulation of esomeprazole was approved for injection and infusion in the US in 2005 for the indication of short-term (up to 10 days) treatment of gastroesophageal reflux disease (GERD) and healing of non-steroidal anti-inflammatory drug (NSAID) induced ulcers in patients for whom oral administration is not possible or appropriate.

The purpose of the current application is to support the use of esomeprazole I.V. for the indication of (b) (4) The dose of esomeprazole used / proposed for this indication is 80 mg as intravenous infusion

over 30 minutes followed by continuous infusion of esomeprazole at the rate of 8 mg/hour for next 71.5 hours. Single pivotal trial with 767 patients randomized into two treatment groups (Esomeprazole=376, Placebo=391), was submitted in support of the indication. It should be noted that while study was being conducted the applicant modified the protocol where patients receiving intravenous PPI in dose of ≥40 mg were excluded midway through the study and also made changes in the study analysis.

1.3.2. Efficacy

The applicant submitted the results of single pivotal, phase 3, randomized, double blind, multicenter, multi- national, parallel-group, placebo controlled study D961DC00001, in patients with peptic ulcer bleeding after complete hemostasis of the initial bleeding was achieved with endoscopic treatment. Of the total 767 patients 376 were randomized to receive esomeprazole I.V. 80 mg for 30 min followed by esomeprazole I.V. 8 mg/hr for 71.5 hours and 391 received placebo I.V. for 30 min followed by placebo I.V. for 71.5 hours. Patients that received I.V. esomeprazole in first 72 hours was called "esomeprazole" group. The group receiving I.V. placebo was designated as "placebo" group. After 72 hours of I.V. treatment both groups (esomeprazole and placebo) received oral esomeprazole 40 mg daily for next 27 days.

Primary Endpoint
The primary efficacy endpoint was rebleeding within 72 hours. Overall 5.9% patients had rebleeding in esomeprazole group compared to 10.3% in placebo group. The difference between the treatment groups was 4.4% with p value of 0.0256.

Secondary Endpoints
The secondary efficacy analysis was done for clinically significant rebleeding within 7 days and 30 days, death within 72 hours and 30 days, requirement for surgery within 72 hours and 30 days, requirement for endoscopic re-treatment within 72 hours and 30 days, number of blood units transfused within 72 hours and 30 days and number of days hospitalized due to rebleeding during the 30-day treatment phase. The treatment effect was primarily observed during 0 to 7 days as most of the secondary variables events occurred during first 7 days.

Limitations of the study
Background changes in study analysis

In the initial protocol dated June 1, 2005, the baseline factors of endoscopic treatment (single vs. combination) and Forrest class (I vs. II) were assumed by the Applicant to influence the probability of rebleeding and that they would be included in the analysis. According to the Applicant, after a review of blind data no difference was seen in rebleeding rate between the Forrest groups. It is important to point out here that it is well accepted fact in medical literature that Forrest class 1a with arterial bleeding has higher risk of rebleeding compared to Forrest class 2b with blood clot on the ulcer base. The sponsor collapsed all the categories of Forrest class into one group. The analysis was therefore changed in the Statistical Analysis Plan (dated Dec. 17, 2007) to only be stratified for endoscopic treatment (single vs. combination). No protocol amendment

documenting this change was issued. The Applicant stated that: "All changes were made prior to unblinding of study data" (Section 5.8.2 on page 74 of study report).

Further, interim analysis of the study data was done twice. DSMB reviewed unblended data at these formal interim analysis meetings on 21 November 2006 and 13 March 2007. Recommendations to continue the study were communicated to the applicant after those meeting. This was apparently due to not achieving the robust efficacy data.

In the present submission although the study demonstrated a reduction in rebleeding for esomeprazole during the 72 hours (primary Endpoint) compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted by the FDA's statistician to assess the robustness of the single study did not give results consistent with protocol-specified analyses. Sensitivity analyses for the primary efficacy endpoint of rate of rebleeding were carried out to evaluate how the pre-specified study findings hold up when alternative analyses were performed. According to the FDA's statistician, the following analyses did not support the primary results:

1. Country Analysis and its effect on study results.
2. Analysis of certain centers and their effect on the study results.
3. Analysis based on Forrest Class.
4. Analysis on endoscopic therapy (excluding Injection therapy alone).

Lack of support from pharmacodynamic evaluation

The clinical study was not adequately supported by the two supportive PK/PD studies. For adequate hemostasis and preventing clot lysis it is imperative to achieve pH > 6 as proposed in the hypothesis for the present trial. The two supportive PK/PD studies (D961DC00015, D961DC00004) submitted in this submission did not demonstrate achieving intragastric pH of ≥ 6 adequately with the dose and mode of administration used in the trial. Intragastric pH of > 6 could be achieved only for less than 50 % of the time in 24 hour (D9615C00015=52.3%; D961DC00004=44.6%). Only one subject had an intragastric pH > 6 more than 90% of time in 24-hour period.

Conclusions

The efficacy results of this single, non-US, study did not provide substantial evidence of effectiveness to support the sought indication

In the absence of replication the robustness of the primary results was not established or proved by alternative sensitivity analyses. There was insufficient proof of the superiority of high dose I.V. esomeprazole over placebo to support the proposed indication for (b) (4) (b) (4) (b) (4) The weakness of the study was evident throughout the execution of the trial during the two interim analyses. The two PK/PD studies were also not supportive of the clinical study. In order to resolve these deficiencies, the applicant should provide at least one additional adequate and well-controlled study to demonstrate the proposed clinical benefit. The study should include some US centers.

1.3.3. Safety

In the safety review of pivotal study (D961DC00001) during I.V. treatment (72 hours) local administration site adverse events related to skin and vascular systems occurred at a significant higher rate with esomeprazole when compared to placebo. However, the overall safety profile was deemed comparable between the two experimental arms (esomeprazole versus placebo).

The focus of the current safety review was on determining the safety profile of the high dose continuous I.V infusion of esomeprazole compared with placebo during the I.V. treatment phase (within 72 hours). In particular distribution by treatment arm of serious adverse events (SAE), adverse events (AE), and AEs leading to withdrawal was assessed.

The safety of esomeprazole I.V. Nexium in the dose of 20 mg or 40 mg daily was previously reviewed for the indication of short term use (7 to10 days) in GERD and erosive esophagitis at the time of the original submission of I.V. Nexium approved in 2005. The safety profile of I.V. Nexium as an injection or infusion was found to be similar to the oral administration. Neither the Adverse Events (AE) pattern nor any other safety assessments implied any safety concerns for I.V. administration of esomeprazole in the dose of 20 mg or 40 mg daily for 7 to 10 days.

SAEs

SAEs were numerically fewer in esomeprazole compared to placebo group during the first 72 hours of I.V phase of treatment (Eso=8.8%; Placebo=10.5%). This was partly accounted for by a lower incidence of rebleeding in esomeprazole group.

SAEs were similar in the two treatment groups during the oral treatment period from 4 to 30 days (Eso=8.4%; Placebo=8.0%).

The majority of SAEs during the study were related to primary efficacy variable i.e. rebleeding from the peptic ulcer, the underlying clinical condition. SAEs related to other systems were few and equally spread out in the two treatment groups. No particular trend was noticed.

Discontinuation due to AE

Proportion of patients that discontinued due to AEs in the first 72 hours were fewer in esomeprazole than placebo group (Eso=8.3%; Placebo=10%). This was primarily due to lower incidence of rebleeding in esomeprazole group. Majority of AEs that led to discontinuation were related to GI rebleeding which is also primary efficacy variable. Proportion of patients that discontinued due to AEs was similar during 4 to 30 days (Eso=1.7%; Placebo=2.8%). Rebleeding was the most common AE for discontinuation.

Overall AEs

Overall incidence of adverse events seen during high dose continuous I.V. infusion of esomeprazole was numerically lower than the placebo during first 72 hours (Eso=39.2%,

Pla=41.9%). Incidence of AEs related to GI system was numerically lower in esomeprazole group than placebo group (Eso=12.3%, Pla=19.8%). This was accounted for primarily by the lower incidence of rebleeding in the esomeprazole group. However incidence of AEs related to administration site and vascular systems were numerically higher in esomeprazole group compared to placebo (Eso=13.6%, Pla=9.2%). The AEs related to other systems were comparable in the two groups.

Incidence of AEs related to administration site and local vascular disorders remained numerically higher in esomeprazole group than placebo group (Eso=11.2%, Pla=7.7%) during oral administration of esomeprazole (4 to 30 days). Incidence of AEs during this period related to other systems was comparable in two treatment groups. The most common adverse events reported (≥ 1%) were peptic ulcer bleeding, constipation, diarrhea, nausea, pyrexia, edema, urinary tract infection, thrombophlebitis, dyspnoea, abdominal pain, cough, headache, and dizziness.

Laboratory data
Increases in mean ALP values at 72 hours and 30 days compared to baseline were observed in both treatment groups. The increase at 72 hours was numerically higher for esomeprazole compared to placebo (12.6% and 5.2% respectively). The corresponding increase at 30 days was also numerically higher in the esomeprazole than placebo group (43.1% versus 30.9%). In the majority of patients ALP increase was within the reference range. Further the increase in ALP was not associated with increases in other liver function tests, i.e. ALT, AST or bilirubin. There were no noticeable differences in the two treatment groups. The changes related to the other laboratory tests were balanced in the two experimental groups and did not show any trend.

1.3.4. Dosing Regimen and Administration

N.A.

1.3.5. Drug-Drug Interactions

Drug-interactions with oral esomeprazole have been described. No drug-drug interaction studies with high dose, continuous infusion of esomeprazole were performed in this clinical development program.

1.3.6. Special Populations

High dose continuous infusion of esomeprazole has not been studied in enough patients with renal insufficiency, hepatic insufficiency, age ≤18 years, or women who are pregnant or nursing to assess safety and efficacy in these populations. The Medical Officer reviewer recommends that the pediatric studies in the age group ≤ 18 years be performed. The applicant should submit pediatric plan along with the next submission. The applicant should also include enough patients with renal and hepatic insufficiency in the proposed supportive study.

2. INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

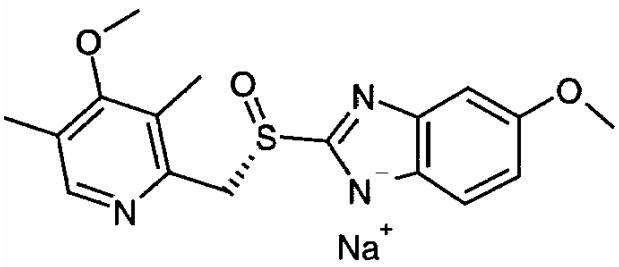
The chemical name, empirical formula, molecular weight, structure formula, established name, proposed trade name, and pharmacological class are as follows:

Chemical Name: (*S*)-5-methoxy-2[[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulfinyl]-1 *H*-benzimidazole sodium.

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

Molecular weight: 367.4 g/mol

Structure formula:



Established name: Esomeprazole sodium
Proposed trade name: Nexium I.V.
Pharmacological class: Proton pump inhibitor

Esomeprazole is S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole and shares the same mechanism of action. Both omeprazole and esomeprazole work through an inhibition of the final step in gastric acid production (the H+/K+-ATPase, located in the secretory membranes of the parietal cells in the gastric oxyntic mucosa), resulting in a profound inhibition of gastric acid secretion. Omeprazole has an asymmetric centre at the sulphur atom and can thus be resolved into the S-enantiomer esomeprazole (H 199/18) and the R-enantiomer H 199/19. The pharmacodynamic (PD) effects of the enantiomers do not differ from each other or from the racemate *in vitro*, since both enantiomers are chemically converted to the same active molecule (the achiral sulphenamide), in the gastric parietal cell.

Oral esomeprazole (Nexium) is currently approved for use in adults, adolescents (12 to 18 years of age), and in children from 1 year of age in the EU, US and Canada. The intravenous (I.V.) formulation of esomeprazole was approved for injection and infusion in the US in 2005. The approved indication is for short-term (up to 10 days) treatment of gastroesophageal reflux disease (GERD) and healing of non-steroidal anti-inflammatory drug (NSAID) induced ulcers in patients for whom oral administration is not possible or appropriate.

The purpose of this present application is to support the use of esomeprazole I.V. for the indication of (b)(4) The dose of esomeprazole used / proposed for this indication is 80 mg as intravenous infusion over 30 minutes followed by continuous infusion of esomeprazole at the rate of 8 mg/hour for next 71.5 hours.

2.2 Currently Available Treatment for Indications

Currently, there is no approved treatment for this patient group.

2.3 Availability of Proposed Active Ingredient in the United States

Oral and intravenous formulations are approved for marketing in U.S.

2.4 Important Issues with Pharmacologically Related Products

There are no important issues with pharmacologically related products.

2.5 Pre-submission Regulatory Activity

Esomeprazole (Nexium) I.V. was approved in 2005 for the treatment of Gastroesophageal Reflux Disease (GERD) in adults in the dose of 20 mg or 40 mg daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 to 30 minutes) for 7 to 10 days when oral treatment is not possible or appropriate.

The sponsor had accepted Divisions written responses dated 2/9/2004 in lieu of meeting for Nexium I.V. phase 3 clinical development program (b) (4) The Division agreed on placebo as comparator during first 72 hours (I.V. phase), primary endpoint of rebleeding and inclusion criteria. Division suggested that sponsor obtain pharmacodynamic data in a subgroup of patients during I.V. to oral switch (on day 1, 4, and 8) and additional analysis based on age be included.

2.6 Other Relevant Background Information

Globally, oral formulation of esomeprazole has been available worldwide for the healing of erosive esophagitis, maintenance of healing of erosive esophagitis, symptomatic GERD, risk reduction of NSAID associated gastric ulcer, treatment of *H.Pylori* infection and duodenal ulcer (in combination with amoxicillin and clarithromycin) and pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Esomeprazole Intravenous formulation is approved for treatment of GERD when oral treatment is not possible or appropriate. Off label use of Intravenous formulation is common worldwide for variety of conditions where acid suppression is required (head

injury, burns, patients receiving high doses of steroids etc), including peptic ulcer bleeding.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The supplement proposes the use of the existing (approved) drug product. No CMC-related labeling changes were provided (Description, How Supplied sections). The proposed dose is available from the currently marketed product.

The only CMC-related review issue involves Environmental Assessment (EA), due to the possibility that action on this supplement could increase use of the product. The supplemental application was consulted to HFD-003 (Raanan Bloom, Ph.D.) for EA assessment and evaluation.

The supplement was reviewed with the recommendation of FONSI (Finding of No Significant Impact). See EA review for NDA 21-689/SE1-014, dated 14-OCTOBER-2008, R. Bloom, Ph.D., reviewer.

Thus, from the standpoint of CMC, this supplement has been recommended to be approved.

3.2 Animal Pharmacology/Toxicology

Pharmacology-Toxicology review was done by Dr Zhang Kee. From the pre-clinical standpoint of NEXIUM I.V. was recommended for the proposed indication. Please see Pham-Tox review for details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is primarily based on data from clinical trial conducted by the applicant. Post marketing reports also contributed to this review.

4.2 Tables of Clinical Studies

The table 1 summarizes the clinical trials conducted as part of the development for the new indication “Maintenance of hemostasis and risk reduction of rebleeding of gastric and duodenal ulcer”. The result of Study D961DC00001 forms the primary basis for this review.

Table 1: Clinical Studies of Esomeprazole-sodium

Study	Objectives	Design	Test product Dosage regimen	Population	Number enrolled	Treatment Duration
D961DC00001	To assess prevention of rebleeding in patients that have undergone successful primary endoscopic hemostasis of a bleeding peptic ulcer	Randomized, double-blind, parallel-group, placebo-controlled	80 mg I.V. infusion in 30 minutes followed by I.V. continuous infusion at the dose of 8 mg/h for 71.5 hours	Patients with bleeding peptic ulcer	767	72 hours
D961DC00004	To assess the effect on 24-hour intragastric pH and pharmacokinetics in healthy subjects.	Double-blind, randomized, 2-way cross-over	80 mg I.V. infusion in 30 minutes followed by I.V. continuous infusion at the dose of 8 mg/h for 23.5 hours	Healthy subjects	39	24 hours
D961DC00015	To assess effect on 24-hour intragastric pH & pharmacokinetics in healthy subjects.	Open, randomized, five-way crossover dose finding study	40, 80, and 120 mg followed by a continuous infusion of 8 or 4 mg/h	Healthy subjects	25	24 hours

4.3 Review Strategy

Clinical review of the efficacy and safety of single pivotal study D961DC00001 was done by this reviewer, Dr Anil Nayyar. Additional safety data from healthy subjects was also reviewed from two PK/PD studies D961DC00004, D961DC00015. Dr Sonia Castillo reviewed the statistical aspects of the submission. Clinical pharmacology results were reviewed by Dr Tien Mien Chen from the office of Clinical Pharmacology. In addition Pharmacology/ Toxicology review was done by Dr Ke Zhang.

4.4 Data Quality and Integrity

Not applicable.

4.5 Compliance with Good Clinical Practices

The applicant stated that Studies D961DC00001, D961DC00004, and D961DC00015 were each carried out in accordance with International Conference on Harmonization (ICH) / Good Practice (GCP) guidelines.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology review was done by Dr Chen, Tien Mien. The important PK/PD information related to the clinical trial is discussed below.

5.1 Pharmacokinetics

Mean PK parameters obtained from Study D961500015 and D961D00004 are summarized in table 2 for comparisons.

Table 2: Mean (± SD) PK Parameters of Esomeprazole and Omeprazole after Given the Same Dosing Regimen (80 mg by 0.5-hr infusion followed by 8 mg/hr continuous infusion for 23.5 hrs)

Study No.	AUC_{0-24} (µmole-h/L)	C_{max} (µmole/L)	C_{ss}[1] (µmole/L)
I. **D9615C00015** (n=26) Esomeprazole	**109.9 (± 23.1)** Male: 107.8 (± 26.0) Female: 115.7 (± 11.1) Homo-EM: 105.1 (± 18.8) Hetero-EM: 123.2 (± 31.5) PM: 105.4 (Suject # 20; M)	**14.2 (± 2.6)** Male: 13.4 (± 2.4) Female: 16.7 (± 1.5) Homo-EM: 13.9 (± 3.0) Hetero-EM: 14.5 (± 1.2) PM: 17.0	**4.0 (± 1.0)** Male: 4.1 (± 1.1) Female: 4.0 (± 0.5) Homo-EM: 3.9 (± 0.9) Hetero-EM: 4.4 (± 1.5) PM: 3.7
II. **D961DC00004** (n=39) Esomeprazole	**98.6 (± 25.9)** Male: 100.0 (± 24.7) Female: 96.5 (± 28.4) Homo-EM: 90.4 (± 18.1) Hetero-EM: 107.9 (± 30.6) PM: 86.9	**13.1 (± 2.8)** Male: 12.9 (± 3.2) Female: 13.4 (± 2.3) Homo-EM: 12.3 (± 2.2) Hetero-EM: 14.0 (± 3.3) PM: 14.0	**3.4 (± 1.0)** Male: 3.5 (± 0.9) Female: 3.2 (± 1.1) Homo-EM: 3.1 (± 0.8) Hetero-EM: 3.7 (± 1.1) PM: 2.7
Omeprazole	**89.1 (± 30.5)** Male: 91.2 (± 29.2) Female: 85.9 (± 33.1) Homo-EM: 76.8 (± 21.2) Hetero-EM: 100.3 (± 34.2) PM: 122.7 (Suject # 7; M)	**11.6 (± 2.8)** Male: 11.7 (± 3.0) Female: 11.3 (± 2.7) Homo-EM: 10.3 (± 1.8) Hetero-EM: 12.6 (± 2.8) PM: 14.0	-----[2]

1. C_{ss}: Mean steady-state plasma level.
2. The C_{ss} was reportedly not determined for omeprazole due to continuous increase of plasma level towards the end of 24 hr infusion.

EM=Entensive metabolizer, PM= Poor metabolizer
(Above table taken from table 7 of clinical pharmacological review)

These are the results of two PK/PD studies:

1. For inter-study comparison of esomeprazole PK data, Study D9615C00015 had around 8-18 % higher in PK parameters than those obtained from Study D961DC00004.
2. Compared to the same dose of omeprazole (within Study D961DC00004), esomeprazole had slightly larger (11-13%) mean PK parameters which is consistent with previous

findings that R-isomer of omeprazole (a racemate) is eliminated faster than the S-isomer (esomeprazole).

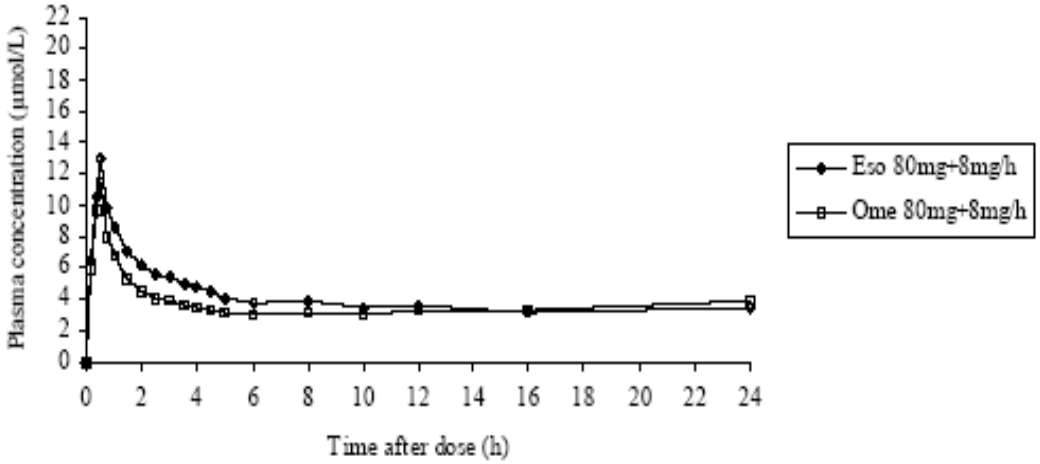
3. Between males and females, their mean esomeprazole PK parameters are comparable.
4. Homo-EM had slightly lower (4-16%) mean esomeprazole PK parameters than those of Hetero-EM.
5. Only one PM was included in each of the above two studies and their PK parameters are not as high as expected for a PM and the values are within the range for EMs.

The reason for the PM having similar PK data as those of Homo-PM or Hetero-PM is not known, however, it could be due to 1) only one PM being included in each study, 2). Esomeprazole and omeprazole also inhibiting CYP 2C19 after multiple dose (or continuous infusion), and PM being less influenced by this inhibition mechanism on 2C19, and 3) crossover study design of I.V. infusion (washout period being 13 days) complicating the inhibition mechanism on 2C19 for EMs.

It was reported that C_{ss} (based on at least 3 consecutive time points during continuous infusion) for omeprazole could not be determined nor was CL calculated since omeprazole plasma levels tended to increase during the continuous infusion.

Mean plasma profiles of esomeprazole and omeprazole and their median 24-hr intragastric pH profiles obtained from D961DC00004 are shown in figures 1 and 2.

Figure 1: Mean plasma concentrations following I.V. single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy subjects (N=39) (D961DC00004)

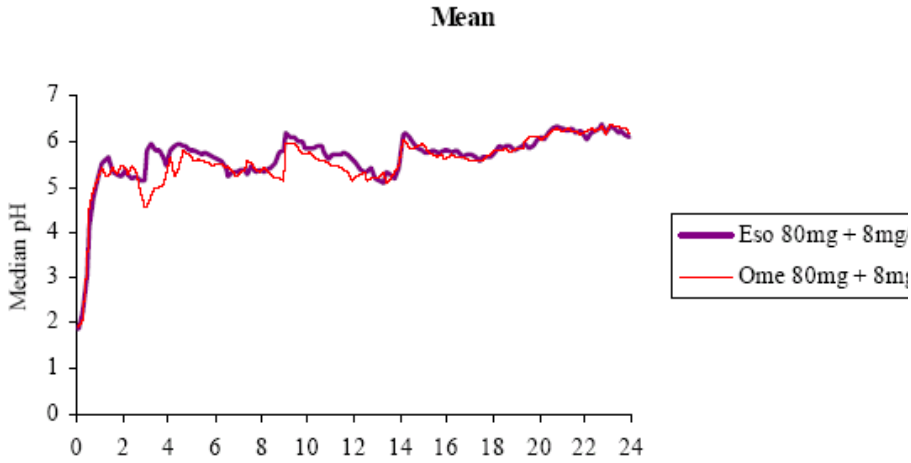


(Above Figure taken from Figure 5 of clinical pharmacology review)

5.2 **Pharmacodynamic data**

Mean intragastric pH profile following the similar dose and mode of administration of esomeprazole and omeprazole in healthy subjects during 24 hours is shown in figure 2.

Figure 2: Median intragastric pH profile following I.V. doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy subjects (N=39) (D961DC00004)



(Above Figure taken from Figure 6 of clinical pharmacology review)

The comparisons of mean % of time for intragastric pH>6.0 during the 24-hr period between esomeprazole and omeprazole are shown below in table 3.

Table 3: Comparison of % Time for 24-hr intragastric pH > 6.0 between Esomeprazole vs. Omeprazole (D961DC00004)

Variable	Treatment	N	Estimate	95% CI	
pH>6 (0-24h)	Baseline	39	2.3	1.3	3.4
	Esomeprazole	39	44.6	38.6	50.7
	Omeprazole	39	41.4	35.4	47.5

(Above Table taken from Table 8 of clinical pharmacology review)

According to the clinical pharmacology reviewer the above PD results obtained from Study D961DC00004 showed that

a. For esomeprazole and omeprazole, mean % of time for pH>6.0 in 24-hr period were 44.6 and 41.4%, respectively and there were no major differences in PD (p-value of 0.6789) observed.
b. The above mean % of time obtained from this study were lower than that from D9615C00015 (around 50%)
c. Mean time to reach pH>6 for esomeprazole and omeprazole are calculated to be 7.26 (± 6.85) hrs and 8.54 (± 7.78) hrs which were longer than that from Study D9615C00015 [5.67 (± 6.97) hr for esomeprazole].

The differences between inter-study comparisons are complicated due to different fasting status. The sponsor indicates that there is no other obvious explanation for these differences.

Comments:
The PK/PD information is of limited value because these PK/PD studies were conducted in healthy subjects for the duration of 24 hours and not in the target population.

According to the sponsor's data the relevant PD values with dose used in the trial show that mean time to reach pH of >6 was about 8 hours and pH of >6 was maintained for only 45% of the time during 24 hours (table 3).

During 24 hours of study, the pH of ≥6 was not reached in first 18 hours and majority of the time fluctuating between pH 5 to 6 (figure 2). This is considered inadequate to achieve the desired PD effects on the blood clot.

In addition patients with moderate to severe liver disease were not analyzed in adequate number to assess the PK/PD data for dose adjustment.

For details please see Dr Chen, Tien Mien, the Clinical Reviewer's review.

6 INTEGRATED REVIEW OF EFFICACY

In this review, efficacy data generated from the study D961DC00001 are discussed.

6.1 Indication

In the "Indication and Usage" section, the Applicant proposed the following wording for the rebleeding of gastric and duodenal ulcer after endoscopic treatment indication:

(b) (4) *risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric and duodenal ulcer.*

6.1.1 Methods

The clinical data from single pivotal, randomized, double blind, parallel-group, placebo controlled (Study D961DC00001) were analyzed. The reviewer has approached this submission first by focusing upon what the sponsor has requested, and what evidence has been submitted in support of that request. The materials reviewed include all data pertinent of clinical trial with emphasis on the protocol and clinical study report.

This review followed a stepwise fashion directed to determine the factual clinical evidence to support the sponsor's proposed use of esomeprazole. The one clinical trial and two PK/PD trials were examined (D961DC00001, D961DC00004, D961D500015). The protocol was examined first and then the reported data for efficacy and safety. The reviewer's final judgment on safety and efficacy submitted in support of the proposed indication was based on the safety profile and whether the stated primary objective endpoint analysis was achieved. Since this was a single clinical study robustness of the data was assessed by sensitivity analysis.

The primary variable, rebleeding within 72 hours, was analyzed with a Mantel-Haenszel test, stratified for type of endoscopic treatment at baseline. Mantel- Haenszel test or log-

rank test for dichotomous variables and Wilcoxon two-sample test for continuous variables, were used in the analysis of secondary variables, with adjustment for type of endoscopic treatment at baseline.

It should be noted that the applicant amended the protocol on June 21, 2006. The applicant added exclusion criteria. Patients receiving intravenous PPI exceeding a total dose of 40 mg within 24 hours prior to enrollment were not included in the study. The applicant also made changes in the analysis of the efficacy data which is presented in details in statistics section by Dr Sonia Castillo.

6.1.2 General Discussion of Endpoints

The primary endpoint was clinically significant rebleeding within 72 hours during the continuous infusion of esomeprazole or placebo. Clinically significant rebleeding was diagnosed by the criteria (table-2)

Comments:
Clinically significant rebleeding after the first 72 hours was assessed during 4 to 7 days and subsequently during 7 to 30 days. The primary thinking for this analysis was to avoid cumulative incidence of rebleeding/non-bleeding during 72 hours being reflected later in subsequent periods after 72 hour (during 4 to 7 days and 7 to 30 days). Further with the background knowledge that the majority of rebleeding in peptic ulcers occurs within 7 days, the analysis was focused on rebleeding during first 7 days. Similar analysis was done for other secondary variables i.e. need for surgery or endoscopic retreatment for rebleeding.

Primary variable:
Clinically significant rebleeding within 72 hours of continuous infusion of esomeprazole or placebo.

Methods of assessment
The diagnosis of rebleeding could be based on either A, B, or C (see table 4).
The recommendation was to always confirm the diagnosis of rebleeding by endoscopy. However, if no bleeding was detected at re-endoscopy the patient was defined as a rebleed if he/she fulfilled C (vomiting of >200 mL of fresh blood) and/or B.

The time of a clinically significant rebleeding was defined as the time of demonstrating the first clinical sign of a rebleeding (B1, B2 or B3) which was subsequently confirmed by endoscopy. In case of an active bleeding endoscopic re-treatment was recommended.

When the patient was discharged from the hospital, he/she was given information card, detailing signs and symptoms that might be associated with rebleeding. Patients were advised to contact investigator or the hospital without delay to be evaluated for rebleeding, if they experienced any such signs or symptoms.

Table 4: Diagnosis criteria for clinically significant rebleeding

Rebleeding diagnosed by:	Criteria for diagnosis
"A" Endoscopy – initiated by clinical signs of bleeding defined as: one of B1 or B2 or B3 and Endoscopic verification, i.e., one of A1 or A2. It is the result of the endoscopy that defines if there is a rebleeding or not	A1 Blood in the stomach (this criterion was not used during the first 6 hours after primary endoscopic hemostasis) A2 A verified active bleeding from a peptic ulcer (Forrest class Ia, Ib)
"B" A true clinically based definition included at least 2 of B1 and/or B2 and/or B3	B1 Vomiting of fresh blood or fresh blood in a gastric tube or hemetochezia or melena after a normal stool. B2 Decrease in Hb>20 g/L (or Hct>6%) during 24 Hours or an increase in Hb<10 g/L (or Hct<3%) despite ≥2 units of blood has been transfused during 24 hours B3 Unstable circulation systolic BP ≤90 mmHg or pulse ≥110/min (after have had a stable circulation)
C Hematemesis	C Vomiting significant amounts (>200 mL) of fresh blood as estimated by the investigator

(Above Table is taken from Table 4 of Clinical Study Protocol for Study D961DC00001)

Primary outcome variable:
Rebleeding within 72 hours was calculated from the date and time for significant rebleeding, as recorded in the CRF. Patients who left the study prematurely without having had a rebleeding were considered as having no rebleeding.

Comments:
The assessment and criteria of significant rebleeding for primary endpoint are adequate. However patients with less significant bleeding should have been also accounted for to assess information on the total risk of rebleeding.

Secondary variables:

There were multiple secondary variables proposed by the sponsor:

- Clinically significant rebleeding within 7 days and 30 days: Rebleeding within 7 days and 30 days was calculated from the date and time for significant rebleeding, as recorded in the CRF.

- Death within 72 hours and 30 days: Death within 72 hours and 30 days was calculated from the date of death as recorded in the CRF.

- Death related to rebleeding within 30 days was judged by the EpC: The EpC evaluated and determined whether death was related to rebleeding or not based on clinical and laboratory data collected in the CRF, including autopsy reports if available.

- Requirement for surgery within 72 hours and 30 days: Any surgery (except endoscopic treatment) initiated within 72 hours or 30 days caused by rebleeding was recorded in the CRF. The decision to perform surgery was based on several factors such as the patient's age, co-morbidities, primary endoscopic findings, the patient's actual status and the progress of the actual bleeding.

  Recommendations for surgery:

  - Extensive continuous bleeding as judged by massive hemetemesis and/or hemetemesis with shock (shock was defined as a systolic BP ≤90 mm Hg or pulse≥110 beats/min) and when endoscopy/endoscopic treatment was not judged to be an alternative.

  - Significant rebleeding (after primary successful endoscopic treatment) and attempt of endoscopic treatment was not able to control the bleeding.

  - Clinical signs of persisting significant continuous bleeding after 4 units of blood had been given within 24 hours

  - Clinical signs of persisting significant continuous bleeding after a total 8 units of blood had been given irrespective of time.

- Requirement for endoscopic re-treatment within 72 hours and 30 days:
  In case of rebleeding endoscopic re-treatment was recommended if the rebleeding was classified as Forrest class Ia, Ib, IIa or IIb. The need for endoscopic re-treatment was based on investigators assessment and not on the presence of a confirmed clinically significant rebleeding.

Comments:

This secondary variable of requirement of endoscopic retreatment is investigator dependent and may not be uniform across the study.

- Number of blood units transfused within 72 hours and 30 days: The number of blood units (whole blood and packed red cells) transfused to the patient during the study was recorded in the CRF.

  Recommendations on when a blood transfusion should be given:
  - Deficit in oxygen transporters was best substituted with red blood cells.
  - Hemodynamic instability was best substituted with crystalloids or plasma expanders.
  - Transfusion of red blood cells (whole blood or packed cells) was recommended when:
    - Extensive continuous bleeding (as judged by massive hematomas and/or hematemesis with shock
    - When the hemoglobin concentration was <100 g/L

In patients with an increased peripheral oxygen demand (patients with cardiac diseases, patients in shock) transfusions were given at a higher hemoglobin concentration where as in otherwise healthy patients transfusion were initiated at a lower hemoglobin concentration than 100 g/L.

Comments:
The analysis of blood transfusions units required in the two treatment groups during different time frame and overall was appropriate. The recommendations on when a blood transfusion should be given are acceptable.

Number of days hospitalized due to rebleeding during the 30-day treatment phase:

The number of extra days hospitalized due to rebleeding during the 30-day treatment period was calculated (excluding hospitalization for conditions already present at the time of primary bleeding).

Calculation or derivation of outcome variable

The number of days from clinically significant rebleeding to the day of discharge from hospital was calculated from CRF data.

Overall comments on primary and secondary endpoints criteria:

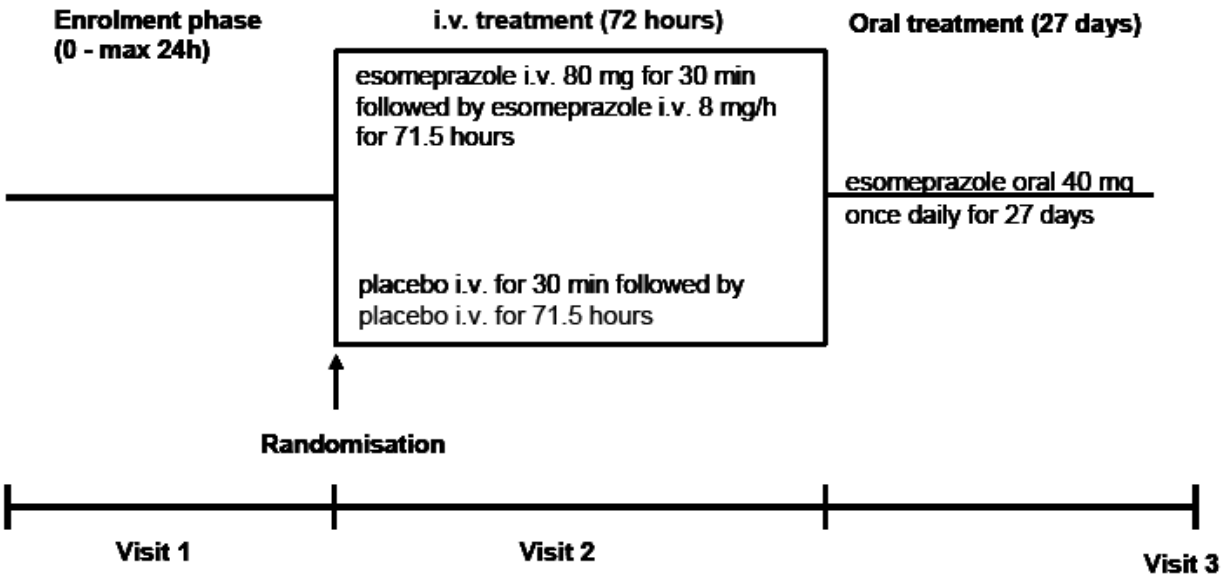
The sponsor's selection of endpoints and criteria used provide reasonable assessment of the primary endpoint i.e. clinically significant rebleeding, as these assessments are widely used in clinical practice. However the study does not address the overall rebleeding that may be higher than the clinical significant rebleeding as per above criteria.

The multiple secondary endpoint variables related to mortality and morbidity in this group of patients with peptic ulcer bleeding are appropriate except the criteria for endoscopic retreatment which is investigator dependent and may vary.

6.1.3 Study Design

Study D961DC00001 was a phase 3, randomized, double blind, multicenter, multi-national, parallel-group, placebo controlled study in patients with peptic ulcer bleeding after complete hemostasis was achieved with endoscopic treatment. Patients were randomized to receive either esomeprazole I.V. 80 mg for 30 min followed by esomeprazole I.V. 8 mg/hr for 71.5 hours or placebo I.V. for 30 min followed by placebo I.V. for 71.5 hours. After 72 hours of I.V. treatment both I.V. groups (esomeprazole and placebo) received oral esomeprazole 40 mg daily for 27 days. The study was to include patients of both sexes, ≥18 years of age who had undergone successful endoscopic haemostatic treatment of a bleeding gastric or duodenal ulcer (for details of inclusion and exclusion criteria see Table 5). It was estimated that approximately 2500 patients were needed to be enrolled in order to randomize 760 to 800 patients and the patients were to be recruited at approximately 80 centers in 17 countries.

Study flow Chart



Comments:
The study design seems appropriate. The assessment of the sponsor's esomeprazole dose selection in the current submission needs validation as the target pH of > 6 was not achieved 50% of the time in 24 hours in the two PK/PD studies.

Table 5: Main inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age > 18 years. 2. Upper GI bleeding (hemetemesis, melena or hemetochezia) or with such sign within the last 24 hours. 3. Gastric or duodenal ulcer, at least 5 mm in diameter, classified as Forrest Ia, Ib, IIa, or IIb. classification of PUB (Forrest et al 1974): Ia = arterial bleeding Ib = oozing bleeding IIa = non-bleeding visible vessel IIb = adherent clot In case of Forrest IIb (adherent clot), all efforts were made to remove the clot. If the clot could not be removed, it was classified as follows: If the clot could be removed with 5 min of high-pressure water irrigation (Laine et al 1996) or by cold snare, the ulcer was to be reclassified and only Forrest Ia, Ib and IIa were included. If the clot could not be removed despite these measures, the patient was included as Forrest IIb. 4. Successful hemostasis (which was considered to have been established if bleeding was stopped and, if applicable, formerly bleeding vessels were flattened or cavitated) achieved by endoscopic treatment with: - Injection therapy (epinephrine, dilution 1:10000) and/or one of the following: - Coagulation with heater probe - Electrocautery - Haemoclips	1. Malignancy or other advanced disease with a life expectancy of <6 months. 2. The ASA classification of physical status >3. 3. Severe hepatic disease defined as Child-Pugh B or C. 4. Severe renal disease, defined as patient requiring dialysis or in imminent need of dialysis. 5. Major cardiovascular event at enrollment or within 3 months prior to study start, (Stroke, myocardial infarction, or hospitalization for treatment of unstable angina pectoris). 6. Hemorrhagic disorder, platelets <100x109/L, INR>1.5, APTT>1.5x upper limit of normal (ULN), or treatment with low-molecular weight heparin. 7. Endoscopic suspicion of gastric malignancy or juxta pyloric stenosis. 8. Sign of multiple bleeding peptic ulcers or concomitant other GI bleeding from esophageal varices, reflux esophagitis, gastritis, Mallory Weiss rifts, Dieulafoy's lesion, colon, small bowel, or ulcer distal to the stoma in Billroth resected patients. 9. Need for treatment during the first 7 days of the study with NSAIDs, Cyclooxygenase-2 (COX-2) inhibitors, acetyl salicylic acid (ASA) (including low dose) and clopidogrel. 10. Known or suspected hypersensitivity to any component of any PPI (esomeprazole, omeprazole, lansoprazole, rabeprazole, or pantoprazole). 11. Planned treatment with medication that could interact with esomeprazole; ie, Phenytoin, clarithromycin, itraconazole, ketoconazole, warfarin (including other vitamin K antagonists), cisapride, atazanavir and ritonavir. 12. Chemotherapy or radiation therapies within 2 weeks prior to study start or planned during the course of the study. 13. Pregnancy, planned pregnancy or lactation. Women of childbearing potential had to use reliable and medically accepted methods of birth control. 14. Known or suspected alcohol, drug or medication abuse, or any condition associated with poor compliance. 15. Participation in any study of investigational drugs within the preceding 30 days prior to enrollment. 16. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff and staff at the investigational site). 17. Previous enrollment in the present study. 18. Intravenous administration of a PPI (esomeprazole, omeprazole, lansoprazole, rabeprazole, or pantoprazole) exceeding a total dose of 40 mg within 24 hours prior to enrollment.

(Above Table is compiled from information on pages 40 to 42 of Clinical Study Protocol for Study D961DC00001)

Comments:
Inclusion and exclusion criteria used by the sponsor are adequate and appropriate.

Restrictions
Restrictions concerning endoscopy
Endoscopic treatment with argon plasma coagulation, injection of water, thrombin, fibrin glue or sclerosing agents (lipidocanol, ethanol), was not allowed.

Routine "second look" endoscopy without clinical signs of rebleeding was not done to avoid misclassification of non-significant rebleeding.

Restrictions concerning *H. pylori* treatment
Treatment of *H. pylori* infection was initiated after the completion of the study.

Method of assigning patients to treatment groups
Patient eligibility was established before randomization. Patients were randomized sequentially, as patients were eligible for randomization. If a patient discontinued from the study, the E-codes and randomization codes were not reused, and the patient was not allowed to re-enter the study.

Patients were randomized to esomeprazole or placebo in equal proportions. A computer generated block randomization schedule, containing randomization code and treatment, was provided by AstraZeneca. The study medication was packed according to this schedule. At Visit 1, patient received the lowest E-code available at the centre after fulfilling all inclusion criteria and none of the exclusion criteria.

Discontinuation of patients from treatment or assessment:
- Treatment was stopped if the patient had significant rebleeding, required endoscopic re-treatment or surgery due to rebleeding. Thereafter such patients were treated according to local guidelines.

- Patients were further discontinued from study treatment and assessments for the following specific reasons:

    - Safety reasons (e.g., histological confirmed malignancy if routine biopsies were taken at Visit 1)
    - Patient lost to follow-up
    - Severe non-compliance to protocol.
    - Other reason specified by the investigator

- Voluntary discontinuation by a patient: Patients who discontinued were asked about the reason(s) for their discontinuation and about the presence of any adverse events (AEs). In case of AEs adverse events were followed up.

Comments:
The criteria used for discontinuation due to rebleeding, requirement of surgery or endoscopic treatment were related to the primary efficacy variable and were appropriate.

Other reasons for discontinuation i.e. safety reason, lost to follow-up and severe non-compliance were also appropriate.

Concomitant Therapy:

The following concomitant treatments were prohibited:

Prior to enrollment:

- Chemotherapy or radiation therapies within 2 weeks prior to study start.

- Intravenous administration of a PPI (esomeprazole, omeprazole, lansoprazole, rabeprazole or pantoprazole) exceeding a total dose of 40 mg within 24 hours prior to enrollment

During the study:

- PPIs (other than study medication), H_2RAs, sucralfate, and prostaglandins

- Somatostatin and tranexamic acid.

- Heparin (Low molecular weight heparin at prophylactic doses was allowed)

- NSAIDs, COX- 2 inhibitors, acetyl salicylic acid (including low-dose, i.e., 75 to 325 mg daily), and clopidogrel during the first 7 days of the study

- Treatment of *H. pylori* infection was initiated after the study.

- The following drugs were prohibited due to their interactions with PPIs: Phenytoin, clarithromycin, itraconazole, ketoconazole, warfarin (including other Vitamin K antagonists), cisapride, atazanavir and ritonavir.

- Chemotherapy or radiation therapy

- Routine "second look" endoscopy without clinical signs of rebleeding was not done.

Comments:

Because they may be potentially confounding, the concomitant treatments not allowed during the study are adequately justified. It seems that postponement of treatment for H.Pylori till the end of trial may not be justified.

Treatment compliance:

The actual times of start and stop as well as the infused volume and the infusion rate of the I.V. infusion were recorded in the CRF. Patients were termed compliant if they received ≥ 70 % to ≤ 125% of the total intended I.V. dose. If patients had rebleeding

before the intended dose was given they were considered compliant if I.V. treatment was discontinued ≤4 hours before the rebleeding.
For the oral treatment patients were instructed to return all unused study medication and the empty drug container at the follow-up visit. Returned capsules were counted and documented in the CRF.

Comments:
The assessment and criteria used to assess compliance are acceptable.

Screening and demographic measurements before randomization

The following data and assessments were collected and recorded in the CRF before randomization:

• Date of birth, sex and race

• Vital signs (BP, pulse rate)

• ECG (normal/abnormal)

• Hb, Hct, APTT, PTC and platelets (local lab)

• ASA class

• Concomitant medication

• Pregnancy test in female patients with childbearing potential

Endoscopy:
An endoscopic examination of the esophagus, stomach and duodenum was performed on each patient during the enrollment phase. All patients enrolled in the study were evaluated for signs of bleeding, with baseline criterion of least 5 mm size peptic ulcer. The signs of bleeding were classified according to the Forrest classification. Forrest classification of PUB (Forrest et al 1974):

Ia = arterial bleeding
Ib = oozing bleeding
IIa = non-bleeding visible vessel
IIb = adherent clot
==========

IIc = hematin spots	Not to be included in the study
III = clean ulcer base	Not to be included in the study

In case of Forrest IIb (adherent clot), if the clot could be removed with 5 min of high-pressure water irrigation (Laine et al 1996) or by cold snare, the ulcer was reclassified

and only Forrest Ia, Ib and IIa were included. If the clot could not be removed despite these measures, the patient was included as Forrest IIb.

The bleeding ulcer was documented with photograph. Patients with bleeding from other sources than a peptic ulcer, or with more than 1 bleeding gastric or duodenal ulcer, were not randomized into the study.

Routine "second look" endoscopy without clinical signs of rebleeding was not allowed.

Endoscopic treatment
Endoscopic treatment was administered for the peptic ulcer bleeding (PUB) of all enrolled patients having Forrest classification Ia, Ib, IIa and IIb. Patients with successful endoscopic treatment (bleeding stopped and, bleeding vessels flattened or cavitated) were included into the study.

Only following Endoscopic treatments were used:

- Injection therapy (epinephrine, dilution 1:10,000)
  and/or one of the following:
- Coagulation with heater probe
- Electrocautery
- Hemoclips

The injected volume of epinephrine was recorded in the CRF. Endoscopic treatment with Argon plasma coagulation, injection of water, thrombin, fibrin glue or sclerosing agents (lipidocanol, ethanol), was not allowed.

Screening and demographic measurements after randomization:

The following data were collected and recorded in the CRF after randomization but before administration of study drug:

• Vital signs (BP, pulse rate)

• Nicotine use

• Physical examination (general appearance, cardiovascular, lungs and abdomen).

• Medical and surgical history

• Weight and height
• Clinical laboratory tests (central lab) including *H. pylori* testing.

Comments:
Screening, demographic measurements and recording of vitals after randomization and before administration of drug are adequate.

Table 6 gives overview of objectives and outcome variables for each analysis.

Table 6: Efficacy objectives and outcome variables:

Objectives	Summary outcome variables for analysis (including time point and population)
Primary: Compare, in patients with PUB after successful endoscopic hemostasis, the efficacy of 72 hours continuous iv infusion of either esomeprazole or placebo by assessment of the rate of clinically significant rebleeding during the iv treatment period.	Primary outcome variable: Clinically significant rebleeding within 72 hours of continuous infusion of esomeprazole or placebo
Secondary Compare, in patients with PUB after successful endoscopic hemostasis, 72 hours continuous iv infusion of either esomeprazole or placebo with regard to the following, where the time period begins at start of I.V. treatment:	Secondary outcome variables
• The rate of clinically significant rebleeding within 7 days and 30 days	Clinically significant rebleeding within 7 days and 30 days.
• Proportion of mortalities within 72 hours and 30 days	Death within 72 hours and 30 days
• Rate of "bleed-related" mortalities within 30 days, based on the assessments by the End Point Committee (EpC)	Death related to rebleeding within 30 days as judged by the End Point Committee (EpC).
• Proportion of patients who, within 72 hours and 30 days, had surgery (except endoscopic treatment) due to rebleeding	Requirement for surgery within 72 hours and 30 days.
• Proportion of patients who within 72 hours and 30 days, had endoscopic re-treatment due to rebleeding	Requirement for endoscopic re-treatment within 72 hours and 30 days.
• Number of blood units transfused within 72 hours and 30 days	Number of blood units transfused within 72 hours and 30 days
• Number of days hospitalized due to rebleeding within 30 days	Number of days hospitalized due to rebleeding during the 30-day treatment period

(Table above is modified from Table 30 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
Efficacy objectives and outcome variables as shown in table 6 are appropriately addressed.

Patient-Reported Outcomes (PROs) measurements and variables

Not applicable

Efficacy Assessment Schedule:

Table 7 shows the key assessments at baseline during 0 to 72 hours and 4 to 30 days.

Table 7: Key Study assessments are summarized below:

Procedures	**Baseline**	**0-72 h**	**4-30 days**
Physical examination	x	x	x
ASA class	x		
Endoscopy (Forrest classification)	x		
Endoscopy Treatment	x		
Labs	x	x	x
Concomitants medication	x	x	x
Sign of rebleeding		x	x
AE recording		x	x

(Above Table is taken from Table 1 of Clinical Study Protocol for Study D961DC00001)

During I.V. treatment the following assessment and monitoring were done:

- Vital signs (pulse and BP) every 8 hours.
- Hb and Hct (local lab) every 8 hours.
- Adverse events (AEs) every 24 hours
- Clinical signs of rebleeding
- Concomitant medication
- Clinical laboratory tests (central lab) after end of the I.V. treatment

Analysis Plan:
For the primary efficacy analysis, the ITT study population was used. The primary efficacy parameter was the proportion of patients in each treatment group that had not achieved treatment success at 72 hours, defined as rebleeding from the primary peptic ulcer site. The primary variable, rebleeding within 72 hours, was analyzed with a Mantel-Haenszel test, stratified for type of endoscopic treatment at baseline. There were multiple secondary efficacy variables which were analyzed by using Mantel- Haenszel test or log-rank test for dichotomous variables and Wilcoxon two-sample test for continuous variables, with adjustment for type of endoscopic treatment at baseline.

Protocol amendment: Sponsor made the following changes during the study:

1. Amendment to Clinical Study Protocol:

- Addition of exclusion criterion: Intravenous administration of a PPI exceeding a total dose of 40 mg within 24 hours prior to enrolment.
- A total of 382 patients of 767 were randomized into the study prior to amendment (June 21, 2006).

2. Administrative Change:

- Study period was extended from Q4 2006 to Q2(April 10, 2007).

3. Amendment to Informed Consent Form (ICF):

- ICF signature was obtained before the endoscopy in 6 of the 16 countries and after the endoscopy in remaining countries.

4. Changes to Planned Analyses are summarized in table 8

Comments:

Intravenous administration of a PPI dose prior to enrolment may affect the primary variable in the study. The use of higher doses may lower the rate of rebleeding, and a difference in clinical effect between the two study arms will be difficult to confirm especially in these 382 patients enrolled before this amendment.

Table 8: Changes to planned analyses

Details of change	Reason for change
Forrest class (I vs. II) was not used as a stratification variable in the analysis	After a blind review of data no difference in rebleeding rate was seen between the 2 Forrest classes
Rate of rebleeding within 7 days was analyzed with Mantel-Haenszel test, stratified for the type of endoscopic treatment instead of a log-rank test.	Rebleeding was not considered to be time dependent during this short time period and a late rebleed is not less important than a early rebleed. The number of dropouts during this time period was low and therefore the advantage of censoring patients are low.
Country treatment interaction for the primary variable was tested instead of the centre treatment interaction.	The number of patients at several centers were too few to make this calculation possible.
Blood transfusions (number of blood units) and hospitalization (number of days hospitalized) were analyzed by a Wilcoxon 2-sample test instead of an ANCOVA	The variables are skew.
Mortality and bleed-related mortality were not stratified for the type of endoscopic treatment at baseline and a Fisher's exact test was used instead.	There was a low number of deaths

(Above Table is taken from Table 9 of Clinical Study Protocol for Study D961DC00001)

Comments:
It is important to note that the incidence of risk of rebleeding has been defined according to the Forrest classification; higher category in Forrest class has higher risk. Applicant changed the planned analysis and combined all classes based on observation that there was no difference in incidence of rebleeding during a blind analysis. This reviewer thinks that analysis be done as per original protocol i.e. separate analysis for each Forrest class 1a,1b, 2a, 2b, and compare these results with overall study result.

This study was conducted in 91 centers in 16 countries with variations in the investigators expertise and patient care. This reviewer proposes a statistical analysis using country variation in model to adjust for these variations.

6.1.4 Efficacy Findings

For the primary efficacy variable rebleeding within 72 hours, 764 of the 767 randomized patients were included in the ITT-analysis. The full analysis (ITT) set consisted of all randomized patients with at least 1 data point and signed informed consent. One patient in the esomeprazole treatment group did not take any study medication and 2 patients in placebo group did not sign the informed consent form and they were therefore excluded from the ITT analysis.

The per-protocol (PP) analysis is based on 608 patients since 83 patients in esomeprazole and 73 patients in placebo group had major protocol violations and were excluded from PP analysis.

Demographic and baseline characteristics, ITT population
All the demographic characteristics of the ITT population were comparable between the two treatment groups (Esomeprazole and Placebo). The tables 9, 10, 11, and 12 show the demographic profile of patients and some observations made by this reviewer follow each table.

Table 9: Demographic and baseline characteristics (gender, age, race smoking history), ITT population

Characteristic	Eso (n=375)	Placebo (389)
Gender,(%)		
• Male	67.7%	68.9%
• Female	32.3%	31.1%
Race		
• Caucasian	86.7%	87.9%
• black	1.1%	1 3%
• Oriental	7.2%	6 9%
• Others	5.1%	3 9%
Age		
• Mean (SD)	62.1 (17.1)	60.2 (17.6)
• Min-Max	18-95	18-98
Age (Years)		
• <65	48.5%	54%
• ≥65	51.5%	46%
Smoker	27.5%	28.3%
Non-smoker	72.5%	71%

(Table above is taken from Table 13 of Applicant's Clinical Study Report for Study D961DC00001)

Table 10: Demographic and baseline characteristics (ASA class, H/o peptic ulcer, its complication, and H.Pylori status), ITT population Cont:

Characteristic	Eso (n=375)	Placebo (389)
ASA class (%) • 1 • 2 • 3	 37.1(%) 50.1(%) 12.8(%)	 41.4(%) 45.8(%) 12.9(%)
Shock • No • Yes	 95(%) 5(%)	 95(%) 5(%)
H.*pylori* status (%) • Negative • Positive • Trace/missing	 25(%) 65(%) 10(%)	 30(%) 58(%) 12(%)
H/O peptic ulcer • No • Yes	 70(%) 30(%)	 69(%) 30(%) (Missing-1%)
Previous PU complications • No • Yes	 88 12	 89 11
Prior medication • NSAIDs Non-selective NSAID • Clopidogrel • Warfarin • SSRI	 40(%) 16.8(%) 3.2(%) 2.4(%) 2.4(%)	 40(%) 18.8(%) 2.8(%) 3.3(%) 3.6(%)

(Table above is taken from Table 13 of Applicant's Clinical Study Report for Study D961DC00001)
Shock defined as a systolic blood pressure ≤ 90 mm Hg or pulse ≥ 110 beats/min
The following cut-off values were applied for *H. pylori* IgG antibodies in serum:
positive: ≥1.1 U/mL
trace: ≥0.9 U/ml and <1.1 U/mL
negative: <0.9 U/mL
Any dose given within 2 weeks prior to enrollment

Table 11: Demographic and baseline characteristics (Presentation), ITT population Cont:

Characteristic	Eso (n=375)	Placebo (389)
Hemetemesis • No • Yes	 54(%) 46(%)	 53.5(%) 46.5(%)
Melena • No • Yes	 12.5(%) 87.5(%)	 11(%) 89(%)
Hematochezia • No • Yes	 92.5(%) 7.5(%)	 93.8(%) 6.2(%)

(Table above is taken from Table 13 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
The treatment groups were similar in majority of demographic characteristics. The following is to be noted:

Majority of patients in the study were Caucasians (86.7-87.9%) and very small number of black patients (1.1-1.3%). In the placebo group there were higher proportion of healthy patients (ASA class 1) compared with the esomeprazole group (41.1% versus 37.1). This could influence the efficacy in favor of esomeprazole.

Table 12: Demographic and baseline Characteristics (Endoscopic findings at baseline), ITT population (Cont):

Characteristic	Eso (n=375)	Placebo (389)
Forrest class, (%) • 1a • 1b • IIa • IIb	 7.5% 44.3% 36.3% 11.2%	 10.3% 41.9% 38.8% 8.7%
Endoscopic Treatment • Single • combination • None	 47% 51% 2%	 46.5 % 51.5% 2%
Ulcer Size, mm • Mean (SD) • Min-Max	 12.5(7.2) 4-50	 12.4 (7.8) 3-50
Ulcer location Stomach Duodenum	 42% 58%	 40% 60%
Number of ulcers larger than 2 cm ≤2 cm >2 cm	 92.3% 7.7%	 89.7% 10.3%
Number of patients with multiple ulcers Single Multiple Missing	 78.4% 13.6% 8%	 75.6% 18.5% 5.9%

(Table above is taken from Table 14 of Clinical Study Report for study D961DC00001)

Comments:
The baseline characteristics of ulcers in the two treatment groups were comparable i.e. endoscopic treatment, ulcer size and location of the ulcer in stomach and duodenum. However numerically lower proportion of patients in the esomeprazole group had:

- *Grade 1a (Severe) stigmata of risk of bleeding compared to the placebo group (7.5% versus 10.3%).*

- *Large ulcers > 2 cm compared to the placebo group (7.7% versus 10.3%).*
- *Multiple ulcers compared to the placebo group (13.6 versus 18.5%)*
- *In addition proportion of patients with missing data (on number of patients with multiple ulcers) were also more compared to placebo group (8% versus 5.9%)*

Comments:
All the above mentioned factors may influence the efficacy. The esomeprazole group had fewer patients with above characteristics i.e. Grade1a stigmata of risk of rebleeding, large ulcers, and multiple ulcers, and is therefore inherently less likely to rebleed. It is also noted that in table 14 CSR size of the ulcer ranges from 4 to 50 mm in esomeprazole group and 3 to 50 mm in placebo group. In the inclusion criterion, size of the ulcer has to be ≥ 5 mm for enrolment. (Unless these are additional ulcer after first 5 mm index ulcer).

Design: *Sponsor made an exclusion amendment to the study midway when 382 patients were already randomized. Patients who were treated with esomeprazole ≥ 40 mg I.V. 24 hours prior to the enrollment were not excluded in the first half of the study. Effect of this prior I.V. therapy may have carried over to the first 72 hours of the study affecting the primary variable.*

Subject Disposition
Approximately 90% of the patients completed the study in both treatment groups. Patients who discontinued were evenly distributed between the two treatment groups (See table 13).

Table 13: Proportion of patients discontinued and the reasons for discontinuation

Patient completion status	Eso[a] (n=376)	Placebo[b] (n=391)
Completed[c]	337(89.6%)	349(89.3%)
Discontinued	39(10.4%)	42(10.7%)
Reason for discontiuation:		
Incorrect Enrolment	1(0.3%)	3(0.8%)
Adverse Event	10(2.7%)	15(3.8%)
Voluntary Discontinuation by Subject	13(3.5%)	7(1.8%)
Subject Lost to Follow-up	8(2.1%)	6(1.5%)
Severe Non-Compliance to Protocol	2(0.5%)	2(0.5%)
Death	3(0.8%)	5(1.3%)[d]
Safety Reasons	1(0.3%)	2(0.5%)
Other	1(0.3%)	2(0.5%)

(Table above is taken from Table 11 of the Clinical Study Report for StudyD961DC00001)

Protocol Deviations*: The protocol deviations are shown in table 14.*

Table 14: Protocol Deviation

Deviations	**Esomeprazole Group** (N=375) n (%)	**Placebo Group** (N=389) n (%)
Overall	83 (22.1%)	73 (18.8%)
Inclusion/Exclusion Criteria	22 (5.9%)	26 (6.7%)
Excluded Medication	15 (4.0%)	21 (5.4%)
Insufficient Medicine intake	23 (6.1%)	13 (3.3%)
Others	23 (6.1%)	12 (3.1%)

(Information in Table above is taken from Table 12 of the Clinical Study Report for Study D961DC00001)

Comments:
The number of patients with protocol deviations was balanced between the two treatment groups (See table 15).

Data sets Analyzed

The results in table 15 show patient populations analyzed for all randomized, intent to treat, and per-protocol patients. The intent-to-treat (ITT) study population included all patients who were randomized and took at least the 70% of the intended I.V. dose during first 72 hours. For the primary efficacy analysis, the ITT study population was used.

Table 15: Study Population and protocol deviations

Category	**Esomeprazole group**	**Placebo Group**
All randomized Patients	376	391
Patients not dosed	1	2
Intent-to-treat Patients	375	389
Per-Protocol Patients	292	316
Patients non-evaluable for PP	83 (22.1%)	73 (18.8%)
Inclusion/Exclusion Criteria	22 (5.9%)	26 (6.7%)
Excluded Medication	15 (4.0%)	21 (5.4%)
Insufficient Medicine intake	23 (6.1%)	13 (3.3%)
Others	23 (6.1%)	12 (3.1%)

(Table above is taken from page 79 Table 12of the Clinical Study Report for Study D961DC00001)

Comments:
The table 15 shows study population for intent-to-treat and per-protocol population. Overall proportions of patients non-evaluable for per-protocol analysis were comparable between the two groups (Eso=22.1%, Placebo=18.8%). The criteria for non-evaluabilty for per-protocol were similar in the two treatment groups.

Efficacy Results:
Intent-to-treat Population

Primary Efficacy Analysis
The primary efficacy endpoint was rebleeding within 72 hours. Overall 5.9% patients had rebleeding in esomeprazole group compared to 10.3% in placebo group. The difference between the treatment groups is 4.4% with p value of 0.0256. (See table 16)

Table 16: 1^0 Endpoint: Proportion of patients with clinically significant rebleeding within 72 hours

Time	Esomeprazole (n=375)	Placebo (n=389)	p-value
72 hours	22 (5.9%)	40 (10.3%)	0.0256

(Above table is taken from table 21 of Clinical Study Protocol of the Study D916DC00001)

Comments:
Treatment difference in favor of esomeprazole is maintained for Caucasian population (table 17). The number of patients in other racial groups was small to draw firm conclusion. The treatment effect was equal for males and females. There is an important observation about patients older than 65 yrs. The treatment difference is reduced/ not maintained, compared to the result of the overall study, for this age group. This observation is of some concern because this age group is known to be associated with higher morbidity and mortality due to GI bleeding therefore needs better efficacy/protection.

Table 17: 1^0 Endpoint: Rebleeding by Race, Age, and Gender within 72 hours

Subgroup	Eso	Placebo
Race		
• Caucasian	18/325 (5.5%)	37/342 (10.8%)
Age		
• <65	10/182 (5.5%)	25/210 (11.9%)
• ≥65	12/193 (6.2%)	15/179 (8.4%)
Gender		
• Male	15/254 (5.9%)	28/268 (10.4%)
• Female	7/121 (5.8%)	12/121 (9.9%)

(Information in above table is taken from Table 22 of Clinical Study Protocol of the Study D961DC00001)

Secondary Variables:
Clinically significant rebleeding after the first 72 hours was assessed during 4 to 7 days and subsequently during 7 to 30 days (table 18 and figure 3). The primary thinking for this analysis was to avoid cumulative incidence of rebleeding/non-bleeding during 72 hours being reflected later in subsequent periods after 72 hour (during 4 to 7 days and 7

to 30 days). Further with the background knowledge that the majority of rebleeding in peptic ulcers occurs within 7 days, the analysis was focused on rebleeding during first 7 days. Similar analysis was done for other secondary variables i.e., need for surgery or endoscopic retreatment for rebleeding.

Table 18: 2^0 Endpoint, Rebleeding during 4 to 7 days and 7 to 30 days

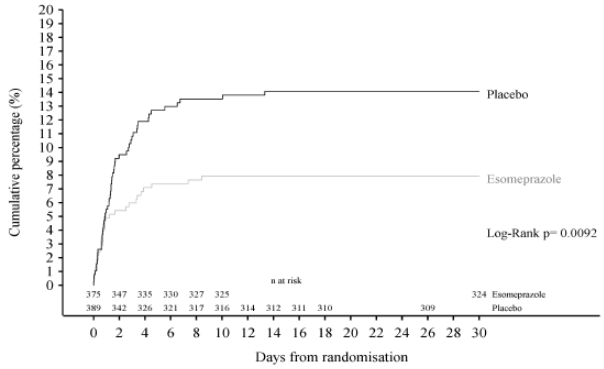
Time	Esomeprazole (n=375) (n)	Placebo (n=389) (n)
4-7 days	5	10
7-30 days	2	3

(Above table compiled by reviewer from page 90 of Clinical Study Protocol for Study D961DC00001 and Table 3 of Applicants response document dated 15 August, 2008)

Comments:

Rebleeding during 4 to 7days occurred in 5 patients in esomeprazole group compared to 10 in placebo group. The overall treatment difference/effect is maintained during 4 to 7 days. Between 7 to 30 days only 2 and 3 patients had rebleeding in the two groups. The data further support that majority of rebleeding occurs within 7 days (figure 3).

Figure 3: Kaplan-Meier Estimate of the Cumulative % of Patients with Rebleeding in 30 days



Time	*Eso (n=375)*	*Placebo (n=389)*	*p-value*
72 hours	*22 (5.9%)*	*40 (10.3%)*	*0.0256*
4-7 days	*5*	*10*	*-*
7-30 days	*2*	*3*	*-*

(Above Figure is taken from Figure 3 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:

Figure 3 shows rebleeding on Kaplan Meier survival curve and compared with the data just shown. The difference in cumulative percentage of patients with rebleeding in two groups is observed at 72 hours which gradually rises until 7 days and thereafter plateaus and difference between the two groups is maintained.

Requirement for surgery due to rebleeding

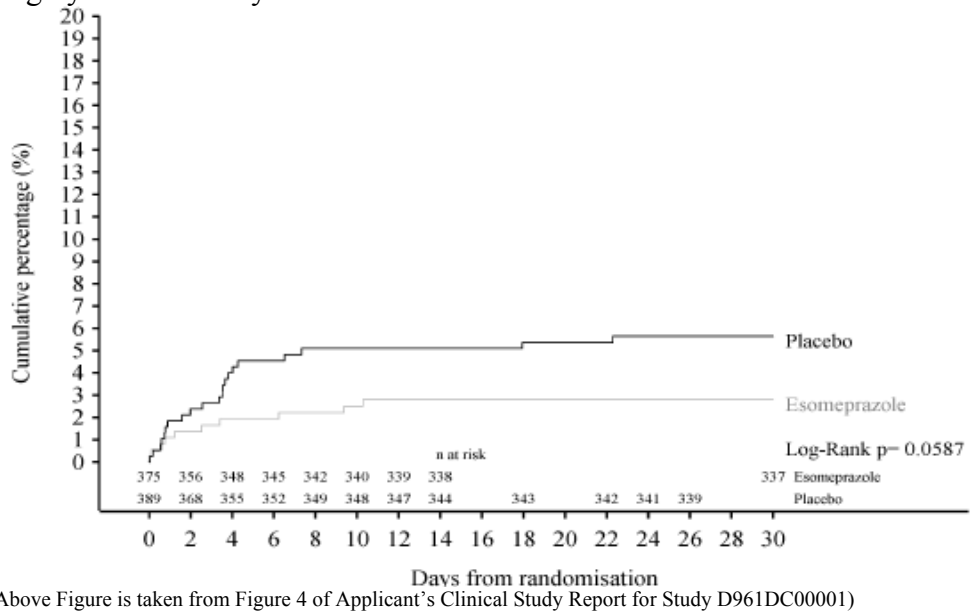
The results in table 19 and figure 4 show proportion of patients requiring surgery during 72 hours, 4 to 7 days and 7 to 30 days.

Table 19: 2^0 Endpoint, Surgery due to rebleeding

Time	Eso (n=375)	Placebo (n=389)	p-value
72 hours	5 (1.3%)	9 (2.3%)	0.3124
4-7 days	2	8	
7-30 days	3	4	

(Above table compiled by the reviewer)

Figure 4: Kaplan-Meier Estimate of the cumulative percentage of patients requiring surgery within 30 days



(Above Figure is taken from Figure 4 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:

In this picture proportion of patients requiring surgery is shown on Kaplan Meier survival curve. This survival curve is compared with the numerical data in table 19 above. The majority of surgical procedures are required within the first 4 days of the study. There is a numerical advantage for the esomeprazole group. The difference in cumulative percentage of patients requiring surgery in two groups is seen at 72 hours and peaks at 7 days and thereafter maintains plateau.

Requirement for endoscopic retreatment due to rebleeding

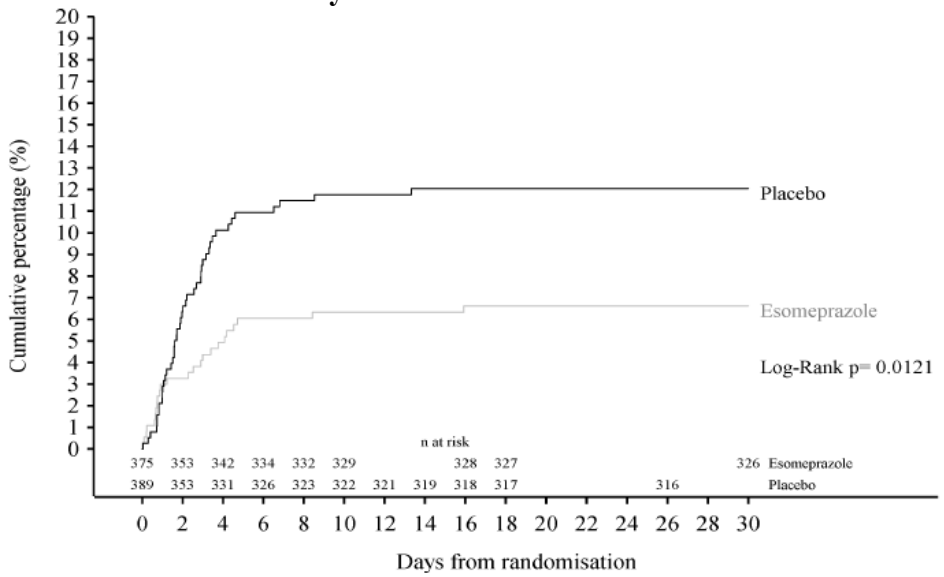
Results in table 20 and figure 5 shows proportion of patients requiring endoscopic retreatment during 72 hours, 4 to 7 days and 7 to 30 days.

Table 20: 2^0 Endpoint: Endoscopic Retreatment

Time	Eso (n=375)	Placebo (n=389)	p-value
72 hours	16 (4.3%)	32 (8.2%)	0.0244
4-7 days	6	10	
7-30 days	2	3	

(Above Table compiled by the reviewer)

Figure 5: Kaplan-Meier estimate of the % of patients requiring endoscopic retreatment within 30 days.



(Above Figure is taken from Figure 5 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:

Patients requiring endoscopic treatment are shown on Kaplan Meier survival curve (figure 4). Survival curve is compared with numerical data shown in table 20 above. Patients treated with esomeprazole required less endoscopic treatment due to rebleeding compared with placebo at 72 hours. The difference in cumulative percentage of patients requiring endoscopic treatment in two groups is seen at 72 hours and peaks at 7 days and thereafter maintains plateau. Majority of the endoscopic retreatments were required/performed during the first 7 days of the study.

Number of blood units transfused

Table 21 shows number of blood units required/transfused during first 72 hours, 4 to 7 days and 7 to 30 days.

Table 21: 2^0 Endpoint, Number of blood units transfused

Time	Eso (n=375)	Placebo (n=389)	p-value
72 hours	492	738	0.0472
4-7 days	60	138	
7-30 days	37	59	

(Table above is taken from Table 3, Applicant's response document dated 15 August, 2008 for Study D961DC00001)

Comments:
Patients treated with esomeprazole needed less number of blood transfusions compared to placebo during the I.V. phase of the study (p=0.0472). It is difficult to explain why the number of blood units required is less in esomeprazole group even during days 4 to 30 when both treatment groups received oral esomeprazole 40 mg daily.

Number of days hospitalized due to rebleeding

Table 22 compares number of days patients were hospitalized in two treatment groups during 72 hours, 4 to 7 days and 7 to 30 days.

Table 22: No. of Days Hospitalized Due to Rebleeding

Days	Eso (n=375)	Placebo (n=389)	p-value
0	346 (92.3%)	336 (86.4%)	
1 to 5	11 (2.9%)	12 (3.1%)	
6 to 10	6 (1.6%)	21 (5.4%)	
>10	12 (3.2%)	20 (5.1%)	
Total number of Days	284	500	0.0080

(Table above is taken from Table 29 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
Patients in esomeprazole group required less number of days of hospitalization compared to placebo group.

Per-Protocol Population
The per-protocol efficacy analysis for first 72 hours of high dose continuous I.V. infusion demonstrated fewer patients with rebleeding in esomeprazole group compared with placebo group (4.8% versus 10.4%; see table 23).

Table 23: 1^0 Endpoint, Rebleeding within 72 hours PP Population

Time	Eso (n=292)	Placebo (316)	p-value
72 Hours	14 (4.8%)	33 (10.4%)	0.0093

(Table above is taken from Table 4 of Applicant's response document dated 15 August, 2008 for Study D961DC00001)

Statistical Issues and Findings:

Statistics review was done by Dr Sonia Castillo. The information presented below is taken from her review.

Study D961DC00001, Non-US, single pivotal study was conducted in 16 countries and 91 centers for the present indication. Sponsor also made some changes in analysis during the study. Therefore the assessment was focused on establishing robustness of such a single study and to adjust the results for variability of physician expertise and standard of care in different countries.

There are two statistical issues in this submission. They are: 1) the final analysis model was revised in the Statistical Analysis Plan (SAP) with no protocol amendment and 2) the clinical concern about country variation in physician expertise and standard of care were not accounted for in the analyses. To address these statistical issues, Dr Sonia Castillo, the statistics reviewer conducted the primary efficacy analysis with the pre-specified model and sensitivity analyses for the country issues. These results did not provide consistent efficacy conclusions.

Although the study demonstrated a reduction in rebleeding for Nexium compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted to investigate the country variation in physician expertise and standard of care did not give consistent results to the protocol specified analyses.

This review focuses on the primary efficacy endpoint.

Background/Original Plan

In the initial protocol dated June 1, 2005, the baseline factors of endoscopic treatment (single vs. combination) and Forrest class (I vs. II) were assumed by the Applicant to influence the probability of rebleeding and that they would be included in the analysis. According to the Applicant, after a review of blind data no difference was seen in rebleeding rate between the Forrest groups. The analysis was therefore changed in the Statistical Analysis Plan (dated Dec. 17, 2007) to only be stratified for endoscopic treatment (single vs. combination). No protocol amendment documenting this change was issued. The Applicant stated that: "All changes were made prior to unblinding of study data" (Section 5.8.2 on page 74 of study report). Further DSMB reviewed unblended data at formal interim analysis meetings on 21 November 2006 and 13 March 2007. Recommendations to continue the study were communicated to the applicant after those meeting.

The primary efficacy population was the ITT population. The study sample size of 760 subjects (380 subjects per treatment group) was based on assuming 7% (esomeprazole) and 15% (placebo) rebleeding rates within the first 72 hours, a 2-sided chi-square test with 5% significance level and 90% power and 10% of the subjects excluded from the per-protocol analysis.

The primary analysis for the rate of clinically significant rebleeding within 72 hours used a Mantel-Haenszel test, stratified for type of endoscopic treatment at baseline. A two-

sided chi-square test with significance level of 5% was used. The final primary efficacy test significance level is adjusted, to account for two interim analyses done, and is equal to 0.0489. A raw data based estimate of the treatment difference along with a 95% confidence interval and p-value for testing the superiority of esomeprazole to placebo were presented. A Breslow-Day test was used to evaluate the country-treatment interactions.

Applicant Efficacy Results

The Applicant's result for the primary efficacy endpoint of rate of clinical significant rebleeding within 72 hours is presented in Table 24. The rate of clinical significant rebleeding within 72 hours of I.V. treatment after hemostasis decreases by a mean of 4.4% with esomeprazole compared to placebo (p=0.026). Also, no significant country-by-treatment interactions were found based on the Breslow-Day test.

Table 24: Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for ITT population

	Esomeprazole (N=375)	Placebo (N=389)	Esomeprazole - Placebo
% No Rebleed (n)1	94.1% (353)	89.7% (349)	
% Rebleed (n)1	5.9% (22)	10.3% (40)	
Treatment Difference vs. Placebo (95% C.I.)1			-4.4% (-8.3%, -0.6%)
p-value for Treatment Difference3			0.0256

(Source: Table 21 on page 88 and Table 54 on page 135 of Study D961DC00001 report).
[1] Percentages and 95% confidence interval based on raw data
[2] p-value based on Mantel-Haenszel test stratified by type of endoscopic hemostatic treatment used (single vs. combination treatment)

Dr Sonia Castillo's (Statistical Reviewer) Sensitivity Analyses:

Sensitivity analyses for the primary efficacy endpoint of rate of rebleeding were performed to evaluate how the pre-specified study findings hold up when alternative analyses are performed.

First, the protocol-specified Mantel-Haentzsel analysis included Forrest class (I vs. II) and type of endoscopic treatment (single vs. combination) as stratification variables. Using this model, the results are similar to those presented in Table 24 (p=0.0274).

(b) (4)

Second, single endoscopic epinephrine injection (see Section 3.1) is not an acceptable current standard of treatment to stop bleeding ulcers. Given this information, it was thought more appropriate to analyze data by keeping all four Forrest class categories separate and also analyze data after removing patients who received single endoscopic injection treatment.

We had other concerns about the study design, namely, the non-inclusion of U.S. centers and variations across centers/countries with respect to physician expertise and standard of

care. It was thought that not accounting for center or country variations could result in misleading results, especially in the absence of U.S. data.

Analysis of certain centers and their effect on the study results:

Majority of the centers (54 ÷ 91 = 59%) either had a treatment effect of zero or a treatment effect that could not be estimated. Most of these details can be seen in Table 25 which presents center information for those centers that had a non-zero treatment effect.

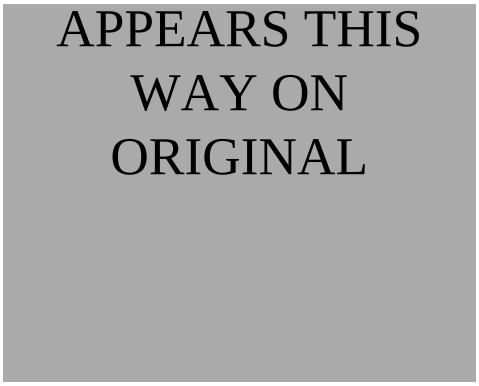


Table 25: Study D961DC00001; treatment effect and 95% confidence interval by center (ITT population)

Center Number	n_{Nexium} / $n_{Placebo}$	Esomeprazole – Placebo (%)	95% C.I.
11	1 / 3	66.67	
12	6 / 6	-16.67	
23	3 / 3	16.67	
41	3 / 4	-25.00	
76	7 / 5	14.29	
82	3 / 4	-25.00	
84	3 / 3	-33.33	
98	7 / 8	-25.00	
99	5 / 5	-20.00	
105	5 / 5	20.00	
106	1 / 2	100.00	
110	1 / 2	-50.00	
121	1 / 2	-100.00	
122	5 / 7	-8.57	
133	1 / 1	-100.00	
138	7 / 6	-16.67	
143	2 / 1	50.00	
144	3 / 4	-50.00	
160	2 / 4	25.00	
163	3 / 2	33.33	
174	2 / 2	-50.00	
175	3 / 5	-20.00	
176	4 / 4	50.00	
177	7 / 11	14.29	
180	7 / 3	-19.04	
183	7 / 6	14.29	
186	3 / 3	-33.00	
201	5 / 3	20.00	
215	8 / 8	-12.50	
21 (Denmark)	13 / 16	-6.25	(-30.23, 18.60)
53 (France)	13 / 13	0.0	(-26.17, 26.17)
78 (Germany)	10 / 10	-20.00	(-56.67, 19.04)
101 (Hong Kong)	25 / 25	-4.00	(-22.22, 13.51)
102 (the Netherlands)	11 / 10	-30.91	(-66.10, 7.99)
127 (Romania)	12 / 12	-8.33	(-38.48, 18.85)
145 (Russia)	12 / 16	-12.50	(-38.48, 14.43)
149 (South Africa)	14 / 15	7.62	(-20,12, 35.97)
184 (Turkey)	12 / 13	-7.69	(-37.57, 18.91)

(Source: Statistical Reviewer's Listing)

Also of note is that all eight of the French centers had a treatment effect of zero; and of the three UK centers, one had a treatment effect of zero and the other two had a treatment effect that could not be estimated. In addition, of the nine centers with at least 20 subjects with a non-zero treatment effect (see shaded part of Table 25), one center from the Netherlands (#102) had the largest treatment effect, in favor of esomeprazole, of

30.9%. Table 26 presents treatment effect information for center #102 from the Netherlands. Note that the 95% confidence interval includes zero.

Table 26: Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for the Netherlands Center #102

	Esomeprazole (N=11)	Placebo (N=10)	Esomeprazole - Placebo
% No Rebleed (n)	90.9% (10)	60% (6)	
% Rebleed (n)	9.1% (1)	40% (4)	
Treatment Difference vs. Placebo			-30.9% (-66.10, 7.99)

(Source: Statistical Reviewer's Listing)

To investigate the influence of the Netherlands center #102 on the protocol specified model results, this center was removed from the analysis. The results are presented in Table 27 below. The treatment effect for the rate of clinically significant rebleeding within 72 hours changed from -4.4% with a significant p-value of 0.0274 to -3.7% with a non-significant p-value of 0.0596.

Table 27: Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours Excluding Netherlands Center #102

	Esomeprazole	Placebo	Esomeprazole – Placebo
N	364	379	-
% No Rebleed (n)	94.23% (343)	90.50% (343)	-
% Rebleed (n)	5.77% (21)	9.50% (36)	-
Treatment Difference vs. Placebo (95% C.I.)	-	-	-3.73% (-7.67%, 0.10%)
p-value			0.0596

(Source: Statistical Reviewer's Listing)
* p-value based on the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II) and type of endoscopic hemostatic treatment used (single vs. combination treatment)

Country Analysis and its effect on study results:

Since it was not feasible to include center as a stratification factor in the formal analysis, we decided that a way to account for variations with respect to physician expertise and standard of care was to include country as a stratification factor in our analyses and to explore treatment effect by country.

Table 28 present the treatment effects and 95% confidence intervals for the 16 countries participating in the study. The treatment effect has a wide range from a minimum of -25.0% (esomeprazole better than placebo) to a maximum of 12.5% (placebo better then esomeprazole). Recall that the overall treatment effect is -4.4% with a 95% C.I. interval of (-8.3%, -0.6%). Note that all the countries' 95% confidence intervals include zero. With an overall treatment effect of -4.4%, one would expect there to be at least a few countries that show a treatment effect in favor of esomeprazole, based on the upper bound of the 95% confidence interval being less than zero.

Analysis based on Forrest Class:

Analysis using the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II) and type of endoscopic hemostatic treatment used (single vs. combination treatment) and now by adding country as a factor resulted in a non-significant p-value of 0.0582. A similar analysis using Forrest class as four separate categories instead of two resulted in a non-significant p-value of 0.1069.

Table 28: Study D961DC00001: Treatment Effect and 95% Confidence Interval for Clinically Significant Rebleeding within 72 hours by Country

Country	$n_{Esomeprazole}$ / $n_{Placebo}$	Treatment Effect (%) (Esomeprazole - Placebo)	95% C.I.* (Exact)
Spain	8 / 8	12.5	(-31.4, 54.5)
South Africa	20 / 22	5.4	(-14.0, 27.5)
Sweden	52 / 49	3.5	(-8.4, 15.6)
Denmark	35 / 36	0.2	(-15.0, 15.6)
France	27 / 31	0.0	(-11.2, 12.8)
UK	4 / 1	0.0	(-97.5, 67.2)
Austria	19 / 24	-3.1	(-22.4, 18.3)
Hong Kong	25 / 25	-4.0	(-22.2, 13.5)
Turkey	24 / 24	-4.2	(-22.9, 13.6)
Netherlands	26 / 27	-7.0	(-28.3, 14.6)
Russia	52 / 59	-8.2	(-19.4, 1.1)
Romania	26 / 24	-8.3	(-27.0, 5.9)
Germany	27 / 26	-11.8	(-33.5, 8.1)
Norway	15 / 16	-18.3	(-46.2, 9.9)
Greece	12 / 13	-23.1	(-53.8, 7.2)
Finland	3 / 4	-25.0	(-81.0, 49.4)
OVERALL	375 / 389	-4.4	(-8.4, -0.5)

(Source: Statistical Reviewer's listing)

* Exact confidence interval calculated using StatXact.

Analysis on endoscopic therapy (excluding Injection therapy alone):

Table 29 below presents results after excluding those subjects who received single endoscopic injection therapy. The treatment effect for the rate of clinically significant rebleeding within 72 hours changed from -4.4% with a significant p-value of 0.0274 to -4.5% with a non-significant p-value of 0.0667 using the protocol specified model and a non-significant p-value of 0.3270 using Dr Sonia's model (see bottom of Table 3.7 for model description).

Table 29: Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for Subjects Not Receiving Single Endoscopic Injection Therapy

	Esomeprazole (N=232)	Placebo (N=247)	Esomeprazole - Placebo
% No Rebleed (n)	94.4% (219)	89.88% (222)	
% Rebleed (n)	5.6% (13)	10.12% (25)	
Treatment Difference vs. Placebo (95% C.I.)			-4.52% (-9.55%, 0.35%)
p-value based on the protocol-specified model[1]			0.0667
p-value based on this Reviewer's model[2]			0.3270

(Source: Statistical Reviewer's Listing)
[1] p-value based on the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II) and type of endoscopic hemostatic treatment used (single vs. combination treatment)
[2] p-value based on the Mantel-Haenszel test stratified by country, Forrest class (Ia, Ib, IIa, IIb), and type of endoscopic hemostatic treatment used (single vs. combination treatment)

For comparison, the results of an analysis using those subjects who did receive single endoscopic injection therapy are presented in table 30. The treatment effect for the rate of clinically significant rebleeding within 72 hours changed from -4.4% with a significant p-value of 0.0274 to -4.3% with a non-significant p-value of 0.2039 using the protocol specified model and a non-significant p-value of 0.2699 using Dr Sonia's model (see bottom of table 30 for model description).

Table 30: Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for Subjects Receiving Single Endoscopic Injection Therapy

	Esomeprazole (N=143)	Placebo (N=142)	Esomeprazole - Placebo
% No Rebleed (n)	93.7% (134)	89.4% (127)	
% Rebleed (n)	6.3% (9)	10.6% (15)	
Treatment Difference vs. Placebo (95% C.I.)			-4.27% (-11.2%, 2.3%)
p-value based on the protocol-specified model			0.2039
p-value based on this Reviewer's model			0.2699

(Source: Statistical Reviewer's Listing)
[1] p-value based on the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II)
[2] p-value based on the Mantel-Haenszel test stratified by country and Forrest class (Ia, Ib, IIa, IIb)

All the above alternative sensitivity analyses to assess the robustness of the single pivotal study do not provide supportive evidence for the overall treatment effect and the protocol-specified model results. With an overall treatment effect of -4.4%, one would expect there to be at least a few countries that show a treatment effect in favor of esomeprazole, based on the upper bound of the 95% confidence interval being less than zero. Also, all p-values for alternative analyses are not significant, a change from the protocol-specified model p-value of 0.0274.

Although the study demonstrated a reduction in rebleeding for esomeprazole compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted to investigate the country variation in physician expertise and standard of care did not give results consistent with protocol-specified analyses. Given that this is a single study whose results are not statistically persuasive, i.e., with a very small p-value, and are not supported by alternative analyses.

6.1.5 Clinical Microbiology

No issues

6.1.6 Efficacy Conclusions

The applicant submitted the results of single pivotal, phase 3, randomized, double blind, multicenter, multi- national, parallel-group, placebo controlled study D961DC00001. The study population consisted of patients with peptic ulcer bleeding after complete hemostasis of the initial bleeding was achieved with endoscopic treatment. Of the total 767 patients 376 were randomized to receive esomeprazole I.V. 80 mg for 30 min followed by esomeprazole I.V. 8 mg/hr for 71.5 hours and 391 received placebo I.V. for 30 min followed by placebo I.V. for 71.5 hours. Patients that received I.V. esomeprazole in first 72 hours constituted "esomeprazole" group. Those receiving I.V. placebo were designated as "placebo" group. After 72 hours of I.V. treatment both groups (esomeprazole and placebo) received oral esomeprazole 40 mg daily for next 27 days.

Primary Endpoint
The primary efficacy endpoint was rebleeding within 72 hours. Overall 5.9% patients had rebleeding in esomeprazole group compared to 10.3% in placebo group. The difference between the treatment groups was 4.4% with p value of 0.0256.

Secondary Endpoints
The secondary efficacy analysis was done for clinically significant rebleeding within 7 days and 30 days, death within 72 hours and 30 days, requirement for surgery within 72 hours and 30 days, requirement for endoscopic re-treatment within 72 hours and 30 days, number of blood units transfused within 72 hours and 30 days and number of days hospitalized due to rebleeding during the 30-day treatment phase. The treatment effect was primarily observed during 0 to 7 days as most of the secondary variables events occurred during first 7 days.

Limitations of the study
In the present submission although the study demonstrated a reduction in rebleeding for esomeprazole during the 72 hours (primary Endpoint) compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted by the FDA's statistician to assess the robustness of the single study did not give results consistent with protocol-specified analyses. Sensitivity analyses for the primary efficacy endpoint of rate of rebleeding were carried out to evaluate how the pre-specified study findings hold up when alternative analyses were performed. According to the FDA's statistician, the following analyses did not support the primary results:

1. Country Analysis and its effect on study results.
2. Analysis of certain centers and their effect on the study results.
3. Analysis based on Forrest Class.
4. Analysis on endoscopic therapy (excluding Injection therapy alone).

Lack of support from pharmacodynamic evaluation

The clinical study was not adequately supported by the two supportive PK/PD studies. For adequate hemostasis and preventing clot lysis it is imperative to achieve pH > 6 as proposed in the hypothesis for the present trial. The two supportive PK/PD studies (D961DC00015, D961DC00004) submitted in this submission did not demonstrate achieving intragastric pH of ≥ 6 adequately with the dose and mode of administration used in the trial. Intragastric pH of > 6 could be achieved only for less than 50 % of the time in 24 hour (D9615C00015=52.3%; D961DC00004=44.6%). Only one subject had an intragastric pH > 6 more than 90% of time in 24-hour period.

Conclusions

The efficacy results of this single, non-US, study did not provide substantial evidence of effectiveness to support the sought indication.

In the absence of replication the robustness of the primary results was not established or proved by alternative sensitivity analyses. There was insufficient proof of the superiority of high dose I.V. esomeprazole over placebo to support the proposed indication for (b) (4) (b) (4) (b) (4) The weakness of the study was evident throughout the execution of the trial during the two interim analyses. The two PK/PD studies were also not supportive of the clinical study. In order to resolve these deficiencies, the applicant should provide at least one additional adequate and well-controlled study to demonstrate the proposed clinical benefit. The study should include some US centers.

7. INTEGRATED REVIEW OF SAFETY

The sponsor had submitted results of one clinical study (D961DC00001), two Phase 1 PK/PD studies (D961DC00004 and D9615C00015), in order to address safety issues related to the clinical trial. Of note this is the first time safety of high dose continuous I.V. infusion of esomeprazole has been assessed.

Short Summary of Safety

The purpose of the safety assessment in this application was to investigate whether there would be any safety concerns with administering esomeprazole I.V. as a continuous infusion regimen over 72 hours, with an initial 80 mg bolus over 30 minutes followed by a continuous infusion of 8 mg/h. The most common AEs in both treatment groups were related to rebleeding, i.e., the efficacy outcome variable. Infusion site reactions (thrombophlebitis, phlebitis, infusion site erythema/reaction/edema) were more common in the esomeprazole treatment group compared to the placebo treatment group. These events were, however, mild, of short duration and did not cause discontinuation of study drug. The alkaline phosphatase (ALP) values increased to a slightly higher degree in the esomeprazole treatment group compared to placebo group.

The adverse event (AE) profile for esomeprazole I.V. did not differ from that expected in an acutely ill patient population with peptic ulcer bleeding (PUB).

Esomeprazole I.V. infusion regimen was also well tolerated in healthy volunteers in doses up to 120 mg bolus and 8 mg/h during 24 hours. The results show that the safety profile of esomeprazole I.V. was similar to placebo I.V. and no safety concerns were raised concerning the esomeprazole oral treatment period.

It is worth reiterating that in the safety review of pivotal study (D961DC00001) during I.V. treatment (72 hours) local administration site adverse events related to skin and vascular systems occurred at a significant higher rate for esomeprazole arm compared to the placebo arm. However, the overall safety profile was deemed comparable between the two arms (esomeprazole versus placebo).

One focus of the current safety review was to determine safety profile of the high dose continuous I.V infusion of esomeprazole compared with placebo during I.V. treatment phase (within 72 hours). In particular distribution by treatment arm of serious adverse events (SAE), adverse events (AE), and AEs leading to withdrawal was assessed.

The safety of esomeprazole I.V. Nexium in the dose of 20 mg or 40 mg daily was previously reviewed for the indication of short term use (7 to10 days) in GERD and erosive esophagitis at the time of the original submission of I.V. Nexium approved in 2005. The safety profile of I.V. Nexium as an injection or infusion was similar to the oral administration. Neither the Adverse Events (AE) pattern nor any other safety assessments implied any safety concerns for I.V. administration of esomeprazole in the dose of 20 mg or 40 mg daily for 7 to 10 days. Since its approval in 2005, Esomeprazole injection for I.V. administration has been marketed in United States.

7.1 Methods and Findings

The safety data for each of the mentioned studies were reviewed in this safety section by reviewing all pertinent safety events that occurred in each study. The safety analyses of high-dose intravenously administered esomeprazole are primarily based on all reported data from 375 patients enrolled in a multi-national Phase 3 study (D961DC00001). Also included is additional information from 64 healthy subjects from two Phase 1PK/PD studies (D961DC00004 and D9615C00015), submitted with this submission. In tabulating adverse events, Medical Dictionary of Regulatory Activities (MedDRA), version 10.1 preferred terms was used.

A general overview of the objectives, design and number of patients and healthy subjects in the clinical program is given in table 31.

Table 31: Clinical Studies

Study	Objectives	Design	Test product Dosage regimen	Population	Number enrolled	Treatment Duration
D961DC00001	To assess prevention of rebleeding in patients that have undergone successful primary endoscopic hemostasis of a bleeding peptic ulcer	Randomized, double-blind, parallel-group, placebo-controlled (esomeprazole)	80 mg I.V. infusion in 30 minutes followed by I.V. continuous infusion at the dose of 8 mg/h for 71.5 hours	Patients with bleeding peptic ulcer	767	72 hours
D961DC00004	To assess the effect on 24-hour intragastric pH and pharmacokinetics in healthy subjects.	Double-blind, randomized, 2-way cross-over (esomeprazole vs omeprazole)	80 mg I.V. infusion in 30 minutes followed by I.V. continuous infusion at the dose of 8 mg/h for 23.5 hours	Healthy subjects	39	24 hours
D961DC00015	To assess effect on 24-hour intragastric pH & pharmacokinetics in healthy subjects.	Open, randomized, five-way crossover dose finding study (esomeprazole)	40, 80, and 120 mg followed by a continuous infusion of 8 or 4 mg/h	Healthy subjects	25	24 hours

(Above table compiled by the reviewer)

Purpose of the clinical safety evaluations with high-dose esomeprazole I.V.

The evaluation is focused on the difference in safety profile of high-dose esomeprazole I.V. compared to placebo, in the target population during the first 72 hours. This was done to observe any causality between high dose esomeprazole and adverse events. Safety data were further analyzed in 2 separate groups: Patients that had experienced peptic ulcer bleeding (PUB) and healthy subjects based on the fact that population and design of phase 3 and phase 1 studies were different. The safety profile of high-dose esomeprazole I.V. was also retrospectively compared to the established safety profiles of standard-dose esomeprazole I.V. and oral esomeprazole to detect any differences.

Study D961 DC00001

The primary objective of the study was:
To evaluate safety during 72 hours of intravenous (I.V.) infusion of esomeprazole compared to placebo. The evaluation was done by assessment of adverse events (AEs), physical examination, laboratory measurements, blood pressure (BP), and pulse rate and rhythm.

The secondary objective of the study was:
To evaluate safety after 30 days treatment with esomeprazole:

- Seventy two hours of I.V. continuous infusion followed by 27 days of oral administration of esomeprazole

The evaluation was done by assessment of adverse events (AEs), physical examination, laboratory measurements, blood pressure (BP), and pulse rate and rhythm.

Comments:
Results of the primary safety evaluation are critical as esomeprazole has been administered in high dose continuous infusion for 72 hours for the first time (268 mg/ 24 h for 72 h in present study versus 40 mg/24 for 7to10 days previously approved). The results of the secondary evaluation are not as critical therefore shall be briefly summarized.

The multi-national study, D961DC00001, was a randomized, double-blind 72-hour treatment period comparing high-dose esomeprazole I.V. with placebo I.V. treatments. The I.V. treatment was followed by open oral treatment with esomeprazole 40 mg od for 27 days for all PUB-patients in both arms of the study. Data for the randomized, double-blind high-dose I.V. treatment period, 0 to72 hours, 4 to 30 days period and the total combined treatment period 0 to 30 days, were presented by the 2 treatment groups (esomeprazole and placebo). Three of the 767 randomized PUB-patients did not receive any study drug (1 in esomeprazole group and 2 in placebo group), thus the safety population comprised 764 PUB patients.

Data from PK/PD trials

The 2 PK/PD studies in healthy subject are summarized and presented by dosage treatment groups. The studies had a randomized cross-over design where treatment was given for 24 hours, with 13-day or more wash-out periods between treatments. In study D961DC00004, 1 of the 40 randomized healthy subjects did not receive any study drug, thus the safety population comprised 39 healthy subjects. In study D9615C00015, one of the 26 randomized healthy subjects did not receive any study drug, thus the safety population comprised 25 healthy subjects.

Study D961DC00015, dose finding study, assessed effect of different doses of esomeprazole on 24-hour intragastric pH and pharmacokinetics in healthy subjects; while study D961DC00004 compared esomeprazole and omeprazole for their effect on 24-hour intragastric pH and pharmacokinetics in healthy subjects. The comparison of esomeprazole I.V. with omeprazole I.V. showed very similar results in safety measurements, though the sample size was small.

The safety information is presented as follows:

- Exposure to the drug, including summary of class safety data, study designs, and demographic characteristics.
- Adverse events, including definitions and methods.
- Clinical laboratory evaluations.
- Vital signs, including electrocardiogram (ECG).
- Safety in special groups and situations.
- Post-marketing data.

Extent of exposure of experimental drugs (esomeprazole versus placebo-dose/duration)

Peptic Ulcer Bleeding Study (D961DC00001)
In the pivotal study 376 patients were randomized to receive high dose continuous infusion of esomeprazole (80 mg as I.V. infusion in 30 minutes followed by 8 mg/hour for 71.5 hours) during first 72 hours (I.V. treatment) and 391 to received I.V. placebos for the same duration. After 72 hours (Oral treatment), all patients that continued in the trial received esomeprazole in the dose of 40 mg daily during 4 to 30 days. Patient (b) (6) randomized to esomeprazole did not receive any study drug, and patients (b) (6) and (b) (6), randomized to placebo, did not sign the informed consent, and were excluded from the safety population. Thus, 375 PUB patients receiving I.V. esomeprazole and 389 patients I.V. placebo for mean period of 72 hours, were evaluated for safety for high dose esomeprazole continuous infusion. During 72 hours of I.V administration 375 patients in esomeprazole group received 652 mg of esomeprazole per patient and 391 patients received placebos during this period.

Drug exposure in peptic ulcer bleeding patients during 72 hours of I.V. administration:
Patients in the peptic ulcer bleeding trial were exposed to 80 mg I.V. bolus of esomeprazole followed by continuous infusion of esomeprazole at the rate of 8 mg/hour for next 71.5 hours. Table 32 shows the drug dose (Mean, S.D and range of dosage) administered as bolus and I.V. infusion within first 72 hours.

Table 32: Drug exposure (Esomeprazole): I.V. bolus and I.V. infusion

	Esomeprazole- I.V. bolus (n=371)	**Esomeprazole-I.V. infusion** (362)
Mean (mL)*	99.84 (80 mg)	675.31 (540 mg)
Standard Deviation	8.33	156.46
Standard Error	0.43	8.22
Range (Min-Max) mL	50-200	12-929

(Reviewer compiled data from the data table D961DC00001/crt/datasets/R-INFSC1.xpt and D961DC00001/crt/datasets/R-INFSCH.xpt)
* 10 mL = 8 mg esomeprazole
# Normal = I.V. bolus- 80 mg, I.V.infusion-572 mg

Drug exposure in healthy subjects (D961DC00004, D9615C00015)
Sixty four healthy subjects participated in two PK/PD studies. These 64 healthy subjects were part of 6 groups that received high-dose esomeprazole I.V. for 24 hours in doses between 174 mg and 308 mg. The dose subsequently chosen for the PUB-patient study 268 mg daily (80 mg I.V. infusion in half an hour + 8 mg/h as continuous infusion x 23.5 h), had the greatest extent of exposure in 63 healthy subjects in these two studies for 1512 hours.

General definitions and guidelines for Adverse Events:

Definitions and methods
The definitions of AE, SAE, and discontinuation of study drug due to AE (DAE), other significant AE (OAE), causality rating and intensity used in the studies by the sponsor are presented below.

Adverse Event (AE)
An AE was the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition could be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE could include an undesirable medical condition occurring at any time, including run-in or wash-out periods, even if no study treatment was administered.

Serious Adverse Event (SAE)
An SAE was an AE occurring during any study phase (i.e. run-in, treatment, wash-out, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfilled 1 or more of the following criteria:

- resulted in death
- was immediately life-threatening
- required in-patient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- was a congenital abnormality or birth defect
- was an important medical event that could have jeopardized the patient or could have required medical intervention to prevent one of the outcomes listed above.

Discontinuation of study drug due to AE (DAE)

A DAE was an AE that caused a discontinuation of study drug intake.

Other significant Adverse Event (OAE)
An OAE was a significant AE of particular clinical importance other than SAEs and AEs leading to discontinuation of study treatment.

Causality rating
Causal relationship between any AE and the study drug or concomitant medication was assessed by the investigators as "Yes" or "No" to a question "Do you consider that there is a reasonable possibility that the event may have been caused by the drug?"

Methods
AE form was used for every subject to record AEs, whether reported upon open questioning by the study personnel, spontaneously reported or revealed by observation or objective measurement. The AE data were presented descriptively.

In PUB-patients study, the efficacy outcome variable clinically significant rebleeding was reported as an SAE if any SAE criterion was fulfilled. AEs continuing into or starting during a drug-free period after last dose of study drug were assigned to the previous treatment period. The AEs presented during the active treatment period include AEs recorded from first intake of investigational drug until and including the last day of administration of investigational drug.

It is to be noted that multiple episodes of the same AE experienced by the same subject/patient during one treatment period are only counted as one AE. The proportion of subjects/patients with AE is expressed as the percentage of the total number of evaluable subjects/patients in each treatment group.

Comments:
The methods, definitions and guidelines for the adverse events were appropriate.

A subject/patient who reported AEs belonging to a particular System Organ Class (SOC) is only counted once within the class but is counted once for each AE belonging to that particular SOC. Within each SOC the AEs are sorted by decreasing order of AE frequency in the esomeprazole group. The following subgroups were also analyzed: gender, age, race and women of childbearing potential.

AEs relating to laboratory examinations
In the patient study (D961DC00001), blood samples were taken regularly during the course of the study. Deterioration in laboratory values was reported as AEs, if the abnormal laboratory tests and other objective measurements or findings met the criteria for a SAE or resulted in discontinuation of investigational product. In healthy subject studies (D9615C00004 and D9615C00015) blood and urine samples were taken. A clinically relevant deterioration, in a laboratory variable compared to pre-entry was defined as an AE.

Terminology and coding
The AEs were classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA) 10.1.

AEs in healthy Subjects:
The overall incidence of AEs in healthy subjects was low in all dose groups as shown in table 33. No fatal or non-fatal SAEs were reported. One AE (arthralgia) leading to discontinuation of treatment occurred in the second highest dose group (296 mg/day). AEs were more often seen in subjects receiving doses similar to the doses given in the trial. The common AEs were headache, nausea, and diarrhea and dizziness. These AEs are listed AEs for standard-dose esomeprazole I.V. and oral formulations. Safety profile is similar to the previously approved indications.

Table 33: Summary of AEs in healthy subjects:

Total Daily Dose (mg)	**174[a] (n=25)**	**228[a] (n=24)**	**268[a] (n=24)**	**268[b] (n=39)**	**296[a] (n=24)**	**308[a] (n=23)**
Number of subjects with any AE (%)	2 (8.0)	5 (20.8)	5 (20.8)	14 (35.9)	5 (20.8)	3 (13.0)
Total number of AE	2	7	9	19	6	3
Infections	0	0	1	1	0	0
CNS	**1**	**2**	**4**	**10**	**4**	**1**
• Headache	1	1	4	9	2	1
• Syncope	0	1	0	0	0	0
• Dizziness	0	0	0	1	2	0
Ear/Labyrinth disorder	0	1	0	0	0	0
Respiratory, thoracic	0	2	0	1	0	1
Gastrointestinal	1	2	1	6	0	0
• Nausea	0	0	1	4	0	0
• Diarrhea	0	1	0	2	0	0
• Abd pain	1	1	0	0	0	0
Musculoskeletal and Connective Tissue	0	0	1	0	1	0
General disorders and administration site conditions	0	0	1	0	1	0
Investigations	0	0	1	0	0	0

a-Study D9615C00015
b-Study D961DC00004
AEs occurring in at least two healthy subjects in any treatment group are displayed
(Data incorporated from Tables 10, 13, and 32 summary of clinical safety for Study D961DC00001)

Safety profile of standard-dose esomeprazole I.V. and esomeprazole oral formulation:

Esomeprazole is usually well tolerated and AEs are generally mild and reversible. Headache, diarrhea, constipation, flatulence, nausea/vomiting and abdominal pain are the most frequent AEs reported from both clinical trials and post marketing surveillance (PMS) and are identified as the most common adverse drug reactions, occurring in the frequency 1/100. No AEs have been found to be dose-related.

In previous clinical studies with standard-dose esomeprazole I.V. it was shown that the safety profile of esomeprazole I.V. is similar to that of esomeprazole oral.

Non-clinical findings with high-dose and standard-dose esomeprazole I.V.

Comments: Pharmacology-Toxicology review was done by Dr Zhang Kee. From the pre-clinical standpoint of NEXIUM I.V. was recommended for the proposed indication. Please see Pham-Tox review for details.

Description of the clinical safety evaluations with high-dose esomeprazole I.V.

All AEs reported during study were analyzed overall, and for various subgroups and categories of AEs. Objective measurements including laboratory data, ECG recordings, vital signs and results from physical examinations were analyzed. In addition, safety experience from the use of oral esomeprazole and standard-dose esomeprazole I.V. was taken into account in the overall safety evaluation of high dose esomeprazole I.V.

Sources of data

The safety evaluation was based on data from the controlled studies on high-dose and standard-dose esomeprazole I.V., controlled studies on oral esomeprazole and post marketing studies (PMS) on standard-dose esomeprazole I.V. and oral esomeprazole. In sponsored clinical studies more than 1900 and 88,000 patients have been exposed to standard-dose esomeprazole I.V. and oral esomeprazole, respectively. As of March 01, 2008 standard-dose esomeprazole I.V. is approved in 90 countries and more than (b) (4) (b) (4) have been delivered to the market. The corresponding numbers for oral formulation of esomeprazole are 115 countries and (b) (4) treatment courses.

Assessment of various demographic subgroups was done to get information on efficacy and safety of high dose I.V. esomeprazole (table 34).

Table 34: Demographic characteristics in PUB-patients, safety population

Characteristic	Eso[a] (n=375)	Placebo[b] (n=389)
Gender, n(%)		
Male	254(67.7%)	268(68.9%)
Female	121(32.3%)	121(31.1%)
Race, n(%)		
Caucasian	325(86.7%)	342(87.9%)
Black	4(1.1%)	5(1.3%)
Oriental	27(7.2%)	27(6.9%)
Other[c]	19(5.1%)	15(3.9%)
Below and above 65 years of age, n(%)		
<65	182(48.5%)	210(54.0%)
≥ 65	193(51.5%)	179(46.0%)
Age, years		
N	375	389
Mean(SD)	62.1(17.1)	60.2(17.6)
Min-Max	18-95	18-98

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Other refers to 31 mixed races, 1 Maghreb, 1 Arubaan and 1 Cape coulored

(Table above is taken from Table 6 of Applicant's Summary of Clinical Safety for Study D961DC00001)

Comments:

There were more male patients as compared to female patients (67.7% versus 32.3%). The majority of patients were Caucasian. The number of patients in the other racial- sub groups were small specifically black patients (1.1 %.). There were also more elderly patients in the esomeprazole treatment group compared to placebo group (51.5% versus 46%).

7.1.1 Deaths:

A total of 13 deaths were reported. Two deaths were excluded from all analysis (1 death occurring before the randomization and 1 death after 3 weeks of completion of study). Two deaths that occurred after early withdrawal but within 30 days were excluded from the safety but included for efficacy analysis. Overall safety analysis therefore included 9 deaths (Table 35).

Of these 9 deaths during the study five deaths occurred during the I.V. infusion phase (72 hours) and four during oral administration (4 to 30 days). In the first 72 hours 3 patients died related to rebleeding (esomeprazole=2, placebo=1) and 2 in the placebo group due to myocardial infarction. During 4 to 30 days one patient in esomeprazole group died due to pre-existing COPD and 3 patients in placebo died, one probably related to the endoscopic procedure.

Comments:
Deaths were related to the rebleeding and exacerbation of pre-existing conditions due to bleeding. No trend was observed related to causality.

Table 35: Number (%) of patients with an AE with fatal outcome within 72 hours, 4-30 days, after start of I.V. treatment.

Interval of observation/outcome	AE with Fatal Outcome	
	Esomeprazole[a] (n=375)	Placebo[b] (n=389)
72 Hours:		
Patients with fatal outcome[c]:	**2 (0.5%)**	**3 (0.8%)**
Acute myocardial infarction	0 (0.0%)	1 (0.3%)
Myocardial infarction	0 (0.0%)	1 (0.3%)
Duodenal ulcer hemorrhage	2 (0.5%)	1 (0.3%)
4-30 Days:		
Patients with fatal outcome[c]:	**1 (0.3%)**	**3(0.9%)**
Myocardial infarction	0 (0.0%)	1 (0.3%)
Duodenal ulcer hemorrhage	0 (0.0%)	1 (0.3%)
Gastric ulcer perforation	0 (0.0%)	1 (0.3%)
Chronic obstructive pulmonary disease, Lung disorder	1 (0.3%)	1 (0.3%)

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Patients with multiple AEs with fatal outcome are counted once
(Table incorporates data from Table 14 and 15 from Summary of Clinical Safety and table 40 from Clinical Study Report for Study D961DC00001)

Abbreviated narratives for the deaths listed in Table 35

Esomeprazole
Patient (b) (6) age 56 with history including of ischemic heart disease, received **Esomeprazole I.V.** treatment for 5 hours. He developed rebleeding from duodenal ulcers on the day of first dose of I.V. treatment with symptoms of hemodynamic instability and shock. Patient died after 2 days of the first dose. Probable cause of death was continuous bleeding despite drug treatment and surgery.

Patient (b) (6) age 35 received **esomeprazole I.V.** treatment for 72 hours. He was discharged after completion of the I.V. phase. Six hours after hospital discharge the patient developed epigastric pain, had an episode of hemetemesis at home, and was brought in dead to the hospital. No autopsy was performed.

Placebo
Patient (b) (6) age 68 with history of hypertension, urolithiasis, chronic pyelonephritis, cholecystectomy and appendectomy, received **placebo I.V.** treatment for 72 hours. She experienced myocardial infarction and died 3 days after the first dose of study drug.

Patient (b) (6), age 84 with history of Alzheimer's disease received **placebo I.V.** treatment for 72 hours. She was operated the next day for rebleeding. Seventeen days

after first dose of study drug she died of an acute peritonitis due to rupture of the anastomosis of the pyloroplasty.

Patient (b) (6) age 81 with history of hypertension and diabetes mellitus experienced rebleeding from duodenal ulcer after receiving **placebo I.V.** for 24 hours. Three days later he developed myocardial infarction and died 5 days after first dose of the study drug.

Abbreviated narratives for the deaths within 4-30 days listed in Table 35 are summarized below.

Esomeprazoel

Patient (b) (6), age 85 with history of chronic obstructive lung disease, hypertension, and elevated liver enzymes, received **I.V. esomeprazole** for 72 hours followed by oral treatment. Nine days after first dose of study drug the patient died due to chronic obstructive lung disease.

Placebo

Patient (b) (6) age 98 with history hypertension, coronary disease, osteomyelitis, pneumonia experienced renal insufficiency due to dehydration the same day as **I.V. placebo** started. Study drug continued and the patient received 72 hour I.V. treatment followed by oral treatment. Fourteen days after first dose of study drug the patient died of pneumonia.

Patient (b) (6) age 84 with history of breast cancer recurrence, mastectomy, urothelial carcinoma, urinary bladder carcinoma and partial nephrectomy, received I.V. placebo for 26 hours. She experienced rebleeding duodenal ulcer and additional rebleeding episodes. After additional endoscopies and embolization the patient still had continuous bleeding and melena. It was decided to abstain from further therapy because of age and co-morbidities. Twelve days after first dose of study drug the patient died.

Patient (b) (6) age 82 with history of hypertension and cerebrovascular disorder experienced myocardial infarction the same day as I.V. placebo started. The I.V. treatment was continued and he received 73 hour I.V. treatment followed by oral treatment for 1 day. On the same days as oral treatment started, the patient experienced perforated gastric ulcer. Four days after first dose of study drug the patient died.

Additional Deaths:

Of the 4 deaths not included in the safety analysis, one occurred prior to the randomization and 3 after study termination. A brief description of these patients is given below:

1. 91 M # Severe respiratory insufficiency/atelectasis due to aspiration/ulcer bleed. Patient died 2 days later.
2. 87 F # Rectal Ca. Patient died after 25 days study completion. (placebo I.V. + oral esomprazole)
3. 68M # Rebleeding, aspiration during endoscopy, cardiorespiratory arrest, on ventilator, withdrawn from the study, died 9 days later.
4. 81M # COPD+ respiratory insufficiency, withdrawn from the study. Died after 2 days.

Death or SAE in healthy subjects (D961 DC00004 and D961 DC00015)
There are no reports of fatal SAEs in healthy subjects.

Other Serious Adverse Events

This reviewer has tried to compare AEs occurring during high dose esomeprazole I.V. administration with period when patients received oral esomeprazole. Reviewer examined placebo controlled data in 72 hours so that information can be obtained on causality of any AEs noticed.

Overall Adverse Event Profile

A summary of the overall treatment emergent AE profile among intent-to-treat patients in the phase 3 study is presented in table. The AEs occurring during high does continuous infusion of esomeprazole (within 72 hours) are compared to AEs occurring during oral administration of esomeprazole (4 to 30 days) to assess any new AEs and causality related to I.V. administration of esomeprazole. There appeared to be a lower incidence of serious adverse events, adverse events and discontinuation due to adverse events in esomeprazole group than in placebo group within 72 hours.

Summary table of Adverse Events:

This reviewer has tried to compare AEs occurring during high dose esomeprazole I.V. administration with period when patients received oral esomeprazole. Overall focus was to looked at placebo controlled data in 72 hours carefully so that information can be obtained on causality of any AEs noticed. AEs, SAEs and proportion of patients who discontinued due to AEs were similar in two treatment groups at 72 hours as well as during 4 -30 days (table 36).

Table 36: Number (%) of patients with at least 1 AE (AE+SAE) and total numbers of AE within 72 hours and during 4 to 30 days.

AE+SAE	72 Hours		4-30 Days	
	Esomeprazole[a] (n=375)	**Placebo[b]** (n=389)	**Esomeprazole[a]** (n=347)	**Placebo[b]** (n=352)
Any AEs	**147 (39.2%)**	**163 (41.9%)**	**116 (33.4%)**	**131 (37.2%)**
Serious AEs	**35 (9.3%)**	**44 (11.3%)**	**30 (8.6%)**	**31 (8.9%)**
SAEs leading to death[d]	2 (0.5%)	3 (0.8%)	1 (0.3%)	3 (0.9%)
SAEs not leading to death	33 (8.8%)	41 (10.5%)	29 (8.4%)	28 (8.0%)
Discontinuations of study treatment due to AE	31 (8.3%)	39 (10.0%)	15 (4.3%)	17 (4.8%)
Related AEs[f]	13 (3.5%)	8 (2.1%)	8(2.3%)	5(1.4%)
Severe AEs	23 (6.1%)	34 (8.7)	21(6.1%)	23(6.5%)
Total number of AEs:				
AEs	224	264	202	217
Serious AEs	44	47	31	35

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
d The AE started within 72 h, but death occurred after 72 h for 4 patients
f Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator
(Above table was complied by reviewer by Incorporating data from Applicant table 34 and 35 Clinical Study Report for Study D961DC00001)

Comments:

- *Within the first **72 hrs, proportion of patients** with AE and SAE was comparable in the two treatment groups (AE=39.2% and 41.9%; SAE=9.3% and 11.3%). Numbers (%) of patients that discontinued treatment due to AE were also comparable in two groups (Eso=8.3% and 10.0%).*

- *During **4 to 30 days** numerically fewer patients had AE in the I.V. group compared to placebo group (33.4% and 37.2%). Proportion of patients having SAE were comparable in the two groups (Eso=8.6%, Placebo= 8.9%).*

- ***Total number AE/SAE:** Number of SAE were comparable in two groups at 72 hrs and 4 to 30 days However, number of AEs were numerically less in I.V. treatment group at 72 hrs and 4-30 days.*

In all there there appeared to be a lower incidence of serious adverse events, adverse events and discontinuation due to adverse events in esomeprazole group than in placebo group within 72 hours.

7.1.2 Serious Adverse Events (SAEs):

One hundred thirty one patients (62 in Esomeprazole group, 69 in placebo group) experienced 142 SAEs (69 in Esomeprazole group; 73 in placebo group) during this clinical program. These SAEs are summarized in table 37 by treatment group. The drug treatment was permanently stopped in 25 SAEs in esomeprazole group and 30 SAEs in placebo group.

SAEs are grouped and compared based on the periods of I.V. treatment (72 hours) and oral treatment (4 to 30 days). Placebo control data in first 72 hours were particularly focused to find information on causality of AEs.

Table 37: Serious adverse events (SAEs) by system organ class and preferred term, n (%) of patients within 72 hours, and 4-30 days.

	72 hours		4 to 30 days	
SAE	**Esomeprazole** (n=375)	**Placebo** (n=389)	**Esomeprazole** (n=347)	**Placebo** (352)
Patients with any SAEs	**33 (8.8%)**	**41(10.5%)**	**29 (8.4%)**	**28(8.0%)**
Total numbers of SAEs	**39**	**43**	**30**	**29**
Gastrointestinal Disorders	**18 (4.8%)**	**30 (7.7%)**	**8 (2.3%)**	**11 (3.1%)**
Cardiac Disorders	6 (1.6%)	5 (1.3%)	3 (0.9%)	3 (0.9%)
Neoplasm benign, malignant etc	3 (0.8%)	1 (0.3%)	1 (0.3%)	4 (1.1%)
Infections and Infestations	**2 (0.5%)**	0 (0%)	3 (0.9%)	2 (0.6%)
Metabolism and Nutrition Disorders	**2 (0.5%)**	0 (0%)	2 (0.6%)	2 (0.6%)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.5%)	3 (0.8%)	0 (0%)	3 (0.9%)
Vascular Disorders	**2 (0.5%)**	0 (0%)	3 (0.9%)	0 (0%)
Hepatobiliary Disorders	**1(0.3%)**	0 (0%)	-	-
Injury, poisoning and procedural complications	1 (0.3%)	1 (0.3%)	2 (0.6%)	0 (0%)
Psychiatric Disorders	1 (0.3%)	0 (0%)	-	-
Skin and Subcutaneous Disorders	1 (0.3%)	0 (0%)	-	-
Investigations	0 (0%)	1 (0.3%)	-	-
Musculoskeletal and Connective Tissue Disorder	0 (0%)	1 (0.3%)	1 (0.3%)	2 (0.6%)
Renal and Urinary Disorders	0 (0%)	1 (0.3%)	-	-
General disorders and administration site conditions	-	-	3 (0.9%)	0 (0.0%)
Nervous System	-	-	3 (0.9%)	2 (0.6%)
Uveitis	-	-	1 (0.3%)	0 (0.0%)

(Values in table above were compiled by this reviewer using the data Tables 41, and 42 on pages 109-113 of the Applicant's CSR for D961DC00001)

Comments:

SAEs during 72 hrs as well as 4 to 30 days were similar in two treatment groups. The majority of SAEs were related to GI and cardiac systems. DU/GU rebleeding formed the predominant SAE in both the treatment groups. Few instances of peptic ulcer perforation in placebo group were probably related to the endoscopic procedures. SAEs related to other systems were few and equally spread out in two treatment groups. No particular trend was noticed. Tables 38/ and 39 are details on GI and cardiac SAE.s

For details regarding SAEs see Appendix 1, tables 81 and 82.

Since the majority of SAEs primarily involved gastrointestinal and cardio-vascular systems; these are summarized in the tables 38 and 39 and described in the subsequent paragraphs:

Table 38: GI related SAE, 72 hours and 4 to 30 days.

SAE	72 hours		4 to 30 days	
	Esomeprazole (n=375)	Placebo (n=389)	Esomeprazole (n=347)	Placebo (n=352)
Patients with any SAEs	33 (8.8%)	41(10.5%)	29 (8.4%)	28(8.0%)
Gastrointestinal Disorders	18 (4.8%)	30 (7.7%)	8 (2.3%)	11 (3.1%)
• DU Bleed	12	14	3	6
• GU Bleed	4	11	3	2
• GI Bleed	1	1	0	0
• Rectal Bleed/melena	1	0	2	0
• DU/Peptic Ulcer Perforation	0	3	0	1
• Acute Pancreatitis	0	1	0	0
• Colonic Polyp	0	0	0	1
• Constipation	0	0	0	1

(Values in table above were compiled by this reviewer using the data Tables 41, and 42 on pages 109-113 of the Applicant's CSR for Study D961DC00001)

Comments:
Rebleeding was the main SAE at all time in both groups of treatment. Few patients of peptic ulcer perforation in placebo group were probably related to the endoscopic procedures.

Table 39: Cardiac related SAE, 72 hours and 4 to 30 days

	72 hours		**4 to 30 days**	
SAE	**Esomeprazole** (n=375)	**Placebo** (n=389)	**Esomeprazole** (n=347)	**Placebo** (n=352)
Patients with any SAEs	**33 (8.8%)**	**41(10.5%)**	**29 (8.4%)**	**28 (8.0%)**
Cardiac Disorders	**6 (1.6%)**	**5 (1.3%)**	**3 (0.9%)**	**3 (0.9%)**
• Myocardial Infarction	4	3	2	2
• Angina Pectoris	1	0	0	0
• Cardiac Failure	1	0	0	0
• AF	0	2	0	1
• Bradycardia	0	0	1	0

(Values in table above were compiled by this reviewer using the data Tables 41, and 42 on pages 109-113 of the Applicant's CSR for Study D961DC00001)

Comments:
Main cardiac related SAEs were similar in two treatment groups.

During the I.V. phase of treatment (within 72 hours) the majority of SAEs were related to primary efficacy variable i.e. rebleeding from the peptic ulcer. Overall there were more rebleeding episodes in the placebo group compared to esomeprazole group (30 and 18 respectively). Most rebleeding episodes in the placebo group were from the Gastric ulcer and were more than the esomeprazole group (11 compared to 4). Rebleeding episodes from the duodenal ulcer in both groups were comparable (placebo-14 and esomeprazole-12). Other SAEs related to the I.V. placebo group were peptic ulcer perforation (3) and acute pancreatitis (1). SAEs related to cardiac system were comparable.

During the period 4 to 30 days (oral treatment) both groups received esomeprazole 40 mg per day. Fifty seven patients (esomeprazole=29, placebo=28) had 57 SAEs (esomeprazole=30, placebo=29). Overall rebleeding SAEs were more in placebo group compared to esomeprazole (11 and 8). In this treatment period rebleeding episodes from the duodenal ulcer were more in placebo group compared to esomeprazole (6 and 3) whereas rebleeding SAE from gastric ulcer was comparable in two groups.

Nine SAEs related of neoplasms were seen (gastric neoplasm-6, testicular cancer-1, carcinoma of pancreas-1, and rectal carcinoma-1).

SAEs assessed by the investigator and thought as causally related to the drug:

Esomeprazole group:

1. (b) (6) 81 years old patient developed urticaria at 3 days while on I.V. treatment. Drug was permanently stopped.

2. (b) (6) 87 years old patient had rebleeding from duodenal ulcer after 3 days of I.V. treatment. Drug was permanently stopped.

3. (b) (6) 73 years old patient developed unstable angina and chest infection on day 1, and cardiac failure and rebleeding from gastric ulcer at second day. Drug was permanently stopped.

4. (b) (6) 83 years old patient developed phlebitis while on oral treatment for 2 days. Treatment was continued. SAE lasted for the duration of 9 days.

5. (b) (6) 50 years old patient developed signs and symptoms of median nerve injury after I.V. treatment. Drug was continued. This was thought to be due to extravasations and reaction at I.V. infusion site. Symptoms were persisting till the follow up.

6. (b) (6) This 73 years old patient developed acute psychosis at three days of I.V. treatment. Drug was stopped and reaction subsided in one day.

7. [redacted] This 65 year old patient developed rebleeding from duodenal ulcer during I.V. treatment at 4 days. Drug was stopped permanently.

Placebo Group:

1. [redacted] Hyponatremia developed 2 days into oral treatment. Drug was continued. The hyponatremic state lasted for 3 days.

2. [redacted] 70 years old had Acute Gastric ulcer rebleeding while on I.V. treatment on day 4. Treatment was stopped permanently.

3. [redacted] 82 years old had duodenal ulcer rebleeding at day two of I.V. treatment. Drug was stopped permanently.

Comments:
SAEs involving other systems were very few and spread over both treatment groups with no particular trend (tables 40 and 41).

Table 40: Uncommon SAE: 72 hours and 4 to 30 days (Cont):

SAE	72 hours		4-30 days	
	Esomeprazole (n=375)	**Placebo (n=389)**	**Esomeprazole (n=347)**	**Placebo (n=352)**
Vascular Disorders	**2 (0.5%)**	**0 (0%)**	**3 (0.9%)**	**0 (0%)**
• Shock	1	0	0	
• Thrombosis	1	0	2	
• Phlebitis			1	
Hepatobiliary Disorders	**1(0.3%)**	0 (0%)	-	
• Cholicystitis	1	0		
Psychiatric Disorders	**1 (0.3%)**	**0 (0%)**	-	-
• Acute psychosis	1	0		
Skin and Subcutaneous Disorders	**1 (0.3%)**	0 (0%)	-	-
• Urticaria	1	0		
General disorders and administration site conditions:	0%	0%	**3 (0.9%)**	**0 (0.0%)**
• Discomfort			1	
• Fatigue			1	
• Pyrexia			1	
Nervous System	0%	0%	**3 (0.9%)**	**2 (0.6%)**
• Peripheral nerve lesion			1	0
• Presyncope/syncope			2	0
• Dizziness			0	1
• TIA)			0	1
Uveitis	0%	0%	1 (0.3%)	0 (0.0%)

(Above Table is taken from Table 41 and 42 of Applicant's Clinical Study Report for Study D961DC00001)

Table 41: Uncommon SAE: 72 hours and 4 to 30 days

SAE	72 hours		4-30 days	
	Esomeprazole (n=375)	**Placebo** (n=389)	**Esomeprazole** (n=347)	**Placebo** (352)
Skin and Subcutaneous Disorders	1	0	-	-
Investigations	0	1	-	-
Musculoskeletal and Connective Tissue Disorder	0	1	1	2
Renal and Urinary Disorders	0	1	-	-
General disorders and administration site conditions:	0	0	3	0
Nervous System	0	0	3	2
Uveitis	0	0	1	0

(Table above is taken from Table 41 and 42 of Applicant's Clinical Study Report for Study D961DC00001)

A list of Non-Gastrointestinal related SAEs and brief patients profile occurring in the esomeprazole group and the placebo group is given in tables 42 and 43.

Table 42: SAEs (other than rebleeding), esomeprazole group.

Patient Number	Age/Sex	Preferred Terms/Details	Associated Conditions	Onset after start of treatment (days)
(b) (6)	68/F	Discomfort due to dehydration	dehydration	9
	84/M	Fatigue	recent hemicolectomy and h/o diabetes	4
	86/F	Right humoral vein thrombosis	Due to long catheter perfusion	5
	86/M	Osteolysis foot and ankle	h/o HTN,hyperurecemia, AF, hyperparathyroidism, psoriasis, PAD, etc	13
	76/F	Melena	No decrease in Hb.	10
	52/M	Shock	Melena, blood loss EGD- negative	2
	73/M	Unstable angina	HTN, DM, COPD, AF, Urinary bladder carcinoma etc	1
	76/M	Dehydration	Gastroenteritis	26
	71/M	Bradycardia	AF, cardiac decomposition	21
	72/M	Anemia	Blood loss, Mallory Weiss	4
	83/F	Phlebitis due to indwelling catheter	Fever	4
	51/M	Left median nerve injury		3
	82/M	Subdural hematoma	h/o fall in the bathroom	28
	74M	Acute psychosis	DM, gout	2
	50/M	Syncope	Hb=9	24
	36/M	Rectal bleed	No significant decrease in Hb	3
	81/F	Urticaria generalized		2
	50/F	Melena with low Hb	EGD and colonoscopy-Negative	15

(Table above is taken from Tables 41 and 42 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:

Main focus for assessing SAEs related to high dose I.V. Esomeprazole was the esomeprazole group primarily within 72 hours. In this group most of the SAEs seem not related to the drug. Two events of acute psychosis and generalized urticaria were noticed that developed within 72 hours. These were SAEs and drug was discontinued in both incidents. These were also considered related to the drug by the sponsor. Two other administration site related SAEs were observed, right humoral vein thrombosis and left median nerve injury in esomeprazole group.

Table 43: SAEs (other than rebleeding), placebo group.

Patient Number	Age/Sex	Preferred Term/Details	Associated Conditions	Onset after start of treatment (days)
(b) (6)	70/M	AF, h/o irregular heart beat	HTN	1
	75/F	Obstipation lasted for 6 days	Arthritis	4
	86/F	UTI	HTN	6
	59/M	Aggravation of dizziness	h/o dizziness HTN, NCCP CT head-Normal	7
	78/F	Hyponatremia with loss of consciousness	HTN, myelodysplasia, DM, UTI, high cholesterol, etc	5
	63/M	Perforated peptic ulcer	Related to study procedure i.e. inj therapy	2
	57/M	Progression of erysipelas	HTN, DM	21
	47/M	TIA (left hemisensory loss), CT-old cerebral infarct	CVA, HTN, DM	4
	59/M	Duodenal perforation	DM, HTN, hypertryglyceridemia	1
	72/M	Carcinoma pancreas	Hepatic abscess, cecal perforation Pain didn't decrease, CT revealed the diagnosis	7
	37/M	DU perforation		3
	77/M	Significant drop in Hb	HTN, DM	3
	42/M	Acute pancreatitis	Hypercholesterolemia schizophrenia	1
	63/M	Pulmonary Embolism Diagnosed by CT done to investigate bleeding	HTN, DM	5

(Information in Table above is taken from Table 41 and 42 of Applicant's Clinical Study Report for Study D961DC00001)

Comments

Although the majority of SAEs were events described in the Nexium package insert, SAE that are not described in the Nexium package insert nor known to be the events associated with Nexium use are summarized below:

1. (b) (6) *81 years old patient developed urticaria on 3rd days while on I.V. treatment. Drug was permanently stopped. Patient improved within one day.*

2. [redacted] *83 years old patient developed phlebitis while on oral treatment for 2 days. Treatment was continued. SAE lasted for the duration of 9 days.*

3. [redacted] *50 years old patient developed signs and symptoms of median nerve injury after I.V. treatment. Drug was continued. This was thought to be due to extravasations and reaction at I.V. infusion site. Symptoms were persisting till the follow up.*

4. [redacted] *This 73 years old patient developed acute psychosis at three days of I.V. treatment. Drug was stopped and reaction subsided in one day.*

Overall, the rate of SAEs reported was similar in the two treatment groups. The most commonly reported SAEs were from the "Gastrointestinal disorders" SOC in both treatment groups. The majority of the primary variable events, clinically significant rebleeding, were reported as SAEs in terms of duodenal ulcer hemorrhage and gastric ulcer hemorrhage.

In total, 84 patients were discontinued from study treatment due to an AE; 65 patients during the I.V. phase and 19 patients during the oral phase. The frequency of the primary variable connected events in the "Gastrointestinal disorder" SOC during the I.V. treatment phase was slightly higher in the placebo treatment group. The DAEs were reported with similar numbers in both treatment groups for the other SOCs during the I.V. treatment phase. During the oral treatment phase, the DAEs were reported with similar frequencies in both treatment groups.

The majority of SAEs were moderate or severe.

SAEs reported did not suggest any new systemic trend or pattern besides local skin and vascular adverse events.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Approximately 10% patients in each treatment group discontinued from the study. Table 44 shows the number of patients and the reasons for discontinuation. The majority of patients discontinued due to adverse events and voluntary discontinuation. The reasons for discontinuation were similar in the two treatment groups (esomeprazole versus placebo).

Table 44: Summary of patient's completion status on randomized patients

Patient completion status	Eso[a] (n=376)	Placebo[b] (n=391)
Completed[c]	337(89.6%)	349(89.3%)
Discontinued	39(10.4%)	42(10.7%)
Reason for discontinuation:		
Incorrect Enrolment	1(0.3%)	3(0.8%)
Adverse Event	10(2.7%)	15(3.8%)
Voluntary Discontinuation by Subject	13(3.5%)	7(1.8%)
Subject Lost to Follow-up	8(2.1%)	6(1.5%)
Severe Non-Compliance to Protocol	2(0.5%)	2(0.5%)
Death	3(0.8%)	5(1.3%)[d]
Safety Reasons	1(0.3%)	2(0.5%)
Other	1(0.3%)	2(0.5%)

(Table above is taken from Table 11 of Applicant's Clinical Study Report for Study D961DC00001)

Dropouts due to AE:

During the study 102 patients (46 in the esomeprazole group, 56 in the placebo group) were withdrawn from the phase 3 studies due to AEs. Seventy patients were withdrawn during the I.V. treatment (esomeprazole =31; placebo =39); and 32 patients during 4 to 30 days of oral treatment (esomeprazole =17; placebo =15).

The incidence of patients who withdrew due to AEs was comparable in esomeprazole and the placebo groups (esomeprazole= 8.3 %; placebo= 10.0%) during I.V treatment. During the oral treatment phase the incidence of withdrawal was similar in the two groups (esomeprazole= 4.3%; placebo= 4.8%). The majority of withdrawals due to AEs in both treatment groups were the result of rebleeding. Rebleeding is also the primary efficacy variable. AEs related to other systems were similar in the two treatment groups.

7.1.3.2 Adverse events associated with dropouts:

AEs that led to the withdrawal of 102 patients (46 in the esomeprazole group; 56 in the placebo group) from the phase-3 study (D961 DC00001) are summarized in table 45. The AEs are grouped according to the treatment periods (within 72 hours and 4 to 30 days) to compare AEs during high dose I.V. continuous infusion with normal dose oral treatment and determine dose-response or time dependency of the withdrawal.

Table 45: Number (%) of patients and Adverse Events that lead to discontinuation of study drug within 72 hours and 4 to 30 days.

AE leading to discontinuation	72 Hours		4 to 30 Days	
	Esomeprazole (n=375)	Placebo (n=389)	Esomeprazole (n=347)	Placebo (n=352)
Patients with an AE leading to discontinuation	**31 (8.3%)**	**39 (10.0%)**	**15 (4.3%)**	**17 (4.8%)**
Gastrointestinal disorders	**20 (5.3%)**	**27 (6.9%)**	**6 (1.7%)**	**10 (2.8%)**
Duodenal ulcer hemorrhage	13 (3.5%)	12 (3.1%)	2 (0.6%)	5 (1.4%)
Gastric ulcer hemorrhage	3 (0.8%)	**10 (2.6%)**	2 (0.6%)	4 (1.1%)
Gastrointestinal hemorrhage	2 (0.5%)	1 (0.3%)	-	-
Diarrhea	1 (0.3%)	0 (0%)	2 (0.6%)	0 (0%)
Hematemesis	1 (0.3%)	0 (0%)	-	-
Duodenal perforation	0 (0%)	**1 (0.3%)**	-	-
Gastrooesophageal reflux disease	0 (0%)	**1 (0.3%)**	-	-
Pancreatitis acute	0 (0%)	**1 (0.3%)**	0 (0%)	1 (0.3%)
Peptic ulcer perforation	0 (0%)	**1 (0.3%)**	-	-
Neoplasms benign, malignant and unspecified (Gastric cancer, Gastrointestinal stromal tumour, Adenocarcinoma pancreas)	3 (0.8%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
Psychiatric disorders (Acute psychosis,Delirium tremens,Psychotic disorder, Confusional state, Nicotine dependence)	3 (0.8%)	2 (0.5%)	1 (0.3%)	0 (0%)
Cardiac disorders (Myocardial infarction)	2 (0.5%)	2 (0.5%)	1 (0.3%)	2 (0.6%)
General and administration site conditions (Catheter site related reaction)	1 (0.3%)	0 (0%)	-	-
Skin and subcutaneous tissue disorders (Urticaria, Rash, Pruritus, Dermatitis, allergic)	1 (0.3%)	2 (0.5%)	1 (0.3%)	1 (0.3%)
Vascular disorders (Hypertension, Hypotension, Venous thrombosis limb)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0%)
Blood and lymphatic system disorders (Anemia)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.3%)
Infections and infestations (Diverticulitis)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.3%)
Investigations (Hemoglobin decreased)	0 (0%)	1 (0.3%)		
Respiratory, thoracic and mediastinal disorders (Respiratory failure, Pulmonary oedema)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.3%)
Injury, poisoning and procedural complications (Dislocation of joint prosthesis, Subdural hemorrhage)	-	-	2 (0.6%)	0 (0%)
Nervous system disorders (Presyncope)	-	-	1 (0.3%)	0 (0%)

(Above Table above is incorporated from Table 75 and 76 of Applicant's Clinical Study Report for Study D961DC00001)

As shown in Table 45, during the first 72 hours, 70 patients (esomeprazole=31, placebo=39) were withdrawn from the phase 3 study due to AEs. The majority of AEs were related to the gastrointestinal system. More patients had rebleeding and possible procedure related complications in the placebo group compared to the esomeprazole group (6.9% versus 5.3%). The proportion of patients who withdrew due to other organ systems AEs was similar between treatment and placebo group.

During the 4 to 30 days period 32 patients (esomeprazole=15, placebo=17) were withdrawn from the phase 3 study. More patients in placebo group compared to esomeprazole group withdrew due to rebleeding (2.8% versus 1.7%). The percentage of patients who withdrew due to other organ systems AEs, during 4 to 30 days, were similar

in both treatment groups. Details of adverse events leading to discontinuation of the study during 72 hours and 44 to 30 days are shown in Appendix, tables 83 and 84.

Comments:
Table 45 shows the proportion of patients that discontinued due to AEs. About 8 to 10 % of patients discontinued during the I.V. Treatment and 4 to 5% during oral treatment and they were similar in two treatment groups. GI related AEs were most common in both treatment groups. In the next Table 46 details of the GI related AEs are shown. As we observed predominant AE was rebleeding. This constituted the major group responsible for discontinuation in both treatment groups within 72 hours and during 4 to 30 days. AEs related to other systems were similar in the two treatment groups.

Table 46: Discontinuation: GI Related AEs (Cont)

AE Leading to Discontinuation	**72 Hours**		**4 to 30 Days**	
	Esomeprazolea (n=375)	**Placebob (n=389)**	**Esomeprazolea (n=347)**	**Placebob (n=352)**
Patients with an AE leading to discontinuation	**31 (8.3%)**	**39 (10.0%)**	**15 (4.3%)**	**17 (4.8%)**
Gastrointestinal disorders	**20 (5.3%)**	**27 (6.9%)**	**6 (1.7%)**	**10 (2.8%)**
• Duodenal Ulcer Hemorrhage	13 (3.5%)	12 (3.1%)	2 (0.6%)	5 (1.4%)
• Gastric Ulcer Hemorrhage	3 (0.8%)	**10 (2.6%)**	2 (0.6%)	4 (1.1%)
• GI Hemorrhage	2 (0.5%)	1 (0.3%)	-	-
• Diarrhea	1 (0.3%)	0 (0%)	2 (0.6%)	0 (0%)
• Hematemesis	1 (0.3%)	0 (0%)	-	-
• Duodenal Perforation	0 (0%)	**1 (0.3%)**	-	-
• Gastroesophageal Reflux Disease	0 (0%)	**1 (0.3%)**	-	-
• Acute Pancreatitis Peptic	0 (0%)	**1 (0.3%)**	0 (0%)	1 (0.3%)
• Ulcer Perforation	0 (0%)	**1 (0.3%)**	-	-

(Information in Table above is taken from Table 75 and 76of Applicant's Clinical Study Report for Study D961DC00001)

Discontinuation due to uncommon adverse events:
Tables 47 to 49 show uncommon adverse events that lead to discontinuations according to system organ class and preferred terms.

Table 47: Discontinuation: Uncommon AE (Cont)

AE leading to discontinuation	72 Hours		4 to 30 Days	
	Esomeprazole[a] (n=375)	Placebo[b] (n=389)	Esomeprazole[a] (n=347)	Placebo[b] (n=352)
Patients with an AE leading to discontinuation	31 (8.3%)	39 (10.0%)	15 (4.3%)	17 (4.8%)
Skin and subcutaneous tissue disorders	1 (0.3%)	2 (0.5%)	1 (0.3%)	1 (0.3%)
• Urticaria	1	1		
• Rash		1		
• Pruritis			1	
• Dermatitis allergic				1

(Information in Table above is taken from Table 75 and 76 of Applicant's Clinical Study Report for Study D961DC00001)

Table 48: Discontinuation: Administration Site Related AE

AE leading to discontinuation	72 Hours		4 to 30 Days	
	Esomeprazole[a] (n=375)	Placebo[b] (n=389)	Esomeprazole[a] (n=347)	Placebo[b] (n=352)
Patients with an AE Leading to Discontinuation	31 (8.3%)	39 (10.0%)	15 (4.3%)	17 (4.8%)
General and Administration Site Conditions (Catheter site related reaction)	1 (0.3%)	0 (0%)	-	-
Vascular Disorders (Hypertension, Hypotension, **Venous thrombosis limb)**	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0%)

(Information in Table above is taken from Table 75 and 76 of Applicant's Clinical Study Report for Study D961DC00001)

Table 49: Discontinuation: Neuro-psychiatric AE

AE	72 Hours		4 to 30 Days	
	Esomeprazole[a] (n=375)	**Placebo[b]** (n=389)	**Esomeprazole[a]** (n=347)	**Placebo[b]** (n=352)
Patients with an AE leading to discontinuation	**31 (8.3%)**	**39 (10.0%)**	**15 (4.3%)**	**17 (4.8%)**
Psychiatric disorders	**3 (0.8%)**	**2 (0.5%)**	**1 (0.3%)**	**0 (0%)**
• Acute psychosis	1	0	0	
• Delirium tremens	1	0	1	
• Psychotic disorder	1	0	0	
• Confusional state	0	1	0	
• Nicotine dependence	0	1	0	
Nervous system disorders				
• (Presyncope)	-	-	**1 (0.3%)**	0 (0%)

(Information in Table above is taken from Table 75 and 76 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
AEs related to skin were few and no particular trend was observed. (except one case of urticaria).

Though the number of administration site and vascular related AEs were common in esomeprazole group, only two patients had to discontinue the study due to these AEs. Though only 2 patients in esomeprazole group developed psychotic reactions compared to none in placebo group during the I.V. phase, these were important because they developed during I.V. infusion and were serious enough to cause discontinuation from the study. A brief summary is given below.

Narratives of selected AEs which are not described in the NEXIUM insert are given below.

1. (b) (6), 78/F: Patient developed **itching while receiving I.V esomeprazole** on second day of treatment. Itching was graded as severe AE and thought to be related to the drug treatment. Itching lasted for 10 days. He had multiple other diseases and was receiving many concomitant medications.

2. (b) (6) 85/F: Patient was noticed to have **Right humoral vein thrombosis (RHVT)** after 5 days of start of treatment. RHVT was considered as SAE but investigator thought this SAE was not related to the drug treatment. It was persisting till the reports were collected. *Reviewer thinks this instance of RHVT was possibly related to the I.V. infusion and should be incorporated into the NEXIUM label*

3. (b) (6) 84/M: Patient developed **transitory psychotic syndrome (TPS)** on the first day while receiving **I.V. esomeprazole, i**t lasted for one day. This case of TPS was termed as moderate AE; the investigator considered it not related to the drug

treatment. Although the patient had other diseases and concomitant medications the Medical Officer reviewer thinks it may be related to the drug that keeping into account the temporal profile of drug intake and development of symptoms and should be incorporated into the NEXIUM label.

4. (b) (6) 73/M: This patient developed **acute psychosis** on first day of **I.V. esomeprazole** treatment. This was termed as SAE and was considered by the investigator as related to the drug. Symptoms improved in two days of discontinuation of drug treatment. The Medical Officer reviewer agrees with the investigators assessment. This case of acute psychosis should be incorporated into the NEXIUM label.

5. (b) (6), 81/F: Patient developed **urticaria while on I.V. esomeprazole** on the third day of treatment. The urticaria was termed as SAE and considered by the investigator to be related to the drug treatment. Symptoms cleared within one day of stopping the drug treatment. *This SAE is already listed on Nexium Package Insert. Since it developed during I.V. treatment and drug had to be discontinued, reviewer thinks it is important to be stressed in the label.*

*All five patients had multiple other diseases and concomitant medications.

7.1.3.3 Other significant adverse events:

No other significant adverse events were appreciated that are not already in the current labeling for Nexium (Injection)

7.1.4 Other Search Strategies:

No other search strategies were performed

7.1.5 Common Adverse Events:

An adverse event was defined as any undesirable event that occurred to a participant during the course of the study, whether or not that event was considered study drug related.
Also, in the event that a subject was withdrawn from the study because of an adverse event, it had to be recorded on the CRF as such.

7.1.5.1 Appropriateness of adverse event categorization and preferred terms.

Treatment emergent adverse events were reported using Medical Dictionary of Regulatory Activities (MedDRA), version 10.1. In all cases, tables show the incidence of events using preferred terms (PTs). Within MedDRA, the PT level represents distinct medical concept.

7.1.5.2 Incidence of adverse events:

Overall AEs within 72 hours (I.V. treatment)
During the first 72 hours of I.V. treatment, 310 patients (esomeprazole=147, placebo group=163) had AEs. The details of adverse events during first 72 hours are shown in appendix, table 85.

As in the case of AEs associated with dropouts, this reviewer compared AEs occurring during the high dose esomeprazole I.V. administration with the period when patients received oral esomeprazole. Placebo-controlled data in 72 hours was looked at carefully so that information can be obtained on causality of any AEs noticed.

Table 50 summarizes commonly occurring AEs according to system organ class (AEs occurring ≥2% of patients in either treatment group) in these patients.

Table 50: Adverse Events occurring in ≥2% by SOC, within 72 hours

Overall AE	Esomeprazole (n=375)	Placebo (n=389)
Patients with any AE	**147(39.2%)**	**163(41.9%)**
Gastrointestinal disorders	46(12.3%)	77(19.8%)
General and administration site conditions	27(7.2%)	20(5.1%)
Vascular disorders	24(6.4%)	16(4.1%)
Cardiac disorders	13(3.5%)	13(3.5%)
Infections and infestations	13(3.5%)	16(4.1%)
Respiratory, thoracic and mediastinal disorders	12(3.2%)	13(3.3%)
Nervous system disorders	11(2.9%)	11(2.8%)
Metabolism and nutrition disorders	10(2.7%	6(1.5%)
Musculoskeletal and connective tissue disorders	10(2.7%)	9(2.3%)
Psychiatric disorders	10(2.7%)	20(5.1%)
Skin and subcutaneous tissue disorders	9(2.4%)	6(1.5%)
Investigations	4(1.1%)	11(2.8%)

(Table above is taken from Table 36 of Applicant's Clinical Study Report for Study D961DC00001)

The AEs occurring in the Gastro-intestinal, general and administration site, and local vascular systems are shown in tables 51 to 53. Comments are given after the tables:

Table 51: GI related AEs 72 hours:

Overall AE	Esomeprazole (n=375)	Placebo (n=389)
Patients with any AE	147 (39.2%)	163 (41.9%)
Gastrointestinal Disorders: Bleeding	**12.3%**	**19.8%**
• DU Bleeding	4.3%	4.1%
• GU Bleeding	1.1%	3.3%
• GI Bleeding	0.5%	0.5%
• Rectal Bleeding	0.5%	0%
• Melena	0.3%	0.3%
• Hemetemesis	0.3%	0%
Gastrointestinal Disorders: Non-Bleeding	**46 (12.3%)**	**77 (19.8%)**
• Nausea	2.1%	2.1%
• Constipation	1.6%	2.3%
• Abdominal Pain	1.6%	5.1%
• Diarrhea	0.8%	0%
• vomiting	0.5%	0.3%

(Above table is compiled from Tables 36 and 66 of Applicant's Clinical Study Report for Study D961DC00001)

Table 52: AEs General and administration site, 72 h

Overall AE	Esomeprazole (n=375)	Placebo (n=389)
Patients with any AE	147 (39.2%)	163(41.9%)
General and Administration Site Conditions	**27 (7.2%)**	**21 (5.1%)**
• Pyrexia	13 (3.5%)	11 (2.8%)
• Fatigue	2 (0.5%)	1 (0.3%)
• Edema	2 (0.5%)	1 (0.3%)
• Non-cardiac Chest Pain	1 (0.3%)	1 (0.3%)
• Pain	1 (0.3%)	1 (0.3%)
• Chest Discomfort	1 (0.3%)	0%
• *Injection Site Erythema*	1 (0.3%)	0%
• *Injection Site Inflammation*	1 (0.3%)	0%
• *Injection Site Swelling*	1 (0.3%)	0%
• *Catheter Site Related Reaction*	2 (0.5%)	0%
• *Infusion Site Swelling*	0%	1 (0.3%)
• Chills	1 (0.3%)	1 (0.3%)
• Feeling Cold	1 (0.3%)	0%
• Hyperthermia	0%	2 (0.5%)
• Asthenia	0%	1 (0.3%)
• Sensation of Foreign Body	0%	1 (0.3%)

(Above table is compiled from tables 36 and 66 of Applicant's Clinical Study Report for Study D961DC00001)

Table 53: AEs: General and Administration Site (Vascular) 72 hours

Overall AE	Esomeprazole (n=375)	Placebo (n=389)
Vascular Disorders	**24 (6.4%)**	**18 (4.1%)**
• *Phlebitis*	9 (2.4%)	2 (0.5%)
• *Thrombophlebitis*	2 (0.5%)	0 (0%)
• *Phlebitis superficial*	1 (0.3%)	0 (0%)
• *Thrombosis*	1 (0.3%)	0 (0%)
• Accelerated Hypertension	0%	0.5%
• Hypertension	1.3%	1.8%
• Angiodysplasia	0%	0.3%
• Circulatory Collapse	0%	0.3%
• Orthostatic Hypotension	0%	0.3%
• Hypotension	1.1%	1.0%
• Ischaemia	0.3%	0%
• Shock	0.3%	0%

(Above table compiled from sponsors table 66 of Clinical Study Report for Study D961DC00001)

Details of infusion site reactions within 72 hours during I.V. treatment are shown in Appendix, table 87.

More AEs related to the GI tract occurred in the placebo compared to the esomeprazole group (19.8% versus 12.3%).

- Incidence of gastrointestinal bleeding was numerically more in placebo group than esomeprazole group (8.2% versus 7%). This included all HLT terms for GI bleeding.
    - Gastric ulcer rebleeding incidence was more in the placebo than esomeprazole group (3.3% versus 1.1%) whereas rebleeding incidence of duodenal ulcer appeared to be similar and comparable in the two groups (4.3% versus 4.1%). Incidence of non-site specific hemorrhage was higher in esomeprazole than the placebo group (1.6% versus 0.8%).

- Abdominal pain, both upper and generalized, appeared to have higher incidence in the placebo than in the esomeprazole group (5.1 % versus 1.6%). Incidence of nausea was identical in two groups (2.1% versus 2.1%) and symptom of constipation was higher in placebo group than esomeprazole group (2.3% versus 1.6%).

General disorders and administration site conditions were numerically higher in the esomeprazole than the placebo group (7.2% versus 5.1%).

- Pyrexia appears to have slightly higher incidence in the esomeprazole group than placebo group (3.5% versus 2.8%).

- Incidence of injection site related reactions i.e. catheter site related reaction, injection site swelling, injection site inflammation; injection site erythema was higher in esomeprazole group than placebo group (1.5% versus 0%).
- General symptoms of fatigue, edema, chest discomfort and feeling cold were higher in the esomeprazole than placebo group (1.6% versus 0.6%).
- Other symptoms i.e. chills, non cardiac chest pain, and pain were comparable in the two groups (0.9% versus 0.9%).

Incidence of vascular disorders was higher in esomeprazole group than placebo group (6.4% versus 4.1%).

- Local vascular disorders: Infusion related AEs i.e. phlebitis, thrombophlebitis, superficial phlebitis, and thrombosis were higher in esomeprazole than placebo group (3.5% versus 0.5%).
- Generalized vascular disorders: Incidence of hypertension (esomeprazole=1.3%; placebo=1.8%) and hypotension (esomeprazole=1.1%; placebo=1.8%) were comparable.

Comments: *Combining the AEs related to infusion site and local vascular disorders, the incidence of AEs is much higher in the esomeprazole group compared with placebo group (5% versus 0.5%)*

Adverse events related to infections and infestations were numerically higher in placebo than the esomeprazole group (4.1% versus 3.5%).

- Urinary tract infection incidence was the same in the two groups (1.1% each).
- Incidence of lymphangitis, respiratory infection, bacterial diarrhea, bronchitis, and cellulitis and catheter infection was higher in the esomeprazole group than the placebo group (2.5% versus 0.3%).
- Incidence of diverticulitis, oral fungal infection, sepsis, sinusitis and respiratory infection was higher in placebo group (2.4% versus0%).

Overall incidence of respiratory, thoracic and mediastinal disorders is comparable in the two groups (3.2% in esomeprazole, 3.3% in placebo group).

- Cough and dyspnoea accounting for majority of AEs in this category, were slightly higher in placebo group compared to esomeprazole group (2.1% versus 1.6%).
- Incidence of pleural effusion, productive cough, pulmonary edema, tracheal pain was higher in esomeprazole group than placebo group (1.5% versus 0%).
- Incidence of epistaxis, lung infiltration, pulmonary embolism, and rhinorrhoea was higher in placebo group than esomeprazole group (1.2% versus 0%).

Incidence of nervous system disorders was same in two groups (2.9% versus 2.9%). These were mainly accounted for by headache (1.3% in esomeprazol versus 1.8% in placebo group), and dizziness (1.1% in esomeprazole versus 1.8% in placebo group).

Incidence of cardiac AEs was comparable overall (3.5% in esomeprazole group versus 3.6% in placebo group).

Incidence of psychiatric AEs was higher in placebo group than esomeprazole group (5.1% versus 2.7%).

- *However AEs of acute psychosis and hallucination (one each) were noted in the esomeprazole group only. These AEs have not been described in the NEXIUM PI.* Other AEs observed have been described in the Nexium insert.

Incidence of metabolic and nutritional AEs was numerically higher in esomeprazole group than placebo group (2.7% versus 1.5%).

- Incidence of hypoglycemia and inadequate control of diabetes mellitus was higher in the esomeprazole group than placebo group 1.5% versus 0.3%).
- Incidence of hypokalemia/hyperkalemia was comparable in two groups (1.3% in placebo, 1% in esomeprazole group). One incidence of exacerbation of gout occurred in esomeprazole group only.

Musculoskeletal and connective tissue AEs were slightly more in the esomeprazole group than placebo group (2.7% versus 2.3%). Incidence of pain in extremities and tendon was higher in esomeprazole group than placebo group (1.2% versus 0%).

Incidence of skin and subcutaneous tissue AEs and anemia was comparable in two groups.

Incidence of AEs related to eye was numerically higher in the esomeprazole group than placebo group (1.3% versus 0.3%). These were mainly accounted for by AEs of blepheritis, dry eye, eye hemorrhage, eye inflammation, and ocular hyperemia in esomeprazole group compared to placebo group (1.3% versus 0%).

Incidence of hepatobiliary AEs was higher in esomeprazole group than placebo group (1.1% versus 0.5%). AEs in esomeprazole group were cholicystitis, hepatic steatosis, hepatocellular damage, and alcoholic cirrhosis whereas in placebo group AEs were hepatic cyst and post cholecystectomy syndrome.

Incidence of neoplasm and procedural complications were apparently not related to the drug treatment.

Isolated event of vertigo was observed in esomeprazole group.

Comments:
Overall the incidence of AEs during I.V. administration (72 hours) was comparable in the esomeprazole and the placebo groups (39.2% versus 41.9%).

The most common AE in both treatment groups was related to rebleeding, i.e., the efficacy outcome variable. Infusion site reactions (thrombophlebitis, phlebitis, infusion site erythema/reaction/edema) were more common in the esomeprazole treatment group compared to the placebo treatment group. These events were, however, of short duration and did not cause discontinuation of study drug. The adverse event (AE) profile for

esomeprazole I.V. did not show any trend or safety concern in an acutely ill patient population with PUB.

Overall AEs within 4 to 30 days (oral treatment)
During this period of oral treatment, 247 patients (esomeprazole-116, placebo-131) had AEs. The details of the adverse events during 4 to 30 days are shown in Appendix, table 86.

The table 54 gives overview of commonly occurring AEs (AEs occurring ≥2% of patients in either treatment group) in these patients. The summary of AEs in each SOC is given following this table.

Table 54: Number (%) of patients and Adverse Events occurring ≥2% by SOC, during 4 to 30 days.

System Organ Class (SOC)	4-30 Days	
	Eso (n=347)	**Placebo** (352)
Patients with any AE	**116 (33.4%)**	**131 (37.2)**
Gastrointestinal Disorders	33 (9.5%)	46(13.1%)
General Disorder and administration site conditions	24 (6.9%)	18 (5.1%)
Infections and Infestations	18 (5.2%)	26 (7.4%)
Vascular Disorders	15 (4.3%)	9 (2.6%)
Respiratory, Thoracic and medistinal disorders	14 (4.0%)	8 (2.3%)
Musculoskeletal and connective tissue disorders	9 (2.6%)	10 (2.8%)
Nervous System Disorder	9 (2.6%)	10 (2.8%)
Cardiac Disorders	8 (2.3%)	8 (2.3%)
Metabolism and Nutrition Disorders	7 (2.0%)	10 (2.8%)
Skin and Subcutaneous Tissue Disorders	7 (2.0%)	9 (2.6%)
Psychiatric Disorders	6 (1.7%)	8 (2.3%)
Blood and Lymphatic System Disorders	5 (1.4%)	8 (2.3%)
Renal and Urinary Disorders	4 (1.2%)	8 (2.3%)

(Table above is taken from Table 37 of Applicant's Clinical Study Report for Study D961DC00001)

Gastrointestinal related AEs were higher in the placebo group than the esomeprazole group (13.1% versus 9.5% table 55). AEs related to bleeding and others (not related to bleeding) are described separately:

Table 55: GI related AEs during 4 to 30 days: n (%) of patients

System Organ Class/Preferred Term	4 to 30 Days	
	Esomeprazole (n=347)	**Placebo** (352)
Patients with any AE	**116 (33.4%)**	**131 (37.2)**
Gastrointestinal Disorders	**33 (9.5%)**	**46 (13.1%)**
• Duodenal Ulcer Hemorrhage	4 (1.2%)	9 (2.6%)
• Gastric ulcer hemorrhage	4 (1.2%)	4 (1.1 %)
• Melena	3 (0.9%)	2 (0.6%)
• Hemetochezia	1 (0.3%)	1 (0.3%)
• Rectal hemorrhage	1 (0.3%)	0 (0%)
• Gastrointestinal hemorrhage	0 (0%)	1 (0.3%)
• Constipation	7 (2.0%)	12 (3.4%)
• Diarrhea	6 (1.7%)	3 (0.9%)
• Nausea	6 (1.7%)	3 (0.9%)
• Vomiting	2 (0.6 %)	1 (0.3%)
• Abdominal pain	1 (0.3%)	7 (2.0%)
• Dyspepsia	1 (0.3%)	2 (0.6%)
• Abdominal pain upper	1 (0.3%)	1 (0.3%)
• Epigastric discomfort	1 (0.3%)	1 (0.3%)
• Aphthous stomatitis	1 (0.3%)	0 (0%)
• Eructation	1 (0.3%)	0 (0%)
• Esophageal varices hemorrhage	1 (0.3%)	0 (0%)
• Abdominal distension	0 (0%)	1 (0.3%)
• Colonic polyp	0 (0%)	1 (0.3%)
• Dry mouth	0 (0%)	1 (0.3%)
• Gastric ulcer perforation	0 (0%)	1 (0.3%)
• Pancreatitis acute	0 (0%)	1 (0.3%)

(Information in Table above is taken from Table 67 of Applicant's Clinical Study Report for Study D961DC00001)

- Incidence of overall gastrointestinal bleeding was numerically higher in placebo than esomeprazole group (4.9% versus 3.9%). This included all HLT terms for GI bleeding.
    - Duodenal ulcer rebleeding incidence was higher in placebo group than esomeprazole group (2.6% versus 1.2%)
    - Rebleeding incidence of gastric ulcer appeared to be similar and comparable in two groups (1.2% versus 1.1%).
    - Incidence of non-site specific hemorrhage was comparable in both treatment groups (esomeprazole=1.5%; placebo=1.2%).

- Abdominal pain, both upper and generalized, had numerically higher incidence in the placebo group than in the esomeprazole group (2.6% versus 0.9%). Symptom of constipation was also more in placebo group than esomeprazole group (3.4% versus 2%). Incidences of nausea and diarrhea were slightly higher in esomeprazole group than placebo group (For nausea 2.3% versus 0.9%, diarrhea 1.7% versus 0.9%).

General disorders and administration site related AEs were numerically higher in esomeprazole group than placebo group (6.9% versus 5.1%; table 56).

Table 56: General Disorder and Administration Site Conditions

System Organ Class/Preferred Term	**4 to 30 Days**	
	Esomeprazole (n=347)	**Placebo** (352)
Patients with any AE	**116 (33.4%)**	**131 (37.2)**
General Disorder and administration site conditions	**24 (6.9%)**	**18 (5.1%)**
• Pyrexia	9 (2.6%)	9 (2.6%)
• Edema peripheral	4 (1.2%)	2 (0.6%)
• Fatigue	3 (0.9%)	1 (0.3%)
• Hyperthermia	2 (0.6%)	2 (0.6%)
➢ **Injection site inflammation**	**2 (0.6%)**	**0 (0%)**
• Discomfort	1 (0.3%)	0 (0%)
• General physical health deterioration	1 (0.3%)	0 (0%)
➢ **Injection site erythema**	**1 (0.3%)**	**0 (0%)**
• Pain	1 (0.3%)	0 (0%)
• Non-cardiac chest pain	0 (0%)	2 (0.6%)
• Asthenia	0 (0%)	1 (0.3%)
• Infusion site swelling	0 (0%)	1 (0.3%)
	0 (0%)	1 (0.3%)

(Information in Table above is taken from Table 67 of Applicant's Clinical Study Report for Study D961DC00001)

- Incidence of injection site related reactions i.e., injection site swelling, inflammation; erythema was higher in the esomeprazole than placebo group (0.9% versus 0.3%).
- General symptoms of fatigue, edema, discomfort and general physical health deterioration were higher in esomeprazole than placebo group (2.7% versus 1.2%).
- Pyrexia appeared to have comparable incidence in the esomeprazole and placebo groups (2.6% versus 2.6%).
- Other symptoms i.e. non cardiac chest pain and asthenia were higher in placebo than esomeprazol group (0.9%versus 0%).

Incidence of vascular disorders was higher in the esomeprazole than the placebo group (4.3% versus 2.6%). These are mainly accounted for by infusion related AEs i.e. phlebitis, thrombophlebitis, superficial phlebitis, and thrombosis which were more in esomeprazole group than placebo group (3.9% versus 0.9 %).

Comments:
AEs related to general disorder showed no trend and were comparable in two groups. Administration site AEs were seen only in esomeprazole group.
If AEs related to I.V. infusion from administration site and vascular disorders are combined, the incidence of infusion related AEs is much higher in esomeprazole group compared with placebo group (4.8% versus 1.2%). This information should be incorporated into the labeling.

Adverse events related to infections and infestations were numerically higher in placebo group than esomeprazole group (7.4 versus 5.2%):

- Incidence of upper respiratory tract and lung infection was higher in esomeprazol group than placebo group (2.1% versus 1.5%), incidence of urinary tract infection and cystitis was numerically higher in placebo group than esomeprazol group (4.2% versus 2.1%) whereas infections related to other organ systems were also higher in the placebo group (3.3% versus 0.9%).

Overall incidence of respiratory, thoracic and mediastinal disorders were numerically higher in the esomeprazole group than placebo group (4% versus 2.3%).

- Cough and dyspnoea accounting for majority of AEs in this category, were numerically higher in esomeprazol group compared to placebo group (2.4% versus 0.6%).
- COPD, epistaxis, pharyngeal pain and respiratory failure AEs were primarily in esomeprazol group than in placebo group (1.5% versus 0%).
- Incidence of lung infiltration, pulmonary embolism, pulmonary edema, ronchi and bronchial disorder was higher in placebo group than esomeprazole group (1.5% versus 0%).

Incidence of nervous system disorders was comparable in two groups (esomeprazol 2.6%, placebo 2.8%). These nervous system disorders were mainly accounted for by headache and dizziness.

Incidence of cardiac AEs was comparable overall (2.3% in esomeprazol group versus 2.3% in placebo group). However a few, not significant, differences are described:

- Incidence of angina pectoris was numerically higher in esomeprazol group than placebo group (0.9% versus 0.3%).
- In the category of rhythm disorder esomeprazol group had higher incidence of bradycardia, palpitations and ventricular extrasystoles (0.9% versus 0.0% in placebo), whereas placebo group had more patients with atrial fibrillation than esomeprazol group (0.9% versus 0%).

- Incidence of myocardial infarction was slightly lower in esomeprazole group than placebo group (0.6% versus 1.2%).

Incidence of psychiatric AEs was higher in placebo group than esomeprazole group (2.3% versus 1.7%). These events were mainly accounted for by the insomnia/sleep disorders which were the same in both groups (1.5% versus 1.5%).
Incidences of metabolic and nutritional AEs were comparable in two treatment groups during 4 to 30 days (esomeprazole=2.8%; placebo=2%).

- Incidence of hypoglycemia and inadequate control of diabetes mellitus was slightly higher in the esomeprazole group than placebo group 0.6% versus 0.3%).
- Incidence of hypokalemia/hyperkalemia was more in placebo group than esomeprazole group (2% in placebo, 0.6% in esomeprazole group).

Musculoskeletal and connective tissue AEs were comparable in two groups (esomeprazole 2.6 % versus placebo 2.8%) however the incidence of pain in extremities and tendon was numerically more in esomeprazole group than placebo group (0.6% versus 0%).

Incidence of skin and subcutaneous tissue AEs was comparable in two treatment groups (placebo 2.6% versus esomeprazole 2%). This difference was primarily due to slight higher incidence of pruritis in placebo group than esomeprazole group (1.1% versus 0.6%). *New AE of eczema, not described in Nexium insert, was described in two patients in esomeprazole group compared to none in placebo group. This AE of eczema should be incorporated into the NEXIUM PI*

Incidence of AEs related to eye was numerically more in the esomeprazole group than placebo group (1.3% versus 0.3%). These were accounted for by AEs of blepheritis, dry eye, eye hemorrhage, ocular hyperemia, and uveitis (one case each) in esomeprazole group compared to placebo group (1.3% versus 0%).

Incidence of hepatobiliary AEs was more in esomeprazole group than placebo group (1.4 % versus 0.9%). AEs in esomeprazole group were hepatic steatosis, hepatocellular damage, alcoholic cirrhosis, and hepatitis (related to hepato-cellular functions) whereas AEs in placebo group were biliary colic, acute cholicystitis, and post cholecystectomy syndrome (not related to hepato-cellular function).

Incidence of neoplasm in two treatment groups was comparable and apparently not related to the drug treatment.

Comments:
The incidence of AEs during the 4 to 30 days of treatment (oral esomeprazole) in the two treatment groups was numerically lower in esomeprazole group compared to placebo group (esomeprazole=33.4%; placebo= 37.2%).
The most common AE in both treatment groups was related to rebleeding, i.e., the efficacy outcome variable. Infusion site reactions (thrombophlebitis, phlebitis, infusion site erythema/reaction/edema) were more common in the esomeprazole treatment group

compared to the placebo treatment group, majority were in continuation from I.V. phase. AEs related to other system organ class were similarly distributed in the two treatment groups.

Overall, the adverse event (AE) profile for esomeprazole I.V. did not show any trend or safety concern in an acutely ill patient population with PUB.

Incidence of common adverse events

7.1.5.4 Common adverse event tables

Treatment with high dose continuous infusion of esomeprazole was similar in overall incidence of adverse reactions compared to placebo infusion except the local administration and vascular adverse events. The most common reactions reported (greater than 1% of all patients treated with high dose esomeprazole) were nausea, constipation, abdominal pain, urinary tract infection, pyrexia, cough, headache, and dizziness. The tables 57 and 58 show the AEs ≥ 1% during I.V. administration and overall (I.V. + oral administration of esomeprazole).

Table 57: Commonly occurring AEs (≥ 1%) with in 72 hours, I.V. phase

System organ class/Preferred Term	Number (%) of patients
Gastrointestinal disorders	
• DU Bleeding	4.3%
• Nausea	2.1%
• Constipation	1.6%
• Abdominal Pain	1.3%
• GU Bleeding	1.1%
General disorders and administration site conditions	
• Pyrexia	3.5%
Vascular disorders	
• Phlebitis	2.4%
• Hypertension	1.3%
• Hypotension	1.1%
Cardiac Disorder	
• Myocardial infarction	1.1%
Infection and infestation	
• Urinary tract infection	1.1%
Respiratory system	
• Cough	1.1%
Nervous system	
• Headache	1.3%
• Dizziness	1.1%

(Information in Table above is taken from Table 66 of Applicant's Clinical Study Report for Study D961DC00001)

Table 58: Commonly occurring AEs (≥ 1%) with in 30 days (I.V. + Oral treatment)

System organ class/Preferred Term	Number (%) of patients
Gastrointestinal disorders	
• DU Bleeding	5.1%
• Nausea	2.9%
• Constipation	2.7%
• Abdominal Pain	1.6%
• GU Bleeding	1.6%
• Diarrhea	1.9%
• Melena	1.1%
General disorders and administration site conditions	
• Pyrexia	4.5%
• Edema	1.3%
• Fatigue	1.3%
Vascular disorders	
• Phlebitis	2.4%
• Hypertension	1.6%
• Hypotension	1.1%
• Thrombophlebitis	1.1%
Cardiac Disorder	
• Myocardial infarction	1.1%
Infection and infestation	
• Urinary tract infection	1.9%
Respiratory system	
• Cough	1.1%
• Dyspnea	1.1%
Central Nervous System	
• Headache	2.1%
• Dizziness	1.6%
Musculoskeletal and connective tissue disorders	
• Arthralgia	1.1%
Psychiatric disorders	
• Insomnia	1.1%

(Information in Table above is taken from Table 68 of Applicant's Clinical Study Report for Study D961DC00001)

7.1.5.5 Identifying common and drug-related adverse events

Comments:
Although majority of the AEs reported in this trial are already listed in the NEXIUM package insert, the incidence of AEs are numerically higher than reported in the package insert. This reviewer recommends that the new AEs be added and incidence of existing AEs on the package insert written accordingly/appropriately/ reclassified.

AEs ≥1% within 72 hours (I.V. treatment)

DU bleeding, GU bleeding, pyrexia, phlebitis, hypertension, hypotension, myocardial infarction, urinary tract infection, cough, and headache.

AEs ≥1% within 30 days (I.V. + oral treatment)

DU bleeding, GU bleeding, melena, pyrexia, edema, fatigue, phlebitis, hypertension, hypotension, thrombophlebitis, myocardial infarction, urinary tract infection, cough, dyspnea, headache, arthralgia and insomnia.

AEs ≤ 1% but are important

Acute psychosis, eczema, median nerve injury, itching and urticaria during I.V. administration of the drug, nephrotic syndrome, renal failure and hypoglycemia

7.1.5.6 Additional analyses and explorations

No additional analyses and explorations were performed.

7.1.6 Less Common Adverse Events

Review of uncommon adverse events in the entire safety database did not identified additional safety concerns not addressed elsewhere in the rev

7.1.7 Laboratory Findings

Laboratory data for serum chemistry, hematology parameters measured in study D961DC00001 were reviewed.

7.1.7.1 Overview of laboratory testing in the development program

White blood count, platelet count, ALAT, ASAT, ALP, serum creatinine and bilirubin were the lab parameters evaluated in Pivotal study of peptic ulcer bleeding (D961DC00001). Clinical laboratory results were presented separately for hematology and clinical chemistry. Results were examined in 3 ways: changes in mean values over time, changes in individual patients over time, and individual clinically important abnormalities. Number of patients exposed to test drug with baseline and follow up test values are shown in table 59 below:

Table 59: Patients with baseline and subsequent values of laboratory tests

Lab variable, Units	**Treatment Group**	
	Esomeprazole (n)	**Placebo (n)**
White blood count	288	288
Platelet count	280	274
ALAT (SGPT), U/L	307	306
ASAT (SGOT), U/L	305	306
ALP, U/L	310	311
Creatinine, µmol/L	238	251
Bilirubin, total, µmol/L	303	300

(Above table Compiled by the reviewer from tables 44 and 45 Clinical Study Report for Study D961DC00001)

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Descriptive statistics for change and percentage change from the baseline in laboratory parameters for intent-to-treat patients are summarized by treatment group value from study D961DC00001. Patients were observed for signal of an effect of the drug on laboratory tests during first the 72 hours and also during 4 to 30 days.

7.1.7.3 Standard analyses and explorations of laboratory data

Hematology

Changes in mean values over time in hematology

A summary of changes in hematology laboratory values over time from baseline to last visit is shown in Table 60. The corresponding data divided into the treatment periods 0 to 72 hours and day 4 to 30 are shown in table 61 and table 62.

Table 60: Mean changes in hematology, patients with both a baseline and a subsequent value

Haematology variable, units	Treatment group[a]	n	Baseline Median	Mean	SD	Last visit Median	Mean	SD	Change Median	Mean	SD
White blood cell count, GI/L	Eso	288	9.55	10.31	3.89	6.90	7.10	2.25	-2.90	-3.21	3.63
	Placebo	288	10.50	11.42	5.64	6.85	7.15	2.50	-3.65	-4.27	5.10
Platelet count, GI/L	Eso	280	226.00	236.95	87.93	271.50	287.11	87.80	45.00	50.16	83.28
	Placebo	274	240.00	260.94	109.30	293.50	319.46	138.29	49.00	58.52	122.09

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

(Above table is taken from Table 43 of Applicant's Clinical Study Report for Study D961DC00001)

Table 61: Mean changes in hematology, at baseline and 72 hours:

Haematology variable, units	Treatment group[a]	n	Baseline Median	Mean	SD	72 hours Median	Mean	SD	Change Median	Mean	SD
White blood cell count, GI/L	Eso	18	9.45	9.46	3.13	7.15	9.20	4.97	-0.55	-0.26	3.68
	Placebo	37	12.90	13.36	7.10	11.10	11.56	4.57	-1.00	-1.80	7.55
Platelet count, GI/L	Eso	17	204.00	210.59	82.86	176.00	229.82	94.23	21.00	19.24	104.68
	Placebo	36	240.00	257.61	88.29	215.00	217.53	78.41	-15.00	-40.08	88.08

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

(Table above is taken from Table 79 of Applicant's Clinical Study Report for Study D961DC00001)

Table 62: Mean changes in hematology patients with a value at day 4 and Day 4 to day 30:

Haematology variable, units	Treatment group[a]	n	Day 4 Median	Mean	SD	Last visit Median	Mean	SD	Change Median	Mean	SD
White blood cell count, GI/L	Eso	14	9.80	10.15	2.86	6.80	8.74	4.45	-1.10	-2.49	4.26
	Placebo	30	13.35	13.74	7.93	11.00	11.52	4.25	-3.50	-3.02	5.09
Platelet count, GI/L	Eso	14	170.00	197.31	79.97	173.50	225.57	109.89	33.00	35.43	76.33
	Placebo	29	265.00	273.00	86.75	225.00	233.76	81.20	70.00	106.21	143.41

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

(Table above is taken from Table 80 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:

Ninety four patients had elevated WBC count above normal range during the study (52 patients in placebo group and 42 patients in esomeprazole group). This could be reaction to the acute illness and other co-existing medical conditions. There seems to be no safety concern due to drug intake.

Overall small changes were seen over time in clinical hematology parameters. It is difficult to assess hematologic profile in patients with Gastrointestinal bleeding because the majority of such patients need blood transfusion and it is difficult to achieve stable parameters in a short time. The changes observed were not clinically significant and no trends were observed.

Clinical chemistry:

Changes in mean values over time in clinical chemistry

A summary of changes in clinical chemistry laboratory values over time from baseline to last visit is shown in Table 63. The corresponding data divided into the treatment periods 0 to 72 hours and day 4 to 30 are shown in Table 64 and 65.

Table 63: Mean changes in clinical chemistry, patients with baseline and a subsequent value, safety population

Laboratory variable, units	Treatment group[a]	n	Baseline Median	Baseline Mean	Baseline SD	Last visit Median	Last visit Mean	Last visit SD	Change Median	Change Mean	Change SD
ALAT (SGPT), U/L	Eso	307	16.00	19.78	18.19	18.00	20.80	11.88	2.00	1.02	18.93
	Placebo	306	16.00	22.14	23.16	17.50	23.67	22.68	2.00	1.53	28.03
ASAT (SGOT), U/L	Eso	305	19.00	22.31	16.30	20.00	22.76	11.61	2.00	0.45	15.08
	Placebo	306	18.50	23.16	18.89	21.00	23.61	15.54	2.00	0.45	19.63
ALP, U/L	Eso	310	53.00	60.47	34.47	77.00	86.51	42.61	22.50	26.04	28.56
	Placebo	311	56.00	67.28	55.91	78.00	88.06	54.90	22.00	20.79	43.51
Creatinine, µmol/L	Eso	238	71.00	76.34	25.27	80.00	83.87	23.13	9.00	7.53	20.51
	Placebo	251	80.00	87.90	47.88	88.00	92.83	56.91	9.00	4.94	32.24
Bilirubin, total, µmol/L	Eso	303	9.00	10.10	7.05	7.00	8.57	5.25	0.00	-1.52	5.80
	Placebo	300	9.00	10.40	12.41	7.00	8.70	6.99	-1.00	-1.70	11.95

(Table above is taken from Table 45 of Applicant's Clinical Study Report for Study D961DC00001)

Table 64: Mean changes in clinical chemistry, patients with baseline and a subsequent value at 72 hours:

Laboratory variable, units	Treatment group[a]	n	Baseline Median	Baseline Mean	Baseline SD	Last visit Median	Last visit Mean	Last visit SD	Change Median	Change Mean	Change SD
ALAT (SGPT), U/L	Eso	318	16.00	25.44	67.75	19.00	28.86	52.64	1.00	3.42	28.96
	Placebo	333	16.00	22.53	24.59	19.00	26.27	30.59	2.00	3.75	23.81
ASAT (SGOT), U/L	Eso	317	19.00	30.19	91.40	22.00	32.88	67.92	2.00	2.70	49.13
	Placebo	333	18.00	23.22	19.24	21.00	26.67	26.86	2.00	3.45	24.09
ALP, U/L	Eso	323	54.00	63.30	43.74	64.00	71.26	46.54	7.00	7.96	15.38
	Placebo	337	56.00	66.69	53.75	59.00	70.19	53.11	4.00	3.50	20.18
Bilirubin, total, µmol/L	Eso	311	9.00	10.25	9.64	7.00	8.92	8.22	-1.00	-1.33	6.42
	Placebo	325	9.00	10.55	12.17	7.00	8.90	7.74	-1.00	-1.65	9.59

Table above is taken from Table 82 of Applicant's Clinical Study Report for Study D961DC00001)

Table 65: Mean changes in clinical chemistry, patients with both a value at day 4 and day 4 -30,

Laboratory variable, units	Treatment group[a]	n	Baseline Median	Baseline Mean	Baseline SD	Last visit Median	Last visit Mean	Last visit SD	Change Median	Change Mean	Change SD
ALAT (SGPT), U/L	Eso	298	19.00	24.82	24.23	18.00	21.02	13.17	-1.00	-3.79	23.55
	Placebo	304	20.00	25.86	23.87	18.00	23.66	22.58	-2.00	-2.19	27.21
ASAT (SGOT), U/L	Eso	297	22.00	27.75	28.93	20.00	22.58	11.15	0.00	-5.16	27.13
	Placebo	304	22.00	26.96	27.80	21.00	23.46	15.45	-1.00	-3.50	25.51
ALP, U/L	Eso	302	63.00	67.70	32.71	77.50	86.51	42.92	14.50	18.82	26.50
	Placebo	309	59.00	70.63	52.65	78.00	87.00	53.53	17.00	16.37	41.37
Bilirubin, total, µmol/L	Eso	297	7.00	8.35	6.74	7.00	8.48	5.17	0.00	0.13	5.42
	Placebo	298	7.00	8.72	7.74	7.00	8.52	6.00	0.00	-0.20	6.06

(Table above is taken from Table 83 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
Increases in mean ALP values at 72 hours and 30 days compared to baseline were observed in both treatment groups. The increase at 72 hours was higher for the esomeprazole group compared to placebo (12.6% and 5.2% respectively). The corresponding increase at 30 days was also higher in the esomeprazole than the placebo group (43.1% versus 30.9%). In the majority of patients ALP increase was within the reference range. Few patients had high ALP values above the reference range both at baseline and after treatment. The increase in ALP was not associated with increases in other liver function tests, i.e. ALAT, ASAT or bilirubin. Moreover there was only one case of AEs related to SOC "Hepatobiliary disorder". There were no noticeable differences in the two treatment groups. The changes related to the other laboratory tests were also balanced in the two groups and did not show any trend.

7.1.7.4 Additional analyses and explorations

No additional analyses and exploration are indicated

7.1.7.5 Special assessments

No evidence of change in liver function tests and heart related AEs were identified in the present study. The elevation of alkaline phosphatase (ALP) and other liver tests (ALAT, ASAT or bilirubin) was comparable in both treatment groups. In addition, the increase in ALP was not associated with increases in other liver function tests. The mechanism behind the ALP increase is not clear.

Comments:
The study had excluded patients with moderate to severe liver disease (Child's Pugh category B and C) and adequate ECG, cardiac enzyme monitoring were not done during high dose continuous I.V. infusion of esomeprazole. The majority of patients with peptic ulcer bleeding were elderly with these co-existing conditions. It would be appropriate to assess safety in this group alone.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the vital signs section, results were examined in different ways: trends or group changes over time, changes in individual patients over time, individual clinically important abnormalities other observations related to safety.

Changes in vital signs over time:
Mean changes in vital signs for patients from baseline to last visit are shown in Table 66: ECG was only collected before randomization for inclusion purpose and it is therefore not part of the safety analysis.

Table 66: Mean changes in vital signs

Vital sign variable, units	Treatment group[a]	n	Baseline Mean	SD	Last visit Mean	SD	Change Mean	SD
Systolic BP, mmHg	Eso	333	125.0	21.5	133.4	21.2	8.6	25.7
	Placebo	352	126.6	22.8	132.2	19.5	5.2	26.0
Diastolic BP, mmHg	Eso	333	72.1	13.3	78.2	11.3	6.2	16.7
	Placebo	351	72.5	13.6	78.3	11.7	5.6	16.7
Pulse rate, beats/min	Eso	333	87.7	16.8	76.9	11.1	-10.5	18.3
	Placebo	353	89.2	17.7	77.8	12.2	-11.6	18.0

(Table above is taken from Table 47 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
Mean BP increased and mean pulse rate decreased in both treatment groups from baseline to follow-up. No clinically relevant changes over time were noted and no difference was observed between the two treatment groups.

Physical findings
New or aggravated physical findings compared to baseline examinations were recorded and presented as AEs.

No clinically abnormal physical findings were observed.

7.1.9 Electrocardiograms (ECGs)

Overview of ECG testing in the development program, including brief review of preclinical results

ECG was only collected before randomization for inclusion purpose and is therefore not part of the safety analysis.

7.1.10 Immunogenicity

The applicant did not provide any clinical or adverse event data regarding immunogenicity in this application

7.1.11 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. These data are N.A.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no clinical information with respect to the potential for abuse, withdrawal. Or rebound effects with use of the I.V. formulation at this high dose used for patients with peptic ulcer bleeding.

7.1.14 Human Reproduction and Pregnancy Data

No pregnancies were reported during the study.

7.1.15 Assessment of Effect on Growth

N.A.

7.1.16 Overdose Experience

Overdose were reported for <5% of the patients during I.V. treatment. The overdoses were caused by unintentionally higher rate of infusion per hour (12 to 33 mL/hour compared to 10mL/hour as stated in the Clinical Study Protocol (CSP).One patient received an overdose during the oral phase, 120 mg daily compared with 40 mg daily as stated in the CSP. The overdose was received during 1 day only. None of the reported overdoses were connected with an AE.

7.1.17 Post-marketing Experience

NA

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Extent of exposure for the safety population was defined as the time (hours) from first known intake up to and including last known intake of investigational drug. Exposure was considered continuous even if it was temporarily stopped.

7.2.1.1 Study type and design/patient enumeration

Peptic Ulcer Bleeding Study (D961DC00001)

In the pivotal study 376 patients were randomized to receive high dose continuous infusion of esomeprazole (80 mg as I.V. infusion in 30 minutes followed by 8 mg/hour for 71.5 hours) during first 72 hours (I.V. treatment) and 391 to received I.V. placebos for the same duration. After 72 hours (Oral treatment), all patients that continued in the trial received esomeprazole in the dose of 40 mg daily during 4 to 30 days. Patient (b) (6) randomized to esomeprazole did not receive any study drug, and patients (b) (6) and

(b) (6) randomized to placebo, did not sign the informed consent, and were excluded from the safety population. Thus, 375 PUB patients receiving I.V. esomeprazole and 389 patients I.V. placebo for mean period of 72 hours, were evaluated for safety for high dose esomeprazole continuous infusion.

7.2.1.2 Demographics

Demographic and baseline characteristics data for the intent-to-treat population for the study are shown in the tables 67 and 68.

Table 67: Demographic and baseline characteristics in PUB-patients, safety population

Characteristic	Eso (n=375)	Placebo (389)
Gender (%)		
• Male	67.7	68.9
• Female	32.3	31.1
Race (%)		
• Caucasian	86.7	87.9
• Black	**1.1**	**1.3**
• Oriental	7.2	6.9
• Others	5.1	3.9
Age (yrs)		
• Min-Max	18-95	18-98
Age (Yrs)		
• <65	48.5	54
• ≥65	51.5	46
Smoker (%)	27.5	28.3
Non-smoker (%)	72.5	71

(Information in Table above is taken from Table 13 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:

The ratio of males to females was 2:1. Patients were primarily Caucasians (88%) and very few black patients (1%). The two treatment groups were comparable with regard to demographic characteristics. The mean age of patients was above 60 years, with slightly more elderly patients in the esomeprazole treatment group.

Table 68: Demographic and baseline characteristics in PUB-patients, safety population

Characteristic	Eso (n=375),%	Placebo (389),%
ASA class (%)		
• 1	37.1	41.4
• 2	50.1	45.8
• 3	12.8	12.9
Shock		
• No	95	95
• Yes	5	5
H. *pylori* status (%)		
• Negative	25	30
• Positive	65	58
H/O peptic ulcer		
• No	70	69
• Yes	30	30 (Missing-1%)
Previous PU complications		
• No	88	89
• Yes	12	11
Prior medication		
• NSAIDs	40	40
• Clopidogrel	3.2	2.8
• Warfarin	2.4	3.3
• SSRI	2.4	3.6

(Information in Table above is taken from Table 13 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
Baseline characteristics of patients regarding H. pylori status, h/o peptic ulcer or its complications and prior intake of medication were balanced across two groups.

Healthy subjects
Table 69 displays the baseline demographic characteristics for the healthy subjects by treatment

Table 69: Demographic profile of the healthy subjects,

Treatment	Esomeprazole iv					
Total daily dose (mg)	174[a] (n=25)	228[a] (n=24)	268[a] (n=24)	268[b] (n=39)	296[a] (n=24)	308[a] (n=23)
Gender						
Male	19 (76.0)	19 (79.2)	18 (75.0)	23 (59.0)	18 (75.0)	18 (78.3)
Female	6 (24.0)	5 (20.8)	6 (25.0)	16 (41.0)	6 (25.0)	5 (21.7)
Race						
Caucasian	25 (100)	24 (100)	24 (100)	39 (100)	24 (100)	23 (100)
Black	0	0	0	0	0	0
Oriental	0	0	0	0	0	0
Other	0	0	0	0	0	0
Age						
Mean (years) (SD)[c]	28.4 (5.7)	28.3 (5.8)	28.6(5.7)	28.4 (4.8)	28.3 (5.7)	28.5 (5.8)
Range (years)	23 - 51	23 - 51	23 - 51	20 - 43	23 - 51	23 - 51

[a] study D9615C00015
[b] study D961DC00004
[c] SD = Standard Deviation

(Table above is taken from Table 7 of Applicant's Summary of Clinical Safety for Study D961DC00001)

Comments:
Demographic characteristics of healthy subjects were similar across treatment groups, except for the gender distribution in D961DC00004. Most healthy subjects were Caucasians. As expected the mean age was comparatively lower compared to patients with peptic ulcer bleeding.

7.2.1.3 Extent of exposure (dose/duration)

Drug Exposure in Peptic Ulcer Bleeding Patients (D916DC00001)
During 72 hours of I.V administration 375 patients were randomized in esomeprazole group to received 652 mg of esomeprazole per patient and 391 patients to receive placebos during this period.

Drug exposure in healthy subjects (D961DC00004, D9615C00015)
Sixty four healthy subjects participated in two PK/PD studies. These 64 healthy subjects were part of 6 groups that received high-dose esomeprazole I.V. for 24 hours in doses between 174 mg and 308 mg. The dose subsequently chosen for the PUB-patient study 268 mg daily (80 mg I.V. infusion in half an hour + 8 mg/h as continuous infusion x 23.5 h), had the greatest extent of exposure in 63 healthy subjects in these two studies for 1512 hours.

Tables 70 to 72 display the extent of I.V. exposure, oral, and total exposure in PUB-patients

An overview of exposure, in terms of duration of treatment and doses received during the first 72 hours, i.e. during the I.V. treatment phase, is presented in Table 70. The **extent of exposure to randomized treatment** was similar between the esomeprazole treatment

group and the placebo treatment group. For the placebo treatment group the mean treatment period was slightly shorter.

Table 70: Duration of exposure of I.V. treatment in PUB-patients, safety population

	Duration of exposure (Hours)	
	Eso	**Placebo**
n	375	389
Mean	67.3	66.3
SD	16.5	16.5
Median	72.0	72.0
Min	0.5	0.4
Max	96.5	91.5

(Table above is taken from Table 32 of Applicant's Clinical Study Report for Study D961DC00001)

Similarly, an overview of duration of exposure in terms of duration of treatment and doses received within day 4 to 30 after start of I.V. treatment, i.e., the **open** oral treatment phase, is presented in Table 71. During the oral treatment period, patients in both treatment groups received esomeprazole 40 mg od. The extent of exposure to randomized treatment was similar between the esomeprazole treatment group and the placebo treatment group. Duration of exposure over 35 days of esomeprazole oral treatment was observed for 2 patients, 1 in esomeprazole and 1 in the placebo treatment group.

Table 71: Duration of exposure oral treatment

Duration of exposure (days)	Eso[a]	Placebo[b]
n	347	352
Mean	26.8	26.8
SD	5.8	5.9
Median	27.0	27.0
Min	0.0	0.0
Max	47.0	58.0

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

Table 72: Duration of exposure during day 1 to 30 (I.V. + Oral) after start of treatment in PUB-patients, safety population

	Duration of exposure (Days)	
	Eso	**Placebo**
n	375	389
mean	27.6	27.0
SD	9.4	10.0
Median	30.0	30.0
Min	0.0	0.0
Max	50.0	61.0

(Results in the table above are taken from Table 33 of Applicant's Clinical Study Report for Study D961DC00001)

Comments:
*The **extent of exposure** of I.V. treatment and total exposure (I.V. treatment +oral treatment) was similar in the esomeprazole and placebo groups.*

Drug exposure in peptic ulcer bleeding patients during 72 hours of I.V. administration:

Three hundred seventy one patients in the peptic ulcer bleeding trial were exposed to 80 mg I.V. bolus of esomeprazole followed by continuous infusion of esomeprazole at the rate of 8 mg/hour for next 71.5 hours. Table 73 shows the drug dose (Mean, S.D and range of dosage) administered as bolus and I.V. infusion within first 72 hours.

Table 73: Drug exposure (Esomeprazole): I.V. bolus and I.V. infusion

	Esomeprazole- I.V. bolus (n=371)	**Esomeprazole-I.V. infusion** (362)
Mean (mL)*	99.84 (80 mg)	675.31 (540 mg)
Standard Deviation	8.33	156.46
Standard Error	0.43	8.22
Range (Min-Max) mL	50-200	12-929

(Reviewer calculated from the data table D961DC00001/crt/datasets/R-INFSC1.xpt and D961DC00001/crt/datasets/R-INFSCH.xpt)
* 10 mL = 8 mg esomeprazole
# Normal = I.V. bolus- 80 mg, I.V.infusion-572 mg

Drug exposure in peptic ulcer bleeding patients during 4 to 30 days of oral administration: During this period of 27 days all patients (n=767) received open label esomeprazole 40 mg daily by oral administration.

Drug exposure in healthy subjects (D961DC00004, D9615C00015)
Sixty four healthy subjects participated in two PK/PD studies. These 64 healthy subjects were part of 6 groups that received high-dose esomeprazole I.V. for 24 hours in doses between 174 mg and 308 mg as shown in table 74.

Table 74: **Drug exposure in healthy subjects undergoing PK/PD assessments**

	Esomeprazole iv					
Total daily dose (mg):	**174[a]**	**228[a]**	**268[a]**	**268[b]**	**296[a]**	**308[a]**
Dosage:	**80 mg (0.5 h) + 4 mg/h (23.5 h)**	**40 mg (0.5 h) + 8 mg/h (23.5 h)**	**80 mg (0.5 h) + 8 mg/h (23.5 h)**	**80 mg (0.5 h) + 8 mg/h (23.5 h)**	**120 mg (2.0 h) + 8 mg/h (22 h)**	**120 mg (0.5 h) + 8 mg/h (23.5 h)**
Duration of exposure (hours)	**(n=25)**	**(n=24)**	**(n=24)**	**(n=39)**	**(n=24)**	**(n=23)**
Mean (SD)[c]	23 (4.2)	24 (0)	24 (0)	24 (0)	23 (3.3)	24 (0)
Range	3-24	24-24	24-24	24-24	8-24	24-24
Total[d]	579	576	576	936	560	600

[a] study D9615C00015
[b] study D961DC00004
[c] SD = Standard Deviation
[d] Total indicates the sum of treatment hours for all healthy subjects in the respective treatment groups.

(Above Table is taken from Table 5 of Applicant's Summary of Safety for Study D961DC00001)

Comments:
The daily dose subsequently chosen for the PUB-patient study, 80 mg in 0.5 h + 8 mg/h for 23.5 h (268 mg daily), had the greatest extent of exposure in 63 healthy subjects (1512 hours), while lower and higher dosage treatment groups were exposed for 560 to 600 hours. Predominant AE were headache, nausea and diarrhea. Safety profile was similar to the previously approved indications

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

NA

7.2.2.2 Post marketing experience

The studies included in the sNDA were all in a finalized state at submission. No other studies relevant to this indication have been performed.

Search was performed for any report of Nexium IV with a daily dosage of 80 mg or an infusion rate of 8 mg/hour during the period covering 01 January 2008 through 31 August 2008. A total of 9 spontaneous adverse event reports describing 6 serious adverse events (AEs) and 6 non-serious AEs were identified from the AstraZeneca Global Patient Safety Database. Five of the 9 reports (2008GB00784, 2008UW13624, 2008AP00310, 2007CG01678, 2008UW12042) described 6 serious AEs (i.e. renal failure, nephrotic syndrome, anemia, hypoglycemia, white blood cell count decreased, and thrombocytopenia). There were no reports of death. The 9 reports involved patients between the ages of 32 to 84 years of age. Seven of the patients were male and 2 were female. In 5 of the reports, esomeprazole I.V. doses ranged from 40 - 160 mg daily; dosage was not reported in 4 reports. Time to event onset, from initiation of

esomeprazole I.V. therapy ranged from 1 to 4 days in 3 reports and was unknown in 5 of the reports. Additionally, in 1 report (2007CG01678), the onset of the AE preceded the initiation of esomeprazole I.V. and continued after discontinuation. In 6 of the 9 reports, the indication for use was a type of gastrointestinal bleeding (often unspecified). Summaries of the 9 reports, including brief narratives are presented in Appendix, table 88.

Comments:
During this same period, there were 9 spontaneous reports describing 12 AEs entered into the sponsors Global Patient Safety Database. Five of the reports were serious. Three of the 6 serious AEs are not labeled in the Nexium IV US package insert (renal failure, nephrotic syndrome, and hypoglycemia); the 6 non-serious AEs are all labeled in the Nexium IV US package insert. The majority of these adverse event reports contained limited information precluding causality assessment or were confounded by factors such as concomitant medications or concomitant illness

7.2.2.3 Literature

This safety review does not contain a significant review of the scientific literature on high dose continuous infusion of esomeprazole

7.2.3 Adequacy of Overall Clinical Experience

The database in the study is sufficiently large to allow for assessment of safety trend of high dose continuous infusion of esomeprazole, although events that occurred rarely may not have been detected. There is need for more number of patients using the similar high dose to address the safety adequately (PMC/PMR)

The demographics of patients treated with I.V. Esomeprazole in this trial are adequate for the purposes of analyzing the safety for the prevention of rebleeding after endoscopic treatment. The number of non-Caucasian patients exposed to the high dose I.V. esomeprazole in clinical trial was small, but the known characteristics of neither esomeprazole nor peptic ulcer bleeding suggest that the safety profile of high dose esomeprazole would be appreciably different in non-Caucasian population.

There has been no experience with high dose I.V. esomeprazole in the pediatric population. It must be noted that the safety profile of Esomeprazole may be different in patients younger than. The safety data currently available can not necessarily be extrapolated to children, and adolescents.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing
The protocol defined clinical testing and safety assessments were adequate given the extensive safety of the oral formulation.

7.2.5 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate. The methods for acquisition of laboratory and adverse events data in the development program are described in the relevant sections. ECGs were done at the onset to rule out cardiac event i.e. as exclusion criteria. This reviewer feels cardiac monitoring and ECGs should have been done during the high dose continuous infusion period of 72 hours.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The clinical pharmacology data submitted by the sponsor as a part of the application was considered by the Clinical Pharmacology Team as not supportive in patients with moderate to severe liver disease.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The database in the study is sufficiently large to allow for assessment of safety trend of high dose continuous infusion of esomeprazole, although events that occurred rarely may not have been detected. There is further need to assess the safety adequately in larger number of patients using the similar high dose in Post Marketing Safety Analysis or as PMC/PMR. Since Sponsor had excluded patients with Child-Pugh score 'B' and 'C' from the study and also end stage kidney disease, we need to assess the safety profile in this group of patients. As discussed before, a larger number of patients may be needed to identify safety adequately.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

NA

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the single pivotal study (D916DC00001) patients received high dose continuous infusion of esomeprazole (n=375) or placebo (n=389) for first 72 hours followed by all patients receiving oral administration of esomeprazole from 4 to 30 days. Overall, a comparable safety profile between esomeprazole (I.V.) and placebo was found during first 72 hours with some notable points.

SAEs were less common in Esomeprazole group than in placebo group during I.V. treatment within 72 hours (Eso=9.3%, Pla=11.3%); this is partly accounted for by a lower incidence of rebleeding in esomeprazole group. The majority of SAEs were related

to GI and cardiac systems. DU/GU rebleeding, which is also the primary efficacy endpoint, formed the predominant SAE in both the treatment groups. Few patients of peptic ulcer perforation in placebo group were probably related to the endoscopic procedures. SAEs related to other systems were quite few and equally spread out in two treatment groups. No particular trend was noticed.

During 4 to 30 days (oral treatment) both groups received esomeprazole 40 mg per day. Fifty seven patients (esomeprazole=29, placebos=28) had 57 SAEs (esomeprazole=30, placebo=29). Rebleeding was the main SAE during this period also. SAEs were comparable in two treatment groups (Eso=8.6%, Pla=8.9%).

Withdrawals due to AEs were lower in esomeprazole group compared to placebo group during first 72 hours (Eso=8.3%, Pla=10 %). This was primarily due to lower incidence of rebleeding in esomeprazole group. Withdrawals due to AEs were comparable between the two treatment groups during 4 to 30 days (Eso=4.3%, Pla=4.8%). GI related AEs were most common in both treatment groups at all time. Rebleeding constituted the major group responsible for discontinuation. The other AEs in the two treatment groups were similar.

Overall incidence of adverse events seen with high dose continuous I.V. infusion of esomeprazole was lower numerically than the placebo during first 72 hours (Eso=39.2%, Pla=41.9%). Incidence of AEs related to GI system was lower in esomeprazole group than placebo group (Eso=12.3%, Pla=19.8%). However incidence of AEs related to administration site and vascular systems were higher in esomeprazole group compared to placebo (Eso=13.6%, Pla=9.2%). Patients with AEs related to other systems were comparable in two groups. During 4 to 30 days overall incidence of AEs was comparable in two treatment groups. Incidence of AEs related to administration site and local vascular disorders was higher in esomeprazole group than placebo group (Eso=11.2%, Pla=7.7%). Incidence of AEs related to other systems was comparable in two treatment groups. The most common adverse events reported (≥ 1%) were peptic ulcer bleeding, constipation, diarrhea, nausea, pyrexia, edema, urinary tract infection, thrombophlebitis, dyspnoea, abdominal pain, cough, headache, and dizziness.

Increases in mean ALP values at 72 hours and 30 days compared to baseline were observed in both treatment groups. The increase at 72 hours was higher for esomeprazole group compared to placebo group (12.6% and 5.2% respectively). The corresponding increase at 30 days was also higher in esomeprazole group than placebo group (43.1% versus 30.9%). In majority of patients ALP increase was within the reference range. Few patients had high ALP values above the reference range both at baseline and after treatment. The increase in ALP was not associated with increases in other liver function tests, i.e. ALAT, ASAT or bilirubin. Moreover there was only one case of AEs related to System Organ Class (SOC) "Hepatobiliary disorder". There were no noticeable differences between the two treatment groups. The changes related to the other laboratory tests were also balanced in the two groups and did not show any trend.

After the submission of this efficacy supplement (NDA 21,689), 9 spontaneous reports describing 12 AEs were entered into the sponsors Global Patient Safety Database. Five of the reports were serious. Three of the 6 serious AEs are not labeled in the Nexium IV US package insert i.e. renal failure, nephrotic syndrome, and hypoglycemia; the 6 non-serious AEs are all labeled in the Nexium IV US package insert. Sponsor states that the majority of these adverse event reports contained limited information precluding causality assessment or was confounded by factors such as concomitant medications or concomitant illness. The details are given in Appendix, table 88.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

N.A

7.4.1.2 Combining data

N.A.

7.4.2 Explorations for Predictive Factors

N.A.

7.4.2.1 Explorations for dose dependency for adverse findings

N.A.

7.4.2.2 Explorations for time dependency for adverse findings

No particular exploration for time dependency of adverse events was conducted.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup analyses of AE data for gender, age, and race were performed on data from the Phase 3 studies. In addition, women of potential childbearing age (<45 years) were also analyzed.

Gender

The overall frequencies of all AEs, deaths, SAEs, and drug stopped due to AE in PUB-patients treated with esomeprazole IV (Within 72 hours) are presented in Table 75.

Table 75: Summary of adverse events in PUB-patients within 72 hours (I.V.) by gender.

AE Category	Number(%) PUB-patients who had an AE in each category[c]			
	Eso [a] Male (n=254)	Eso[a] Female (n=121)	Placebo[b] Male (n=268)	Placebo[b] Female (n=121)
Any AE	108(42.5%)	39(32.2%)	105(39.2%)	58(47.9%)
Fatal SAE[d]	2(0.8%)	0(0.0%)	0(0.0%)	3(2.5%)
Non-fatal SAE	19(7.5%)	14(11.6%)	26(9.7%)	15(12.4%)
AE leading to discontinuation of treatment	16(6.3%)	15(12.4%)	23(8.6%)	16(13.2%)
Other significant AE[e]	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Related AEs[f]	10(3.9%)	3(2.5%)	7(2.6%)	1(0.8%)
Severe AEs	16(6.3%)	7(5.8%)	23(8.6%)	11(9.1%)

(This table is taken from page 42 Table 22, of Applicant's Summary of Safety for Study D961DC00001)
a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Patients with multiple events in the same category are counted only once in that Patients with events in more than 1 category are counted once in each of those categories.
d The AE started within 72 h, but death occurred after 72 h for 4 patients
f Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator

Comments:
Compared to males, females had a numerically lower incidence of AEs in the esomeprazole group, while they had a higher incidence of SAEs and AEs leading to discontinuation of treatment.

The most common AEs in PUB-patients, by gender, occurring for at least 2% of the PUB patients in any treatment group are presented in Table 76

Table 76: Number (%) of patients with AEs, within 72 hours (I.V. treatment), presented by gender.

Preferred term	Number(%) of patients[c]			
	Eso[a] Male (n=254)	Eso[a] Female (n=121)	Placebo[b] Male (n=268)	Placebo[b] Female (n=121)
Duodenal ulcer hemorrhage	10(3.9%)	6(5.0%)	9(3.4%)	7(5.8%)
Nausea	3(1.2%)	5(4.1%)	5(1.9%)	3(2.5%)
Pyrexia	8(3.1%)	5(4.1%)	7(2.6%)	4(3.3%)
Phlebitis	7(2.8%)	2(1.7%)	2(0.7%)	0(0%)
Abdominal pain upper	5(2.0%)	0(0%)	6(2.2%)	3(2.5%)
Headache	5(2.0%)	0(0%)	5(1.9%)	2(1.7%)
Gastric ulcer hemorrhage	2(0.8%)	2(1.7%)	7(2.6%)	6(5.0%)
Constipation	4(1.6%)	2(1.7%)	6(2.2%)	3(2.5%)
Hypertension	4(1.6%)	1(0.8%)	7(2.6%)	0(0%)
Myocardial infarction	3(1.2%)	1(0.8%)	1(0.4%)	3(2.5%)
Insomnia	3(1.2%)	0(0%)	4(1.5%)	3(2.5%)
Dyspnoea	2(0.8%)	0(0%)	4(1.5%)	3(2.5%)
Abdominal pain	1(0.4%)	0(0%)	8(3.0%)	3(2.5%)

(This data is taken from page 42 Table 23, of Applicant's Summary of Safety for Study D961DC00001)
a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Number of patients who reported at least 1 AE for a preferred term
AEs occurring in at least 2% of the patients in any group are displayed.

Comments:
The pattern of reported AEs in PUB-patients was similar between males and females.

Age:
To evaluate the frequency of AEs in older versus younger patients, patients were grouped into 2 age categories: <65 years and ≥65 years.

The overall incidence of all AEs, Deaths, SAEs, drug stopped due to AE, are presented by age distribution in Table 77.

Table 77: Adverse events in PUB-patients within 72 hours of start of I.V. treatment, by age:

AE Category	Number(%) PUB-patients who had an AE in each category[c]			
	Eso [a] <65 yrs (n=182)	Eso[a] ≥65 yrs (n=193)	Placebo[b] <65 yrs (n=210)	Placebo[b] ≥65 yrs (n=179)
Any AE	64(35.2%)	83(43.0%)	82(39.0%)	81(45.3%)
Fatal SAE[d]	2(1.1%)	0(0.0%)	0(0.0%)	3(1.7%)
Non-fatal SAE	14(7.7%)	19(9.8%)	20(9.5%)	21(11.7%)
AE leading to discontinuation of treatment	11(6.0%)	20(10.4%)	18(8.6%)	21(11.7%)
Other significant AE[e]	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Related AEs[f]	2(1.1%)	11(5.7%)	1(0.5%)	7(3.9%)
Severe AEs	11(6.0%)	12(6.2%)	18(8.6%)	16(8.9%)

(Above Table is taken from table 24, page 44 of Applicant's Summary of Safety for Study D961DC00001)

Comments:
Patients ≥65 years of age showed a slightly higher incidence of events in all AE categories compared to patients <65 years of age, in both the esomeprazole and the placebo treatment groups.

The most common AEs by age, occurring for at least 2% of the patients in any treatment/age group are presented in Table 78.

Table 78: Number (%) of PUB-patients with AEs within 72 hours, presented by age.

Preferred term	Number(%) of patients			
	Eso[a] <65 yrs (n=182)	Eso[a] ≥65yrs (n=193)	Placebo[b] <65 yrs (n=210)	Placebo[b] ≥65 yrs (n=179)
Duodenal ulcer hemorrhage	7(3.8%	9(4.7%)	7(3.3%)	9(5.0%)
Pyrexia	6(3.3%)	7(3.6%)	7(3.3%)	4(2.2%)
Phlebitis	2(1.1%)	**7(3.6%)**	2(1.0%)	0(0%)
Nausea	2(1.1%)	**6(3.1%)**	5(2.4%)	3(1.7%)
Abdominal pain upper	5(2.7%)	0(0%)	8(3.8%)	1(0.6%)
Constipation	1(0.5%)	5(2.6%)	1(0.5%)	8(4.5%)
Headache	4(2.2%)	1(0.5%)	5(2.4%)	2(1.1%)
Myocardial infarction	0(0%)	**4(2.1%)**	0(0%)	4(2.2%)
Urinary tract infection	0(0%)	**4(2.1%)**	1(0.5%)	3(1.7%)
Gastric ulcer hemorrhage	1(0.5%)	3(1.6%)	7(3.3%)	6(3.4%)
Insomnia	3(1.6%)	0(0%)	7(3.3%)	0(0%)
Dyspnoea	0(0%)	2(1.0%)	2(1.0%)	5(2.8%)
Abdominal pain	0(0%)	1(0.5%)	3(1.4%)	8(4.5%)

(Data collected from Table25 page 44 of Applicant's Summary of Safety for Study D961Dc00001)
(AEs occuring in at least 2% of the patients in any group are displayed).

Comments:
Incidence of nausea, phlebitis, myocardial infarction and urinary tract infection was numerically higher in patients more than 65 years of age in esomeprazole group.

Race:
To evaluate the AEs in different race groups, the PUB-patients were grouped into 4 categories: Caucasian, Black, Oriental and Other races (table 79). Other races included mixed (n=31), Cape colored (n=1), Arubaan (n=1) and Maghreb (n=1).

Table 79: Number (%) of PUB-patients with AEs within 72 hours, presented by race.

Preferred term	Number(%) of PUB-patients[c]							
	Eso[a] Caucasian (n=325)	Eso[a] Black (n=4)	Eso[a] Oriental (n=27)	Eso[a] Other (n=19)	Placebo[b] Caucasian (n=342)	Placebo[b] Black (n=5)	Placebo[b] Oriental (n=27)	Placebo[b] Other (n=15)
Duodenal ulcer haemorrhage	12(3.7%)	0(0%)	0(0%)	4(21.1%)	15(4.4%)	0(0%)	1(3.7%)	0(0%)
Pyrexia	8(2.5%)	0(0%)	4(14.8%)	1(5.3%)	10(2.9%)	0(0%)	1(3.7%)	0(0%)
Hyperkalaemia	0(0%)	0(0%)	2(7.4%)	0(0%)	0(0%)	1(20.0%)	0(0%)	0(0%)
Rash	1(0.3%)	0(0%)	2(7.4%)	0(0%)	0(0%)	0(0%)	1(3.7%)	0(0%)
Phlebitis	8(2.5%)	0(0%)	0(0%)	1(5.3%)	1(0.3%)	0(0%)	0(0%)	1(6.7%)
Back pain	2(0.6%)	0(0%)	0(0%)	1(5.3%)	3(0.9%)	0(0%)	0(0%)	0(0%)
Dizziness	2(0.6%)	0(0%)	1(3.7%)	1(5.3%)	3(0.9%)	0(0%)	0(0%)	0(0%)
Anaemia	1(0.3%)	0(0%)	0(0%)	1(5.3%)	5(1.5%)	0(0%)	0(0%)	0(0%)
Abdominal pain upper	4(1.2%)	0(0%)	1(3.7%)	0(0%)	5(1.5%)	1(20.0%)	3(11.1%)	0(0%)
Constipation	5(1.5%)	0(0%)	1(3.7%)	0(0%)	8(2.3%)	0(0%)	0(0%)	1(6.7%)
Gastric ulcer haemorrhage	3(0.9%)	0(0%)	1(3.7%)	0(0%)	11(3.2%)	0(0%)	1(3.7%)	1(6.7%)
Pain in extremity	2(0.6%)	0(0%)	1(3.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Diarrhoea	2(0.6%)	0(0%)	1(3.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Urinary tract infection	3(0.9%)	0(0%)	1(3.7%)	0(0%)	4(1.2%)	0(0%)	0(0%)	0(0%)
Headache	4(1.2%)	0(0%)	1(3.7%)	0(0%)	7(2.0%)	0(0%)	0(0%)	0(0%)
Cough	3(0.9%)	0(0%)	1(3.7%)	0(0%)	1(0.3%)	0(0%)	0(0%)	0(0%)
Nausea	8(2.5%)	0(0%)	0(0%)	0(0%)	8(2.3%)	0(0%)	0(0%)	0(0%)
Hypertension	5(1.5%)	0(0%)	0(0%)	0(0%)	6(1.8%)	0(0%)	1(3.7%)	0(0%)
Hypotension	4(1.2%)	0(0%)	0(0%)	0(0%)	2(0.6%)	0(0%)	2(7.4%)	0(0%)
Insomnia	3(0.9%)	0(0%)	0(0%)	0(0%)	5(1.5%)	0(0%)	0(0%)	2(13.3%)
Haemoglobin decreased	3(0.9%)	0(0%)	0(0%)	0(0%)	1(0.3%)	0(0%)	0(0%)	1(6.7%)
Hypokalaemia	2(0.6%)	0(0%)	0(0%)	0(0%)	1(0.3%)	0(0%)	3(11.1%)	0(0%)
Vomiting	2(0.6%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(6.7%)
Dyspnoea	2(0.6%)	0(0%)	0(0%)	0(0%)	7(2.0%)	0(0%)	0(0%)	0(0%)
Abdominal pain	1(0.3%)	0(0%)	0(0%)	0(0%)	7(2.0%)	1(20.0%)	3(11.1%)	0(0%)
Accelerated hypertension	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	2(13.3%)
Dyspepsia	0(0%)	0(0%)	0(0%)	0(0%)	2(0.6%)	0(0%)	3(11.1%)	0(0%)

(Above Table is taken from table 27, page 47 of Applicant's Summary of Safety for Study D961DC00001)

Comments:
The numbers of patients in other racial groups were small to draw firm conclusion regarding any safety difference or concern.

7.4.2.4 Explorations for drug-disease interactions

No particular exploration for drug-disease interactions was conducted.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interaction studies were performed in this clinical development program.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

N.A.

8.2 Drug-Drug Interactions

Comments:
Drug interactions have not been specifically investigated for high dose I.V. esomeprazole (I.V. given as a bolus infusion followed by a continuous infusion). Esomeprazole is known to inhibit CYP2C19, but does not seem to interact with any other CYP enzymes (Anderson 2001). Due to the higher dose and continuous administration, a higher potential for interaction with drugs metabolized by CYP2C19 cannot be excluded. Furthermore, a higher potential for interaction with drugs with pH-sensitive absorption may be expected as the result of the more profound effect on intragastric pH compared to oral administration. After switching to oral administration after 3 to 5 days, the similar potential for interaction as for oral od treatment is expected.

Interaction studies for oral esomeprazole have been performed previously. A brief summary of few studies is given:

Effects of oral esomeprazole on the pharmacokinetics of other drugs:

The decreased intragastric acidity during treatment with esomeprazole I.V. may increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. The absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole I.V.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolizing enzyme. Concomitant oral administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction was not thought to have a major clinical relevance. Concomitant oral administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients; however dose adjustment was not required in this study. Concomitant oral administration of 40 mg esomeprazole to warfarin treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post marketed use, cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other Coumadin derivatives.

In healthy volunteers, concomitant oral administration of 40 mg esomeprazole resulted in a 32% increase in AUC and a 31% prolongation of elimination half-life ($t_{1/2}$), but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc

interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Concomitant administration of esomeprazole may reduce the plasma levels of atazanavir.

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effects of other drugs on the pharmacokinetics of esomeprazole oral

Esomeprazole is metabolized by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid) resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than double of the esomeprazole exposure. However, dose adjustment of esomeprazole was not suggested in either of these situations.

8.3 Special Populations

Esomeprazole in high dose continuous I.V. infusion has not been studied in enough patients with moderate/ severe liver disease, end stage kidney disease, and younger patients ≤ 18 years to assess safety and efficacy in these populations. Further studies are required for these groups. Sponsor should submit pediatric plan for all age groups for the indication of peptic ulcer bleeding.

Use in pregnancy and lactation:

Limited data is available for effect of esomeprazole on exposed pregnancies. Animal studies with esomeprazole have not indicated direct or indirect harmful effects with respect to embryonic/fetal development. Animal studies with the racemic mixture omeprazole have not indicated direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. However caution should be exercised when prescribing to pregnant women.
It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore, esomeprazole should not be used during breast-feeding.

Women of potential childbearing age

To evaluate the frequency and pattern of AEs in women of potential childbearing age, the women with PUB were grouped into 2 categories: women aged <45 years and women aged ≥45 years.

The overall frequencies of all AEs, fatal SAEs, non-fatal SAEs, and drug stopped due to AE and AEs with severe intensity, by age, for the female PUB-patients treated with I.V esomeprazole are presented in Table 80.

Table 80: Adverse events within 72 hours in female patients by age

AE Category	Number(%) PUB-patients who had an AE in each category[c]			
	Eso [a] <45 yrs (n=10)	Eso[a] ≥45 yrs (n=111)	Placebo[b] <45 yrs (n=17)	Placebo[b] ≥45 yrs (n=104)
Any AE	2(20.0%)	37(33.3%)	9(52.9%)	49(47.1%)
Fatal SAE[d]	0(0.0%)	0(0.0%)	0(0.0%)	3(2.9%)
Non-fatal SAE	0(0.0%)	14(12.6%)	1(5.9%)	14(13.5%)
AE leading to discontinuation of treatment	1(10.0%)	14(12.6%)	2(11.8%)	14(13.5%)
Other significant AE[e]	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Related AEs[f]	0(0.0%)	3(2.7%)	0(0.0%)	1(1.0%)
Severe AEs	0(0.0%)	7(6.3%)	1(5.9%)	10(9.6%)

(Table above is taken from Table 28 of Applicant's Summary of Clinical Safety Report for Study D961DC00001)

Comments:
The incidence of AEs, except deaths, was numerically higher in female patients in the age group of ≥ 45 years of age in both esomeprazole and placebo treatment groups. However no firm conclusions can be drawn for females patients <45 years in age as the number of patients was very small (Eso=10, Pla=17).

8.4 Pediatrics

Safety and efficacy have not been studied in pediatric patients. Sponsor applied for pediatric waiver as " … studies are impossible or highly impractical because the number of patients is so small and geographically dispersed."

Comments:
There is a definite potential use of this formulation in pediatric patients. This reviewer recommends that applicant should be asked to submit pediatric development plan.

8.5 Advisory Committee Meeting

N.A.

8.6 Literature Review

N.A.

8.7 Post-marketing Risk Management Plan

In this NDA, there are no issues related to risk management to be conveyed to the sponsor at present.

8.8 Other Relevant Materials

N.A.

9 OVERALL ASSESSMENT

9.1 Conclusions

Background changes in study analysis

In the initial protocol dated June 1, 2005, the baseline factors of endoscopic treatment (single vs. combination) and Forrest class (I vs. II) were assumed by the Applicant to influence the probability of rebleeding and that they would be included in the analysis. According to the Applicant, after a review of blind data no difference was seen in rebleeding rate between the Forrest groups. It is important to point out here that it is well accepted fact in medical literature that Forrest class 1a with arterial bleeding has higher risk of rebleeding compared to Forrest class 2b with blood clot on the ulcer base. The sponsor collapsed all the categories of Forrest class into one group. The analysis was therefore changed in the Statistical Analysis Plan (dated Dec. 17, 2007) to only be stratified for endoscopic treatment (single vs. combination). No protocol amendment documenting this change was issued. The Applicant stated that: "All changes were made prior to unblinding of study data" (Section 5.8.2 on page 74 of study report).

Further, interim analysis of the study data was done twice. DSMB reviewed unblended data at these formal interim analysis meetings on 21 November 2006 and 13 March 2007. Recommendations to continue the study were communicated to the applicant after those meeting. This was apparently due to not achieving the robust efficacy data.

Efficacy

The applicant submitted the results of single pivotal, phase 3, randomized, double blind, multicenter, multi- national, parallel-group, placebo controlled study D961DC00001, in patients with peptic ulcer bleeding after complete hemostasis of the initial bleeding was achieved with endoscopic treatment. Of the total 767 patients 376 were randomized to receive esomeprazole I.V. 80 mg for 30 min followed by esomeprazole I.V. 8 mg/hr for 71.5 hours and 391 received placebo I.V. for 30 min followed by placebo I.V. for 71.5 hours. Patients that received I.V. esomeprazole in first 72 hours was called "esomeprazole" group. The group receiving I.V. placebo was designated as "placebo" group. After 72 hours of I.V. treatment both groups (esomeprazole and placebo) received oral esomeprazole 40 mg daily for next 27 days.

Primary Endpoint

The primary efficacy endpoint was rebleeding within 72 hours. Overall 5.9% patients had rebleeding in esomeprazole group compared to 10.3% in placebo group. The difference between the treatment groups was 4.4% with p value of 0.0256.

Secondary Endpoints
The secondary efficacy analysis was done for clinically significant rebleeding within 7 days and 30 days, death within 72 hours and 30 days, requirement for surgery within 72 hours and 30 days, requirement for endoscopic re-treatment within 72 hours and 30 days, number of blood units transfused within 72 hours and 30 days and number of days hospitalized due to rebleeding during the 30-day treatment phase. The treatment effect was primarily observed during 0 to 7 days as most of the secondary variables events occurred during first 7 days.

Limitations of the study
In the present submission although the study demonstrated a reduction in rebleeding for esomeprazole during the 72 hours (primary Endpoint) compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted by the FDA's statistician to assess the robustness of the single study did not give results consistent with protocol-specified analyses. Sensitivity analyses for the primary efficacy endpoint of rate of rebleeding were carried out to evaluate how the pre-specified study findings hold up when alternative analyses were performed. According to the FDA's statistician, the following analyses did not support the primary results:

1. Country Analysis and its effect on study results.
2. Analysis of certain centers and their effect on the study results.
3. Analysis based on Forrest Class.
4. Analysis on endoscopic therapy (excluding Injection therapy alone).

<u>Lack of support from pharmacodynamic evaluation</u>

The clinical study was not adequately supported by the two supportive PK/PD studies. (b) (4) The two supportive PK/PD studies (D961DC00015, D961DC00004) submitted in this submission did not demonstrate achieving intragastric pH of ≥ 6 adequately with the dose and mode of administration used in the trial. Intragastric pH of > 6 could be achieved only for less than 50 % of the time in 24 hour (D9615C00015=52.3%; D961DC00004=44.6%). Only one subject had an intragastric pH > 6 more than 90% of time in 24-hour period.

Conclusions
The efficacy results of this single, non-US, study did not provide substantial evidence of effectiveness to support the sought indication
In the absence of replication the robustness of the primary results was not established or proved by alternative sensitivity analyses. There was insufficient proof of the superiority of high dose I.V. esomeprazole over placebo to support the proposed indication for (b) (4) (b) (4) (b) (4) The weakness of the study was evident throughout the execution of the trial during the two interim analyses. The two PK/PD studies were also not supportive of the clinical study. In order to resolve these deficiencies, the applicant should provide at least

one additional adequate and well-controlled study to demonstrate the proposed clinical benefit. The study should include some US centers.

Safety

Safety data for high dose esomeprazole as continuous I.V. infusion for 72 hours was derived from single study D961DC00001. Of the 767 enrolled patients 376 received esomeprazole (80 mg in 30 minutes followed by I.V. infusion of 8 mg/hour for next 71.5 hours) for a mean period of approximately 72 hours; other 391 patients received placebo during this period. After I.V. phase of 72 hours all patients received oral esomeprazole 40 mg daily from 4 to 30 days. Local administration site adverse events related to skin and vascular systems occurred at a significant higher rate with esomeprazole when compared to placebo. However, the overall, a comparable safety profile was deemed comparable between the two experimental arms (esomeprazole versus placebo).

The focus of the current safety review was on determining the safety profile of the high dose continuous I.V infusion of esomeprazole compared with placebo during the I.V. treatment phase (within 72 hours). In particular distribution by treatment arm of serious adverse events (SAE), adverse events (AE), and AEs leading to withdrawal was assessed.

The safety of esomeprazole I.V. Nexium in the dose of 20 mg or 40 mg daily was previously reviewed for the indication of short term use (7 to10 days) in GERD and erosive esophagitis at the time of the original submission of I.V. Nexium approved in 2005. The safety profile of I.V. Nexium as an injection or infusion was found to be similar to the oral administration. Neither the Adverse Events (AE) pattern nor any other safety assessments implied any safety concerns for I.V. administration of esomeprazole in the dose of 20 mg or 40 mg daily for 7 to 10 days.

SAE

SAEs were numerically fewer in esomeprazole compared to placebo group during I.V. treatment within 72 hours (Eso=8.8%%, Pla=10.5%); this was partly accounted for by a lower incidence of rebleeding in esomeprazole group. The majority of SAEs were related to GI and cardiac systems. DU/GU rebleeding, which is also the primary efficacy endpoint, formed the predominant SAE in both the treatment groups. Few patients of peptic ulcer perforation in placebo group were probably related to the endoscopic procedures. SAEs related to other systems were quite few and equally spread out in two treatment groups. No particular trend was noticed.

During 4 to 30 days (oral treatment) both groups received esomeprazole 40 mg per day. Fifty seven patients (esomeprazole=29, placebos=28) had 57 SAEs (esomeprazole=30, placebo=29). Rebleeding was the main SAE during this period also. SAEs were comparable in two treatment groups (Eso=8.4%, Pla=8.0%).

Withdrawal due to AEs

Withdrawals due to AEs were numerically lower in esomeprazole group compared to placebo group during first 72 hours (Eso=8.3%, Pla=10 %). This was primarily due to lower incidence of rebleeding in esomeprazole group. Withdrawals due to AEs were

comparable between the two treatment groups during 4to 30 days (Eso=4.3%, Pla=4.8%). GI related AEs were most common in both treatment groups at all time. Rebleeding constituted the major group responsible for discontinuation. The other AEs in the two treatment groups were similar.

Overall AEs

Overall incidence of adverse events seen with high dose continuous I.V. infusion of esomeprazole was numerically lower than the placebo during first 72 hours (Eso=39.2%, Pla=41.9%). Incidence of AEs related to GI system was numerically lower in esomeprazole group than placebo group (Eso=12.3%, Pla=19.8%).This was accounted for primarily by the lower incidence of rebleeding in the esomeprazole group. However incidence of AEs related to administration site and vascular systems were numerically higher in esomeprazole group compared to placebo (Eso=13.6%, Pla=9.2%). The AEs related to other systems were comparable in the two groups.

During 4 to 30 days overall incidence of AEs was comparable in two treatment groups. Incidence of AEs related to administration site and local vascular disorders remained numerically higher in the esomeprazole group than placebo group (Eso=11.2%, Pla=7.7%). Incidence of AEs related to other systems was comparable in two treatment groups. The most common adverse events reported (≥ 1%) were peptic ulcer bleeding, constipation, diarrhea, nausea, pyrexia, edema, urinary tract infection, thrombophlebitis, dyspnoea, abdominal pain, cough, headache, and dizziness.

Laboratory Data

Monitoring of the laboratory parameters showed increase in mean ALP values at 72 hours and 30 days compared to baseline in both treatment groups. The increase at 72 hours was numerically higher for esomeprazole compared to placebo (12.6% and 5.2% respectively). The corresponding increase at 30 days was also numerically higher in esomeprazole group than the placebo group (43.1% versus 30.9%). In the majority of patients ALP increase was within the reference range. Few patients had high ALP values above the reference range both at baseline and after treatment. The increase in ALP was not associated with increases in other liver function tests, i.e. ALT, AST or bilirubin. Moreover there was only one case of AEs related to System Organ Class (SOC) "Hepatobiliary disorder". There were no noticeable differences in the two treatment groups. The changes related to the other laboratory tests were also balanced in the two experimental groups and did not show any trend.

After the submission of this efficacy supplement (NDA 21,689), 9 spontaneous reports related to high dose esomeprazole infusion, describing 12 AEs were entered into the sponsors Global Patient Safety Database. Three of the 6 serious AEs are not labeled in the Nexium I.V. US package insert i.e. ***renal failure, nephrotic syndrome, and hypoglycemia****; the 6 non-serious AEs are all labeled in the Nexium I.V. US package insert. Sponsor states that the majority of these adverse event reports contained limited information precluding causality assessment or was confounded by factors such as concomitant medications or concomitant illness. The details are given in appendix, Table 88.*

9.2 Recommendation on Regulatory Action:

The reviewer recommends that NEXIUM Intravenous formulation in the dose of 80 mg in 30 minutes followed by continuous infusion at the rate of 8 mg per hour for next 71.5 hours for the indication of (b) (4) be not approved. The primary efficacy result in this non-US, single study is weak, has not been replicated and does not provide substantial evidence to support the proposed indication.

This reviewer recommends that in order to resolve these deficiencies, the applicant should provide results of at least one additional adequate and well-controlled study to demonstrate the proposed clinical benefit. The study should include some US centers.

9.3 Recommendation on Post-marketing Actions

N.A.

9.4 Labeling Review:

N.A.

9.5 Comments to the Applicant

It is recommended not to approve NEXIUM Intravenous formulation at the proposed dose and mode of administration for the indication of (b) (4) The primary efficacy result in this non-US, single study is weak, has not been replicated and does not provide substantial evidence to support the proposed indication.

In order to resolve these deficiencies, the applicant should provide at least one additional adequate and well-controlled study to demonstrate the proposed clinical benefit. The study should include some US centers.

The appropriateness of the sponsor's esomeprazole dose selection in the current submission needs validation as the target pH of > 6 was not achieved 50% of the time in 24 hours in the two PK/PD studies. This insufficient PD response may be responsible for not achieving robust clinical efficacy data.

The applicant should do a thorough dose finding study to document a dose that can achieve intragastric pH > 6 during ≥ 90% of the time in 72 hours. Further clinical trails should be done only after establishing the dose and PD profile.

Although pediatric studies should be performed after the safety and efficacy of the drug in adults have been established the applicant should submit a pediatric plan along with the next submission.

Also included should be enough number of patients with renal and/or hepatic insufficiency to assess the PK/PD information for possible dose adjustment.

10 APPENDICES

Table 81: Serious adverse events by system organ class and preferred term n (%) of patients within 72 hours after start of treatment, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Patients with any SAE	33(8.8%)	41(10.5%)
Gastrointestinal disorders	18(4.8%)	30(7.7%)
Duodenal ulcer haemorrhage	12(3.2%)	14(3.6%)
Gastric ulcer haemorrhage	4(1.1%)	11(2.8%)
Gastrointestinal haemorrhage	1(0.3%)	1(0.3%)
Rectal haemorrhage	1(0.3%)	0(0%)
Duodenal perforation	0(0%)	1(0.3%)
Duodenal ulcer perforation	0(0%)	1(0.3%)
Pancreatitis acute	0(0%)	1(0.3%)
Peptic ulcer perforation	0(0%)	1(0.3%)
Cardiac disorders	6(1.6%)	5(1.3%)
Myocardial infarction	4(1.1%)	3(0.8%)
Angina pectoris	1(0.3%)	0(0%)
Angina unstable	1(0.3%)	0(0%)
Cardiac failure	1(0.3%)	0(0%)
Atrial fibrillation	0(0%)	2(0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(0.8%)	1(0.3%)
Gastric cancer	2(0.5%)	0(0%)
Gastrointestinal stromal tumour	1(0.3%)	0(0%)
Testicular cancer metastatic	0(0%)	1(0.3%)
Infections and infestations	2(0.5%)	0(0%)
Lower respiratory tract infection	1(0.3%)	0(0%)
Respiratory tract infection	1(0.3%)	0(0%)
Metabolism and nutrition disorders	2(0.5%)	0(0%)
Diabetes mellitus	1(0.3%)	0(0%)
Diabetes mellitus inadequate control	1(0.3%)	0(0%)
Respiratory, thoracic and mediastinal disorders	2(0.5%)	3(0.8%)
Respiratory failure	1(0.3%)	1(0.3%)
Pleural effusion	1(0.3%)	0(0%)
Lung infiltration	0(0%)	1(0.3%)
Pulmonary embolism	0(0%)	1(0.3%)
Vascular disorders	2(0.5%)	0(0%)
Shock	1(0.3%)	0(0%)
Thrombosis	1(0.3%)	0(0%)
Hepatobiliary disorders	1(0.3%)	0(0%)
Cholecystitis	1(0.3%)	0(0%)
Injury, poisoning and procedural complications	1(0.3%)	1(0.3%)
Hip fracture	1(0.3%)	0(0%)
Pneumothorax traumatic	0(0%)	1(0.3%)
Psychiatric disorders	1(0.3%)	0(0%)
Acute psychosis	1(0.3%)	0(0%)
Skin and subcutaneous tissue disorders	1(0.3%)	0(0%)
Urticaria	1(0.3%)	0(0%)
Investigations	0(0%)	1(0.3%)
Haemoglobin decreased	0(0%)	1(0.3%)
Musculoskeletal and connective tissue disorders	0(0%)	1(0.3%)
Gouty arthritis	0(0%)	1(0.3%)
Renal and urinary disorders	0(0%)	1(0.3%)
Renal failure	0(0%)	1(0.3%)

Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Number of patients who reported at least 1 AE for a preferred term
(Table above is taken from Table 41 of Applicant's Clinical Study Report for Study D961DC00001)

Table 82: Serious adverse events by system organ class and preferred term n (%) of patients within 4-30 days after start of treatment, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=347)	Placebo[b] (n=352)
Patients with any SAE	29(8.4%)	28(8.0%)
Gastrointestinal disorders	8(2.3%)	11(3.1%)
Duodenal ulcer haemorrhage	3(0.9%)	6(1.7%)
Gastric ulcer haemorrhage	3(0.9%)	2(0.6%)
Melaena	2(0.6%)	0(0%)
Colonic polyp	0(0%)	1(0.3%)
Constipation	0(0%)	1(0.3%)
Gastric ulcer perforation	0(0%)	1(0.3%)
Cardiac disorders	3(0.9%)	3(0.9%)
Acute myocardial infarction	1(0.3%)	1(0.3%)
Myocardial infarction	1(0.3%)	1(0.3%)
Bradycardia	1(0.3%)	0(0%)
Atrial fibrillation	0(0%)	1(0.3%)
General disorders and administration site conditions	3(0.9%)	0(0%)
Discomfort	1(0.3%)	0(0%)
Fatigue	1(0.3%)	0(0%)
Pyrexia	1(0.3%)	0(0%)
Infections and infestations	3(0.9%)	2(0.6%)
Gastroenteritis	1(0.3%)	0(0%)
Lung infection	1(0.3%)	0(0%)
Pneumonia	1(0.3%)	0(0%)
Erysipelas	0(0%)	1(0.3%)
Urinary tract infection	0(0%)	1(0.3%)
Nervous system disorders	3(0.9%)	2(0.6%)
Peripheral nerve lesion	1(0.3%)	0(0%)
Presyncope	1(0.3%)	0(0%)
Syncope	1(0.3%)	0(0%)
Dizziness	0(0%)	1(0.3%)
Transient ischaemic attack	0(0%)	1(0.3%)
Vascular disorders	3(0.9%)	0(0%)
Phlebitis	1(0.3%)	0(0%)
Thrombosis	1(0.3%)	0(0%)
Venous thrombosis limb	1(0.3%)	0(0%)
Injury, poisoning and procedural complications	2(0.6%)	0(0%)
Dislocation of joint prosthesis	1(0.3%)	0(0%)
Subdural haemorrhage	1(0.3%)	0(0%)
Metabolism and nutrition disorders	2(0.6%)	2(0.6%)
Gout	2(0.6%)	1(0.3%)
Hyponatraemia	0(0%)	1(0.3%)
Eye disorders	1(0.3%)	0(0%)
Uveitis	1(0.3%)	0(0%)
Musculoskeletal and connective tissue disorders	1(0.3%)	2(0.6%)
Osteolysis	1(0.3%)	0(0%)
Gouty arthritis	0(0%)	2(0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(0.3%)	4(1.1%)
Gastric cancer	1(0.3%)	1(0.3%)
Adenocarcinoma pancreas	0(0%)	1(0.3%)
Benign gastric neoplasm	0(0%)	1(0.3%)
Rectal cancer	0(0%)	1(0.3%)
Congenital, familial and genetic disorders	0(0%)	1(0.3%)
Gastrointestinal angiodysplasia haemorrhagic	0(0%)	1(0.3%)
Respiratory, thoracic and mediastinal disorders	0(0%)	3(0.9%)
Lung disorder	0(0%)	1(0.3%)
Pulmonary embolism	0(0%)	1(0.3%)

Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
(Table above is taken from Table 42 of Applicant's Clinical Study Report for Study D961DC00001)

Table 83: Number (%) of patients with an AE leading to discontinuation of study drug within 72 hours after start of treatment, safety population

Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Patients with an AE leading to discontinuation[d]	31(8.3%)	39(10.0%)
Gastrointestinal disorders	20(5.3%)	27(6.9%)
Duodenal ulcer haemorrhage	13(3.5%)	12(3.1%)
Gastric ulcer haemorrhage	3(0.8%)	10(2.6%)
Gastrointestinal haemorrhage	2(0.5%)	1(0.3%)
Diarrhoea	1(0.3%)	0(0%)
Haematemesis	1(0.3%)	0(0%)
Duodenal perforation	0(0%)	1(0.3%)
Gastrooesophageal reflux disease	0(0%)	1(0.3%)
Pancreatitis acute	0(0%)	1(0.3%)
Peptic ulcer perforation	0(0%)	1(0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(0.8%)	1(0.3%)
Gastric cancer	2(0.5%)	0(0%)
Gastrointestinal stromal tumour	1(0.3%)	0(0%)
Adenocarcinoma pancreas	0(0%)	1(0.3%)
Psychiatric disorders	3(0.8%)	2(0.5%)
Acute psychosis	1(0.3%)	0(0%)
Delirium tremens	1(0.3%)	0(0%)
Psychotic disorder	1(0.3%)	0(0%)
Confusional state	0(0%)	1(0.3%)
Nicotine dependence	0(0%)	1(0.3%)
Cardiac disorders	2(0.5%)	2(0.5%)
Myocardial infarction	2(0.5%)	2(0.5%)
General disorders and administration site conditions	1(0.3%)	0(0%)
Catheter site related reaction	1(0.3%)	0(0%)
Skin and subcutaneous tissue disorders	1(0.3%)	2(0.5%)
Urticaria	1(0.3%)	1(0.3%)
Rash	0(0%)	1(0.3%)
Vascular disorders	1(0.3%)	1(0.3%)
Hypertension	1(0.3%)	0(0%)
Hypotension	0(0%)	1(0.3%)
Blood and lymphatic system disorders	0(0%)	1(0.3%)
Anaemia	0(0%)	1(0.3%)
Infections and infestations	0(0%)	1(0.3%)
Diverticulitis	0(0%)	1(0.3%)
Investigations	0(0%)	1(0.3%)
Haemoglobin decreased	0(0%)	1(0.3%)
Respiratory, thoracic and mediastinal disorders	0(0%)	1(0.3%)
Respiratory failure	0(0%)	1(0.3%)

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Patients with multiple (different) events are counted once for each (different) preferred term
d Action taken, investigational product permanently stopped
(Table above is taken from Table 75 of Applicant's Clinical Study Report for Study D961DC00001)

Table 84: Number (%) of patients with an AE leading to discontinuation of study drug during day 4 to 30 after start of treatment, safety population:

Preferred term	Number(%) of patients[c] Eso[a] (n=347)	Placebo[b] (n=352)
Patients with an AE leading to discontinuation[d]	15(4.3%)	17(4.8%)
Gastrointestinal disorders	6(1.7%)	10(2.8%)
Duodenal ulcer haemorrhage	2(0.6%)	5(1.4%)
Gastric ulcer haemorrhage	2(0.6%)	4(1.1%)
Diarrhoea	2(0.6%)	0(0%)
Pancreatitis acute	0(0%)	1(0.3%)
Injury, poisoning and procedural complications	2(0.6%)	0(0%)
Dislocation of joint prosthesis	1(0.3%)	0(0%)
Subdural haemorrhage	1(0.3%)	0(0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2(0.6%)	1(0.3%)
Gastric cancer	2(0.6%)	0(0%)
Adenocarcinoma pancreas	0(0%)	1(0.3%)
Cardiac disorders	1(0.3%)	2(0.6%)
Acute myocardial infarction	1(0.3%)	0(0%)
Myocardial infarction	0(0%)	2(0.6%)
Nervous system disorders	1(0.3%)	0(0%)
Presyncope	1(0.3%)	0(0%)
Psychiatric disorders	1(0.3%)	0(0%)
Delirium tremens	1(0.3%)	0(0%)
Skin and subcutaneous tissue disorders	1(0.3%)	1(0.3%)
Pruritus	1(0.3%)	0(0%)
Dermatitis allergic	0(0%)	1(0.3%)
Vascular disorders	1(0.3%)	0(0%)
Venous thrombosis limb	1(0.3%)	0(0%)
Blood and lymphatic system disorders	0(0%)	1(0.3%)
Anaemia	0(0%)	1(0.3%)
Infections and infestations	0(0%)	1(0.3%)
Diverticulitis	0(0%)	1(0.3%)
Respiratory, thoracic and mediastinal disorders	0(0%)	1(0.3%)
Pulmonary oedema	0(0%)	1(0.3%)

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Patients with multiple (different) events are counted once for each (different) preferred term
d Action taken, investigational product permanently stopped
(Table above is taken from Table 76 of Applicant's Clinical Study Report for Study D961DC00001)

Table 85: Number (%) of patients who had at least 1 AE within 72 hours, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Patients with any AE	147(39.2%)	163(41.9%)
Gastrointestinal disorders	46(12.3%)	77(19.8%)
Duodenal ulcer haemorrhage	16(4.3%)	16(4.1%)
Nausea	8(2.1%)	8(2.1%)
Constipation	6(1.6%)	9(2.3%)
Abdominal pain upper	5(1.3%)	9(2.3%)
Gastric ulcer haemorrhage	4(1.1%)	13(3.3%)
Diarrhoea	3(0.8%)	0(0%)
Gastrointestinal haemorrhage	2(0.5%)	2(0.5%)
Vomiting	2(0.5%)	1(0.3%)
Rectal haemorrhage	2(0.5%)	0(0%)
Abdominal pain	1(0.3%)	11(2.8%)
Flatulence	1(0.3%)	2(0.5%)
Melaena	1(0.3%)	1(0.3%)
Dry mouth	1(0.3%)	0(0%)
Haematemesis	1(0.3%)	0(0%)
Haemorrhoids	1(0.3%)	0(0%)
Tooth loss	1(0.3%)	0(0%)
Dyspepsia	0(0%)	5(1.3%)
Abdominal distension	0(0%)	1(0.3%)
Abdominal pain lower	0(0%)	1(0.3%)
Colitis	0(0%)	1(0.3%)
Duodenal perforation	0(0%)	1(0.3%)
Duodenal ulcer perforation	0(0%)	1(0.3%)
Epigastric discomfort	0(0%)	1(0.3%)
Gastrooesophageal reflux disease	0(0%)	1(0.3%)
Pancreatitis acute	0(0%)	1(0.3%)
Peptic ulcer perforation	0(0%)	1(0.3%)
Peritonitis	0(0%)	1(0.3%)
Reflux oesophagitis	0(0%)	1(0.3%)
General disorders and administration site conditions	27(7.2%)	20(5.1%)
Pyrexia	13(3.5%)	11(2.8%)
Fatigue	2(0.5%)	1(0.3%)
Oedema peripheral	2(0.5%)	1(0.3%)
Catheter site related reaction	2(0.5%)	0(0%)
Chills	1(0.3%)	1(0.3%)
Non-cardiac chest pain	1(0.3%)	1(0.3%)
Pain	1(0.3%)	1(0.3%)
Chest discomfort	1(0.3%)	0(0%)
Feeling cold	1(0.3%)	0(0%)
Injection site erythema	1(0.3%)	0(0%)
Injection site inflammation	1(0.3%)	0(0%)
Injection site swelling	1(0.3%)	0(0%)
Hyperthermia	0(0%)	2(0.5%)
Asthenia	0(0%)	1(0.3%)
Infusion site swelling	0(0%)	1(0.3%)
Sensation of foreign body	0(0%)	1(0.3%)
Vascular disorders	24(6.4%)	16(4.1%)
Phlebitis	9(2.4%)	2(0.5%)
Hypertension	5(1.3%)	7(1.8%)
Hypotension	4(1.1%)	4(1.0%)
Thrombophlebitis	2(0.5%)	0(0%)
Ischaemia	1(0.3%)	0(0%)
Phlebitis superficial	1(0.3%)	0(0%)
Shock	1(0.3%)	0(0%)
Thrombosis	1(0.3%)	0(0%)
Accelerated hypertension	0(0%)	2(0.5%)
Angiodysplasia	0(0%)	1(0.3%)
Circulatory collapse	0(0%)	1(0.3%)
Orthostatic hypotension	0(0%)	1(0.3%)

(Table above is taken from Table 66 of Applicant's Clinical Study Report for Study D961DC00001)

Table 85 (Contd): Number (%) of patients who had at least 1 AE within 72 hours, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Cardiac disorders	13(3.5%)	14(3.6%)
Myocardial infarction	4(1.1%)	4(1.0%)
Cardiac failure	2(0.5%)	1(0.3%)
Palpitations	2(0.5%)	0(0%)
Angina pectoris	1(0.3%)	3(0.8%)
Atrial fibrillation	1(0.3%)	3(0.8%)
Tachycardia	1(0.3%)	1(0.3%)
Angina unstable	1(0.3%)	0(0%)
Cardiac failure congestive	1(0.3%)	0(0%)
Cardiovascular disorder	1(0.3%)	0(0%)
Acute myocardial infarction	0(0%)	1(0.3%)
Hypertensive heart disease	0(0%)	1(0.3%)
Tachyarrhythmia	0(0%)	1(0.3%)
Infections and infestations	13(3.5%)	16(4.1%)
Urinary tract infection	4(1.1%)	4(1.0%)
Lymphangitis	2(0.5%)	1(0.3%)
Respiratory tract infection	2(0.5%)	0(0%)
Cystitis	1(0.3%)	4(1.0%)
Bacterial diarrhoea	1(0.3%)	0(0%)
Bronchitis	1(0.3%)	0(0%)
Catheter sepsis	1(0.3%)	0(0%)
Cellulitis	1(0.3%)	0(0%)
Infection	1(0.3%)	0(0%)
Lower respiratory tract infection	1(0.3%)	0(0%)
Diverticulitis	0(0%)	1(0.3%)
Hepatitis c	0(0%)	1(0.3%)
Oral candidiasis	0(0%)	1(0.3%)
Oral fungal infection	0(0%)	1(0.3%)
Pneumonia	0(0%)	1(0.3%)
Sepsis	0(0%)	1(0.3%)
Sinusitis	0(0%)	1(0.3%)
Upper respiratory tract infection	0(0%)	1(0.3%)
Respiratory, thoracic and mediastinal disorders	12(3.2%)	13(3.3%)
Cough	4(1.1%)	1(0.3%)
Dyspnoea	2(0.5%)	7(1.8%)
Respiratory failure	2(0.5%)	2(0.5%)
Lung disorder	1(0.3%)	0(0%)
Pleural effusion	1(0.3%)	0(0%)
Productive cough	1(0.3%)	0(0%)
Pulmonary oedema	1(0.3%)	0(0%)
Tracheal pain	1(0.3%)	0(0%)
Epistaxis	0(0%)	1(0.3%)
Lung infiltration	0(0%)	1(0.3%)
Pulmonary embolism	0(0%)	1(0.3%)
Rhinorrhoea	0(0%)	1(0.3%)
Nervous system disorders	11(2.9%)	11(2.8%)
Headache	5(1.3%)	7(1.8%)
Dizziness	4(1.1%)	3(0.8%)
Syncope	1(0.3%)	1(0.3%)
Peripheral nerve lesion	1(0.3%)	0(0%)
Lacunar infarction	0(0%)	1(0.3%)
Syncope vasovagal	0(0%)	1(0.3%)
Transient ischaemic attack	0(0%)	1(0.3%)
Metabolism and nutrition disorders	10(2.7%)	6(1.5%)
Hypoglycaemia	3(0.8%)	1(0.3%)
Hypokalaemia	2(0.5%)	4(1.0%)
Hyperkalaemia	2(0.5%)	1(0.3%)
Diabetes mellitus	1(0.3%)	0(0%)
Diabetes mellitus inadequate control	1(0.3%)	0(0%)
Gout	1(0.3%)	0(0%)
Hypophosphataemia	1(0.3%)	0(0%)
Hypercholesterolaemia	0(0%)	1(0.3%)
Hyponatraemia	0(0%)	1(0.3%)

Table 85 (Contd): Number (%) of patients who had at least 1 AE within 72 hours, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Musculoskeletal and connective tissue disorders	10(2.7%)	9(2.3%)
Back pain	3(0.8%)	3(0.8%)
Pain in extremity	3(0.8%)	0(0%)
Arthralgia	2(0.5%)	1(0.3%)
Musculoskeletal chest pain	1(0.3%)	2(0.5%)
Tendon pain	1(0.3%)	0(0%)
Gouty arthritis	0(0%)	1(0.3%)
Groin pain	0(0%)	1(0.3%)
Musculoskeletal pain	0(0%)	1(0.3%)
Psychiatric disorders	10(2.7%)	20(5.1%)
Insomnia	3(0.8%)	7(1.8%)
Anxiety	2(0.5%)	1(0.3%)
Sleep disorder	1(0.3%)	2(0.5%)
Delirium tremens	1(0.3%)	1(0.3%)
Psychotic disorder	1(0.3%)	1(0.3%)
Acute psychosis	1(0.3%)	0(0%)
Hallucination	1(0.3%)	0(0%)
Initial insomnia	1(0.3%)	0(0%)
Delirium	0(0%)	3(0.8%)
Restlessness	0(0%)	2(0.5%)
Aggression	0(0%)	1(0.3%)
Agitation	0(0%)	1(0.3%)
Confusional state	0(0%)	1(0.3%)
Disorientation	0(0%)	1(0.3%)
Nicotine dependence	0(0%)	1(0.3%)
Skin and subcutaneous tissue disorders	9(2.4%)	6(1.5%)
Rash	3(0.8%)	1(0.3%)
Erythema	1(0.3%)	1(0.3%)
Hyperhidrosis	1(0.3%)	1(0.3%)
Urticaria	1(0.3%)	1(0.3%)
Dermatitis contact	1(0.3%)	0(0%)
Dry skin	1(0.3%)	0(0%)
Eczema	1(0.3%)	0(0%)
Pruritus	0(0%)	1(0.3%)
Scar pain	0(0%)	1(0.3%)
Blood and lymphatic system disorders	5(1.3%)	7(1.8%)
Haemorrhagic anaemia	3(0.8%)	0(0%)
Anaemia	2(0.5%)	5(1.3%)
Haemolysis	0(0%)	1(0.3%)
Iron deficiency anaemia	0(0%)	1(0.3%)
Eye disorders	5(1.3%)	1(0.3%)
Blepharitis	1(0.3%)	0(0%)
Dry eye	1(0.3%)	0(0%)
Eye haemorrhage	1(0.3%)	0(0%)
Eye inflammation	1(0.3%)	0(0%)
Ocular hyperaemia	1(0.3%)	0(0%)
Orbital oedema	0(0%)	1(0.3%)
Hepatobiliary disorders	4(1.1%)	2(0.5%)
Cholecystitis	1(0.3%)	0(0%)
Cirrhosis alcoholic	1(0.3%)	0(0%)
Hepatic steatosis	1(0.3%)	0(0%)
Hepatocellular damage	1(0.3%)	0(0%)
Hepatic cyst	0(0%)	1(0.3%)
Post cholecystectomy syndrome	0(0%)	1(0.3%)
Investigations	4(1.1%)	11(2.8%)
Haemoglobin decreased	3(0.8%)	2(0.5%)
Hepatic enzyme increased	1(0.3%)	2(0.5%)
Blood bilirubin increased	0(0%)	1(0.3%)
Blood potassium decreased	0(0%)	1(0.3%)
Blood pressure decreased	0(0%)	1(0.3%)
Blood pressure increased	0(0%)	1(0.3%)
Blood sodium decreased	0(0%)	1(0.3%)
Heart rate increased	0(0%)	1(0.3%)
Urine output decreased	0(0%)	1(0.3%)

Table 85 (Contd): Number (%) of patients who had at least 1 AE within 72 hours, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(0.8%)	3(0.8%)
Gastric cancer	2(0.5%)	0(0%)
Gastrointestinal stromal tumour	1(0.3%)	0(0%)
Adenocarcinoma pancreas	0(0%)	1(0.3%)
Benign gastric neoplasm	0(0%)	1(0.3%)
Testicular cancer metastatic	0(0%)	1(0.3%)
Ear and labyrinth disorders	1(0.3%)	0(0%)
Vertigo	1(0.3%)	0(0%)
Injury, poisoning and procedural complications	1(0.3%)	3(0.8%)
Hip fracture	1(0.3%)	0(0%)
Pneumothorax traumatic	0(0%)	1(0.3%)
Post procedural complication	0(0%)	1(0.3%)
Procedural pain	0(0%)	1(0.3%)
Renal and urinary disorders	1(0.3%)	5(1.3%)
Dysuria	1(0.3%)	0(0%)
Renal cyst	0(0%)	2(0.5%)
Haematuria	0(0%)	1(0.3%)
Renal failure	0(0%)	1(0.3%)
Urinary retention	0(0%)	1(0.3%)

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Number of patients who reported at least 1 AE for a preferred term
(Table above is taken from Table 66 of Applicant's Clinical Study Report for Study D961DC00001)

Table 86: Number (%) of patients, who had at least 1 AE by preferred term, during day 4 to 30, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=347)	Placebo[b] (n=352)
Patients with any AE	116(33.4%)	131(37.2%)
Gastrointestinal disorders	33(9.5%)	46(13.1%)
Constipation	7(2.0%)	12(3.4%)
Diarrhoea	6(1.7%)	3(0.9%)
Nausea	6(1.7%)	3(0.9%)
Duodenal ulcer haemorrhage	4(1.2%)	9(2.6%)
Gastric ulcer haemorrhage	4(1.2%)	4(1.1%)
Melaena	3(0.9%)	2(0.6%)
Vomiting	2(0.6%)	1(0.3%)
Abdominal pain	1(0.3%)	7(2.0%)
Dyspepsia	1(0.3%)	2(0.6%)
Abdominal pain upper	1(0.3%)	1(0.3%)
Epigastric discomfort	1(0.3%)	1(0.3%)
Haematochezia	1(0.3%)	1(0.3%)
Aphthous stomatitis	1(0.3%)	0(0%)
Eructation	1(0.3%)	0(0%)
Oesophageal varices haemorrhage	1(0.3%)	0(0%)
Rectal haemorrhage	1(0.3%)	0(0%)
Abdominal distension	0(0%)	1(0.3%)
Colonic polyp	0(0%)	1(0.3%)
Dry mouth	0(0%)	1(0.3%)
Gastric ulcer perforation	0(0%)	1(0.3%)
Gastrointestinal haemorrhage	0(0%)	1(0.3%)
Pancreatitis acute	0(0%)	1(0.3%)
Reflux oesophagitis	0(0%)	1(0.3%)
General disorders and administration site conditions	24(6.9%)	18(5.1%)
Pyrexia	9(2.6%)	9(2.6%)
Oedema peripheral	4(1.2%)	2(0.6%)
Fatigue	3(0.9%)	1(0.3%)
Hyperthermia	2(0.6%)	2(0.6%)
Injection site inflammation	2(0.6%)	0(0%)
Discomfort	1(0.3%)	0(0%)
General physical health deterioration	1(0.3%)	0(0%)
Injection site erythema	1(0.3%)	0(0%)
Pain	1(0.3%)	0(0%)
Non-cardiac chest pain	0(0%)	2(0.6%)
Asthenia	0(0%)	1(0.3%)
Infusion site swelling	0(0%)	1(0.3%)
Oedema	0(0%)	1(0.3%)
Infections and infestations	18(5.2%)	26(7.4%)
Urinary tract infection	4(1.2%)	9(2.6%)
Cystitis	3(0.9%)	5(1.4%)
Pneumonia	1(0.3%)	3(0.9%)
Bronchitis	1(0.3%)	1(0.3%)
Gastroenteritis	1(0.3%)	1(0.3%)
Upper respiratory tract infection	1(0.3%)	1(0.3%)
Cellulitis	1(0.3%)	0(0%)
Infection	1(0.3%)	0(0%)
Influenza	1(0.3%)	0(0%)
Infusion site infection	1(0.3%)	0(0%)
Lung infection	1(0.3%)	0(0%)
Lymphangitis	1(0.3%)	0(0%)
Nasopharyngitis	1(0.3%)	0(0%)
Respiratory tract infection	1(0.3%)	0(0%)
Sepsis	0(0%)	2(0.6%)
Diverticulitis	0(0%)	1(0.3%)
Erysipelas	0(0%)	1(0.3%)
Gastroenteritis viral	0(0%)	1(0.3%)
Hepatitis c	0(0%)	1(0.3%)
Oral candidiasis	0(0%)	1(0.3%)
Pyelonephritis chronic	0(0%)	1(0.3%)
Tonsillitis	0(0%)	1(0.3%)
Wound infection	0(0%)	1(0.3%)

Table 86 (Contd): Number (%) of patients who had at least 1 AE by preferred term, during day 4 to 30, safety population

System organ class/Preferred term	Number(%) of patients[c]	
	Eso[a] (n=347)	Placebo[b] (n=352)
Vascular disorders	15(4.3%)	9(2.6%)
Phlebitis	6(1.7%)	3(0.9%)
Thrombophlebitis	3(0.9%)	0(0%)
Hypertension	1(0.3%)	4(1.1%)
Arterial stenosis	1(0.3%)	0(0%)
Phlebitis superficial	1(0.3%)	0(0%)
Thrombophlebitis superficial	1(0.3%)	0(0%)
Thrombosis	1(0.3%)	0(0%)
Venous thrombosis limb	1(0.3%)	0(0%)
Angiodysplasia	0(0%)	1(0.3%)
Hot flush	0(0%)	1(0.3%)
Respiratory, thoracic and mediastinal disorders	14(4.0%)	8(2.3%)
Dyspnoea	4(1.2%)	2(0.6%)
Chronic obstructive pulmonary disease	2(0.6%)	0(0%)
Cough	2(0.6%)	0(0%)
Lung disorder	1(0.3%)	1(0.3%)
Dyspnoea exertional	1(0.3%)	0(0%)
Epistaxis	1(0.3%)	0(0%)
Pharyngolaryngeal pain	1(0.3%)	0(0%)
Productive cough	1(0.3%)	0(0%)
Respiratory failure	1(0.3%)	0(0%)
Bronchial disorder	0(0%)	1(0.3%)
Lung infiltration	0(0%)	1(0.3%)
Pulmonary embolism	0(0%)	1(0.3%)
Pulmonary oedema	0(0%)	1(0.3%)
Rhonchi	0(0%)	1(0.3%)
Musculoskeletal and connective tissue disorders	9(2.6%)	10(2.8%)
Arthralgia	2(0.6%)	1(0.3%)
Back pain	1(0.3%)	1(0.3%)
Musculoskeletal pain	1(0.3%)	1(0.3%)
Polyarthritis	1(0.3%)	1(0.3%)
Arthritis	1(0.3%)	0(0%)
Osteolysis	1(0.3%)	0(0%)
Pain in extremity	1(0.3%)	0(0%)
Tendon pain	1(0.3%)	0(0%)
Gouty arthritis	0(0%)	2(0.6%)
Groin pain	0(0%)	1(0.3%)
Muscular weakness	0(0%)	1(0.3%)
Musculoskeletal chest pain	0(0%)	1(0.3%)
Spinal disorder	0(0%)	1(0.3%)
Nervous system disorders	9(2.6%)	10(2.8%)
Headache	3(0.9%)	5(1.4%)
Dizziness	3(0.9%)	3(0.9%)
Syncope	2(0.6%)	1(0.3%)
Peripheral nerve lesion	1(0.3%)	0(0%)
Presyncope	1(0.3%)	0(0%)
Epilepsy	0(0%)	1(0.3%)
Transient ischaemic attack	0(0%)	1(0.3%)
Cardiac disorders	8(2.3%)	8(2.3%)
Angina pectoris	3(0.9%)	1(0.3%)
Myocardial infarction	1(0.3%)	3(0.9%)
Acute myocardial infarction	1(0.3%)	1(0.3%)
Aortic valve incompetence	1(0.3%)	0(0%)
Bradycardia	1(0.3%)	0(0%)
Cardiac failure	1(0.3%)	0(0%)
Mitral valve disease mixed	1(0.3%)	0(0%)
Palpitations	1(0.3%)	0(0%)
Ventricular extrasystoles	1(0.3%)	0(0%)
Atrial fibrillation	0(0%)	3(0.9%)
Myocardial ischaemia	0(0%)	1(0.3%)

Table 86 (Contd): Number (%) of patients who had at least 1 AE by preferred term, during day 4 to 30, safety population

System organ class/Preferred term	Number(%) of patients[c]	
	Eso[a] (n=347)	Placebo[b] (n=352)
Metabolism and nutrition disorders	7(2.0%)	10(2.8%)
Gout	2(0.6%)	1(0.3%)
Hypokalaemia	1(0.3%)	4(1.1%)
Hyperkalaemia	1(0.3%)	3(0.9%)
Acidosis	1(0.3%)	0(0%)
Decreased appetite	1(0.3%)	0(0%)
Diabetes mellitus	1(0.3%)	0(0%)
Hypoglycaemia	1(0.3%)	0(0%)
Diabetes mellitus inadequate control	0(0%)	1(0.3%)
Folate deficiency	0(0%)	1(0.3%)
Hypercholesterolaemia	0(0%)	1(0.3%)
Hyponatraemia	0(0%)	1(0.3%)
Skin and subcutaneous tissue disorders	7(2.0%)	9(2.6%)
Pruritus	2(0.6%)	4(1.1%)
Eczema	2(0.6%)	0(0%)
Blister	1(0.3%)	1(0.3%)
Dermatitis	1(0.3%)	0(0%)
Erythema	1(0.3%)	0(0%)
Hyperhidrosis	1(0.3%)	0(0%)
Rash	0(0%)	2(0.6%)
Dermatitis allergic	0(0%)	1(0.3%)
Scar pain	0(0%)	1(0.3%)
Investigations	6(1.7%)	6(1.7%)
Haemoglobin decreased	2(0.6%)	1(0.3%)
Blood pressure increased	2(0.6%)	0(0%)
Hepatic enzyme increased	1(0.3%)	2(0.6%)
Cardiac murmur	1(0.3%)	0(0%)
Biopsy skin	0(0%)	1(0.3%)
Blood sodium decreased	0(0%)	1(0.3%)
Heart rate increased	0(0%)	1(0.3%)
Psychiatric disorders	6(1.7%)	8(2.3%)
Sleep disorder	2(0.6%)	2(0.6%)
Initial insomnia	2(0.6%)	1(0.3%)
Insomnia	1(0.3%)	2(0.6%)
Delirium tremens	1(0.3%)	0(0%)
Delirium	0(0%)	2(0.6%)
Psychotic disorder	0(0%)	1(0.3%)
Blood and lymphatic system disorders	5(1.4%)	8(2.3%)
Haemorrhagic anaemia	3(0.9%)	0(0%)
Anaemia	2(0.6%)	6(1.7%)
Iron deficiency anaemia	0(0%)	1(0.3%)
Thrombocytopenia	0(0%)	1(0.3%)
Eye disorders	5(1.4%)	1(0.3%)
Blepharitis	1(0.3%)	0(0%)
Dry eye	1(0.3%)	0(0%)
Eye haemorrhage	1(0.3%)	0(0%)
Ocular hyperaemia	1(0.3%)	0(0%)
Uveitis	1(0.3%)	0(0%)
Diplopia	0(0%)	1(0.3%)
Hepatobiliary disorders	5(1.4%)	3(0.9%)
Bile duct stone	1(0.3%)	0(0%)
Cirrhosis alcoholic	1(0.3%)	0(0%)
Hepatic steatosis	1(0.3%)	0(0%)
Hepatitis	1(0.3%)	0(0%)
Hepatocellular damage	1(0.3%)	0(0%)
Biliary colic	0(0%)	1(0.3%)
Cholecystitis acute	0(0%)	1(0.3%)
Post cholecystectomy syndrome	0(0%)	1(0.3%)

Table 86 (Contd): Number (%) of patients who had at least 1 AE by preferred term, during day 4 to 30, safety population

System organ class/Preferred term	Number(%) of patients[c]	
	Eso[a] (n=347)	Placebo[b] (n=352)
Injury, poisoning and procedural complications	4(1.2%)	4(1.1%)
Dislocation of joint prosthesis	1(0.3%)	0(0%)
Fall	1(0.3%)	0(0%)
Hip fracture	1(0.3%)	0(0%)
Medical device complication	1(0.3%)	0(0%)
Subdural haemorrhage	1(0.3%)	0(0%)
Wound complication	1(0.3%)	0(0%)
Feeding tube complication	0(0%)	1(0.3%)
Laceration	0(0%)	1(0.3%)
Pneumothorax traumatic	0(0%)	1(0.3%)
Procedural pain	0(0%)	1(0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4(1.2%)	5(1.4%)
Gastric cancer	3(0.9%)	1(0.3%)
Hepatic neoplasm	1(0.3%)	0(0%)
Adenocarcinoma pancreas	0(0%)	1(0.3%)
Benign gastric neoplasm	0(0%)	1(0.3%)
Rectal cancer	0(0%)	1(0.3%)
Testicular cancer metastatic	0(0%)	1(0.3%)
Renal and urinary disorders	4(1.2%)	8(2.3%)
Renal cyst	2(0.6%)	3(0.9%)
Dysuria	1(0.3%)	2(0.6%)
Calculus urinary	1(0.3%)	1(0.3%)
Incontinence	1(0.3%)	0(0%)
Haematuria	0(0%)	1(0.3%)
Nephrolithiasis	0(0%)	1(0.3%)
Renal failure	0(0%)	1(0.3%)
Renal failure chronic	0(0%)	1(0.3%)
Urinary retention	0(0%)	1(0.3%)
Ear and labyrinth disorders	1(0.3%)	0(0%)
Vertigo	1(0.3%)	0(0%)
Congenital, familial and genetic disorders	0(0%)	1(0.3%)
Gastrointestinal angiodysplasia haemorrhagic	0(0%)	1(0.3%)

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c Number of patients who reported at least 1 AE for a preferred term
(Table above is taken from Table 67 of Applicant's Clinical Study Report for Study D961DC00001)

Table 87: Listing of all patients who had an infusion site reaction within 72 hours after start of treatment, safety population

Treatment[a]	Centre	Patient number	Sex	Age (year)	AE (preferred term)	AE (investigator text)	Onset day relative to investigational product	AE duration (days)	Maximum intensity	Action taken with respect to investigational product	Causality (as assessed by the investigator)
Eso	(b)(6)	(b) (6)	Male	71	PHLEBITIS	phlebitis	3	>2	Mild	None	No
Eso			emale	78	THROMBOPHLEBITIS	thrombophlebitis	2	2	Mild	None	No
Eso			Male	48	ERYTHEMA	redness puncture	1	>2	Mild	None	No
Eso			Male	48	ERYTHEMA	redness puncture	c	4	Mild	None	No
Eso			emale	73	INJECTION SITE INFLAMMATION	inflammation left hand drip site	2	>3	Mild	None	No
Eso			Male	69	INJECTION SITE SWELLING	Drip site swelling	3	1	Mild	None	No
Eso			Male	74	INJECTION SITE ERYTHEMA	old drip site erythema	4	>1	Mild	None	No
Eso			Male	72	PHLEBITIS	Flebitis	4	>1	Mild	None	No
Eso			Male	68	PHLEBITIS	flebitis	4	>1	Mild	None	No
Eso			Male	70	PHLEBITIS	flebitis	3	2	Mild	None	Yes
Eso			emale	83	PHLEBITIS	phlebitis	2	>3	Mild	None	No
Eso			Male	63	PHLEBITIS	Phlebitis	4	>1	Mild	None	No
Eso			Male	42	PHLEBITIS	flebitis	3	>2	Mild	None	No
Eso			Male	39	PHLEBITIS SUPERFICIAL	superficial flebitis	2	>3	Mild	None	No
Eso			Male	72	PHLEBITIS	Phlebitis right arm	2	>3	Mild	None	No
Eso			emale	66	PHLEBITIS	right arm flebitis	3	>2	Mild	None	No
Eso			emale	80	THROMBOPHLEBITIS	Tromboflebit	4	>1	Mild	None	No
Placebo			Male	35	PHLEBITIS	Phlebitis of right cubital v.	4	>1	Mild	None	No
Placebo			Male	35	PHLEBITIS	Phlebitis of right cubital v.	4	4	Mild	None	No
Placebo			Male	57	PHLEBITIS	Phlebitis-Left arm	2	>3	Mild	None	No

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

(Table above is taken from Table 69 of Applicant's Clinical Study Report for Study D961DC00001)

Table 88: Summary of spontaneous adverse event reports from 01 January 2008 through 31 August 08

Report Id # Country / Source Age / Gender	Dose / Schedule Route / Duration Indication	AE(s) (Preferred Term) Time to onset Outcome	Abbreviated narrative Company comment
2008GB00784 Ireland / HCP 73 years / Male	160 mg / UNK Intravenous / 2 days UNK	**Renal Failure*** UNK UNK	Patient treated with esomeprazole iv 160 mg a day for 2 days. Urea and creatinine values elevated at the start of esomeprazole iv; both serum urea and creatinine values continued to increase after discontinuation of esomeprazole iv. Concomitant medications were not specified. Patient was hospitalized for surgical treatment of bowel obstruction. A large cyst was later found on the patient's left kidney. **Company comment**: Renal failure has not been associated with the use of esomeprazole iv. Limited information provided. Reporter noted urea and creatinine increased, improved and increased again. A large cyst on left kidney was considered by the reporter to be the cause of the event. Patient outcome is unknown.
2008UW13624 US / HCP 32 years / Male	UNK / UNK Intravenous / 2 days Gastric Bleeding	**Nephrotic Syndrome*** 1 day UNK	Patient experienced nephrotic syndrome 1 day after starting treatment with esomeprazole iv. Concomitant medication and medical history were not provided. **Company comment**: Report contains scant information, which precludes causality assessment. Provisional diagnosis of nephrotic syndrome was made over the telephone without examining the patient. Diagnosis of nephrotic syndrome is based on clinical and laboratory findings, which were not provided. Outcome is unknown.
2008UW12042 US / HCP 42 years / Male	UNK / 8 mg/hour Intravenous / UNK Duodenal Ulcer	**White blood cell count decreased*** UNK UNK	Patient hospitalized for resection of small bowel and falling white blood cell count was noted. Relevant medical history included duodenal ulcer, chronic obstructive pulmonary disease, end-stage renal failure requiring dialysis and multiple co-morbidities (unspecified). Concomitant medications were not specified. **Company comment**: Limited information precludes causality assessment. Baseline WBC and extent to which it decreased are unknown, thus clinical significance cannot be determined. Causality confounded by underlying history of multiple unspecified concomitant conditions, which could have been contributory. Outcome is unknown.
2008AP00310 Australia/ Regulatory Authority 71 years / Male	80 mg / daily Intravenous / UNK UNK	**Anemia*** **Hypoglycaemia*** UNK Recovered	After starting treatment with esomeprazole iv, patient experienced anemia and hypoglycaemia on (b)(6) Concomitant medication included rosiglitazone, metformin, dimirel, candesartan / hydrochlorothiazide, seretide, tiotropium, furosemide, ramipril, lercanidipine and salbutamol. Concurrent disease included baseline renal impairment. **Company comment**: No lab values were provided to assess baseline status. Causality confounded by history of renal impairment, anti-diabetic medication and polypharmacy including medications, which have been associated with anemia (rosiglitazone) and hypoglycaemia.

Table 88 (contd): Summary of spontaneous adverse event reports from 01 January 2008 through 31 August 2008

Report Id # Country / Source Age / Gender	Dose / Schedule Route / Duration Indication	AE(s) (Preferred Term) Time to onset Outcome	Abbreviated narrative Company comment
2007CG01678 France / HCP; Regulatory Authority 43 years / Male	Not provided Intravenous / 3 days Gastric Ulcer	**Thrombocytopenia*** 2 days Recovered	Patient post renal transplant with lung infection and gastric ulcer. Rituximab was started (b)(6) post transplant. Platelet count was 178 G/l on . Mycophenolate mofetil, tacrolimus, ciprofloxacin and pantoprazole were started on (b)(6) Platelet count was 112 G/l on (b)(6) Pantoprazole was discontinued. Tacrolimus was discontinued on (b)(6) Endoscopy on (b)(6) showed healing of gastric ulcer; esomeprazole iv was started. On (b)(6) search of heparin-induced thrombocytopenia was negative. Platelet count decreased to 56 G/l on (b)(6) Myelogram diagnosed peripheral thrombopenia. Esomeprazole, mycophenolate mofetil, and ciprofloxacin were stopped. On (b)(6) platelet count was 37 G/l. On (b)(6) platelet count was 188 G/l. Rituximab, tacrolimus, mycophenolate mofetil, ciprofloxacin and pantoprazole were also suspect. Concomitant medication included Solu-Medrol. **Company comment**: Thrombocytopenia was present (112 G/l) prior to starting esomeprazole iv. Platelet count decreased to 56 G/l after 2 days of esomeprazole iv. Rituximab, tacrolimus, mycophenolate mofetil, ciprofloxacin, pantoprazole and esomeprazole iv were all considered suspect. Patient recovered after all suspect drugs were stopped. Thrombocytopenia is a labelled event in the Nexium IV USPI. There was no reported clinical sequela (bleeding).
2007CG01649 France/Physician 84 years / Male	80 mg / daily Intravenous/ UNK Digestive Haemorrhage	**Thrombocytopenia** UNK Recovered	The patient experienced thrombocytopenia after receiving esomeprazole iv 40 mg twice daily (dates of therapy not provided) and enoxaparin 0.6 mL twice daily (co-suspect). Medical history of occlusive syndrome treated with enoxaparin. The patient experienced a digestive hemorrhage after starting enoxaparin with a normal platelet count. Enoxaparin was discontinued and esomeprazole started. Ten days later, platelet count decreased to 90,000 cells/mm3. **Company comment**: There was no baseline platelet count for comparison. Thrombocytopenia is a labelled event in the Nexium IV USPI. There was no reported clinical sequela (bleeding).
2008CG00563 France / HCP 76 years / Female	40 mg / UNK Intravenous / 4 days Ulcer	**Fever** **Diarrhea** 4 days Not yet recovered	Patient experienced fever and diarrhea 4 days after switching from esomeprazole oral (co-suspect) to esomeprazole iv. Concomitant drugs included ketoprofen, paracetamol, sodium chlorure + potassium + glucose and acebutolol. Medical history included colon surgery (not specified) 2 weeks prior. **Company comment**: Report contains limited information, which precludes causal assessment. Ketoprofen is known to cause diarrhea. Events of fever and diarrhea are labelled in the Nexium IV USPI.

Table 88 (contd): Summary of spontaneous adverse event reports from 01 January 2008 through 31 August 2008.

Report Id # Country / Source Age / Gender	Dose / Schedule Route / Duration Indication	AE(s) (Preferred Term) Time to onset Outcome	Abbreviated narrative Company comment
2008AP06230 India / HCP 51 years / Female	UNK Intravenous / UNK Peptic Ulcer	**Injection site pruritus** **Injection site erythema** UNK Recovered	Patient experienced pruritus and erythema at injection site. Concomitant medication included ondansetron. Patient recovered. **Company comment**: Injection site pruritus and erythema are labelled events in the Nexium IV USPI.
2008UW03639 US / HCP 59 years / Male	UNK / UNK Intravenous / UNK GI Bleed	**Application site reaction** UNK UNK	Patient developed puffy infiltrate at application site. Concomitant medications included ciprofloxacin, dopamine and nadolol. **Company comment**: Limited information available to assess. Injection site reaction is labelled in the Nexium IV USPI. Extravasated dopamine is known to cause tissue necrosis and sloughing at the site. The outcome is unknown.

* = Serious adverse event, UNK = Unknown, N/A = not applicable, HCP = Health care professional, US = United States, USPI = United States Package Insert
(This information is from Post-Marketing Report submitted by the Applicant)

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/s/

Anil K Nayyar
11/17/2008 10:59:09 PM
MEDICAL OFFICER

Hugo Gallo Torres
11/18/2008 09:58:11 AM
MEDICAL OFFICER
MTL agrees with MO conclusions/RFRA: data from single trial are weak; replication needed. Sponsor needs to identify continuos infusion dose/regimen that produces required sustained PD effect and test that d/r in a clinical trial that includes US sites.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

PRODUCT QUALITY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div II, Branch VI HFD-180	**21-689/ S-014**

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Applicant name: AstraZeneca LP Address: 1800 Concord Pike PO Box 8355 Wilmington, DE 19803-8355	**CBE-30** Letter date: 14 December 2012 Stamp date: 14 December 2012 Received by reviewer: 03 January 2013 PDUFA due date: 14 June 2013

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
NEXIUM®	esomeprazole sodium	

8. SUPPLEMENT PROVIDES FOR:
A new indication (efficacy supplement)

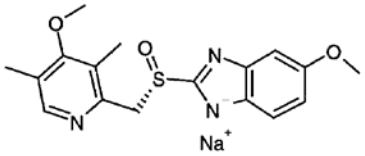
9. PHARMACOLOGICAL CATEGORY:	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Short-term treatment of GERD patients with a history of erosive esophagitis	Rx	
12. DOSAGE FORM	**13. POTENCY**	
IV for injection	20 mg and 40 mg	

14. CHEMICAL NAME AND STRUCTURE

Chemical name: (S)-5-methoxy-2[[(4-methoxy-3,5dimethyl-2-pyridinyl)-methyl]sulfinyl]-1 H-benzimidazole sodium,

Formula: $C_{17}H_{18}N_3O_3SNa$

M.W. 367.4



15. COMMENTS

This submission is a response to a CR letter. As indicated in a memorandum drafted by Dr. M. Kowblansky on 1 January 2013, no change has been proposed in this supplement in comparison with the current approved labeling (approved on 9 October 2012). This supplement, therefore, is recommended for approval from a CMC perspective.

16. CONCLUSION AND RECOMMENDATION

Approval

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Yong Wang	See appended electronic signature sheet	June 5, 2013

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

AP

Chemistry Review Notes

This is an efficacy re-submission that provides for a new indication for the drug product: (b) (4) risk reduction of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. There are no CMC-related changes proposed in the supplement and the product remains as previously approved, containing either 20mg or 40 mg of omeprazole base per vial. The supplement was originally submitted in 2008 and was NOT approved at that time because of clinical deficiencies. The complete response was issued on 11 November 2008. The company resubmitted this application and provided response to the deficiencies in September of 2010. The Agency issued a Complete Response Letter on June 2011.

The current submission, dated December 14, 2012, is a response to the most recent CR letter dated June 2011. In the supplement, the applicant provided a draft labeling. There is no new CMC information provided in this submission.

Comments: As indicated in a memorandum drafted by Dr. M. Kowblansky on 1 January 2013, no change has been proposed in this supplement in comparison with the current approved labeling (approved on 9 October 2012). This supplement, therefore, is recommended for approval from a CMC perspective.

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/s/

YONG WANG
06/05/2013

THOMAS F OLIVER
06/06/2013

Chemist Review: # 1	**1. Division:** ONDQA Division IV, Branch VIII and HFD-180	2. **NDA Number** 21-689

3. Name and Address of Applicant: AstraZeneca LP 1800 Concord Pike P. O. Box 8355 Wilmington, DE 19803-8355	**4. Supplement(s):** **Number:** SE1-014 dated 29-MAY-2008 **Date(s):** User Fee Date: 28-NOVEMBER-2008
5. Name of Drug: Nexium® IV (esomeprazole sodium) for Injection	**6. Nonproprietary name:** Esomeprazole sodium for injection

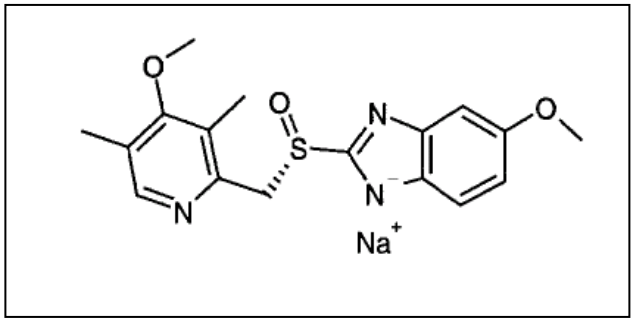
7. Supplement Provides for a new indication (efficacy supplement)	**8. Amendment(s):** None that concern CMC

9. Pharmacological Category: Short-term treatment of GERD patients with a history of erosive esophagitis	**10. How Dispensed:** Rx	**11. Related Documents:** NA
12. Dosage Form: powder for injection	**13. Potency:** 20 and 40 mg per vial	

14. Chemical Name and Structure: Esomeprazole sodium (USAN 2003), $C_{17}H_{19}N_3NaO_3S$, 368.41 g/mol

CAS number 161796-78-7

Structure:



15. Comments: This efficacy (SE1) supplement provides a new indication for the drug product, namely, (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

The supplement proposes the use of the existing (approved) drug product. No CMC-related labeling changes are provided (Description, How Supplied sections). The proposed dose is available from the currently marketed product. The only CMC-related review issue involves Environmental Assessment (EA), due to the possibility that action on this supplement could increase use of the product.

The supplemental application was consulted to HFD-003 (Raanan Bloom, Ph.D.) for EA assessment and evaluation.

The supplement was reviewed with the recommendation of FONSI (Finding of No Significant Impact). See EA review for NDA 21-689/SE1-014, dated 14-OCTOBER-2008, R. Bloom, Ph.D., reviewer.

Thus, from the standpoint of CMC, this supplement may be approved. This supplement is OND-controlled.

16. Conclusions and Recommendations: Recommend approval.

17. Name: **David B. Lewis, Ph.D., Chemist**	**Signature:**	**Date: 30-OCT-2008**
18. Concurrence: **Hasmukh Patel, Ph.D., Branch Chief** **ONDQA/DPME/Branch VIII**	**Signature:**	**Date:**

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/s/

David Lewis
10/30/2008 11:02:12 AM
CHEMIST
Recommend approval from standpoint of CMC.

Hasmukh Patel
10/30/2008 02:33:21 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

ENVIRONMENTAL ASSESSMENT

FINDING OF NO SIGNIFICANT IMPACT

NDA 021-689 S-014

Nexium I.V. Injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

This supplement requests approval of Nexium® (esomeprazole magnesium) Injection for the (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. Nexium for Injection will be used primarily in hospitals throughout the United States. In support of its supplemental new drug application, AstraZeneca LP prepared an Environmental Assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Esomeprazole magnesium is a chemically synthesized drug currently approved for treatment of gastric esophageal reflux disease and maintenance and healing of erosive esophagitis. Esomeprazole is the *S*-enantiomer of the racemate omeprazole. Due to the similarities between esomeprazole and omeprazole, omeprazole is included in evaluating the environmental characteristics of esomeprazole.

Esomeprazole magnesium and its metabolites may enter the aquatic environment from patient use and disposal. In the aquatic environment, both esomeprazole and omeprazole are likely to be rapidly degraded abiotically. The toxicity of esomeprazole magnesium to environmental organisms was characterized. The results indicate that the compound and its metabolites are not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

At U.S. hospitals, clinics, and pharmacies, empty or partially empty packages will be disposed of in accordance to the facility's procedures. Empty or partially empty containers from homes of patients will typically be disposed of by a community's solid waste management system which could include landfills, incineration and/or recycling.

No adverse effects are anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places. The Center for Drug Evaluation and Research has concluded that no adverse environmental effects are expected from the use and disposal of this product. The information provided supports the conclusion that a Finding of No Significant Impact (FONSI) is appropriate.

PREPARED BY:

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Attachment: Environmental Assessment (Confidential Appendices Removed)

AstraZeneca

Environmental Assessment	
Drug Substance	Esomeprazole
Document No.	GI.000-138-437
Date	18 April 2008

Environmental Assessment of Esomeprazole

Author:

Gisela Holm, PhD
Ecotoxicologist
AZ SHE, Operations

TABLE OF CONTENTS PAGE

1. DATE

18 April 2008

2. NAME OF APPLICANT/PETITIONER

AstraZeneca LP

3. ADDRESS

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

4. DESCRIPTION OF PROPOSED ACTION

4.1 Requested approval

AstraZeneca LP is filing a supplemental NDA pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Nexium® for Injection, filled in 5 ml glass vials with bromobutyl rubber stoppers and aluminium caps with polypropylene flip-off seals. An environmental assessment (EA) is being submitted pursuant to 21 CFR part 25. The EA is compiled in accordance with 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

4.2 Need for action

Nexium for Injection is intended to be used in the treatment of various gastric acid-related disorders.

4.3 Locations of use

Usage of Nexium for Injection will primarily occur in hospitals throughout the United States.

4.4 Disposal sites

Empty or partially empty packages from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy, or clinic procedures.

5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

See 3.2.S.1.1 Nomenclature and 3.2.S.1.2 Structure in Module 3.

5.1 Nomenclature

5.1.1 Established name (U.S. Adopted name - USAN)

Esomeprazole sodium

5.1.2 Brand/Proprietary name/tradename

NEXIUM

5.1.3 Chemical names

5.1.3.1 Chemical abstracts (CA) index name

1*H*-Benzimidazole, 5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-, sodium salt

5.1.3.2 Systematic chemical name (IUPAC)

Sodium 5-methoxy-2-{(*S*)[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benzimidazol-1-ate

5.2 Chemical abstracts service (CAS) registration number

161796-78-7

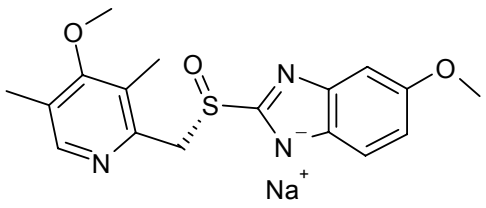
5.3 Molecular formula

$C_{17}H_{18}N_3O_3SNa$

5.4 Molecular weight

367.4 g/mol (esomeprazole sodium)
345.4 g/mol (esomeprazole)

5.5 Structural (graphic) formula



6. ENVIRONMENTAL ISSUES

Esomeprazole is the *S*-enantiomer of the racemate omeprazole. Due to the similarities between esomeprazole and omeprazole, omeprazole is included in evaluating the environmental characteristics of esomeprazole.

6.1 Environmental Fate of Released Substances

6.1.1 Identification of Substances of Interest

Esomeprazole is the *S*-enantiomer of the racemic omeprazole. Esomeprazole is eliminated almost completely by metabolism, as < 1% of the dose can be recovered in the urine as intact drug. The metabolites are mainly renally excreted (approx. 80%) whereas the remaining 20% are excreted via the faeces (Appendix I - **Confidential**). The metabolism of esomeprazole is extensive in that more than 10 metabolites are excreted, all representing less than 10% of the dose given.

The pharmacological effect of two renally excreted metabolites, hydroxy omeprazole (H 195/80) (Fig. 1) and the corresponding carboxylic acid (omeprazole acid, H 193/48) (Fig. 2) was tested in vitro (Appendix II - **Confidential**). The two metabolites represent 5 and 2.5% of the given dose, respectively. For these studies the racemic synthetic metabolites were used, and their effects were compared to that of omeprazole, the racemate. Both were about 100 times less potent than omeprazole and are unlikely to produce significant antisecretory effects in vivo. As omeprazole and esomeprazole are equipotent with respect to pharmacological effect in vitro (Appendix III - **Confidential**), their metabolites can also be expected to be equipotent, irrespective of whether they are formed from the racemate or the pure enantiomer. Thus, both metabolites can be expected to be 100 times less potent than each respective parent compound.

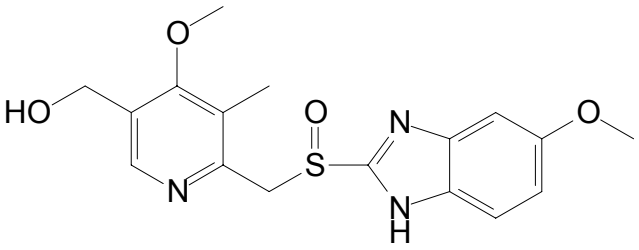


Figure 1. Structural formula of hydroxy omeprazole (H 195/80)

The chemical name for hydroxy omeprazole is: 5-methoxy-2-[[(4-methoxy-3-methyl-5-hydroxymethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole.

CAS numbers: 92340-57-3 (racemate)
196489-27-7 (*S*-enantiomer)
196489-26-6 (*R*-enantiomer)

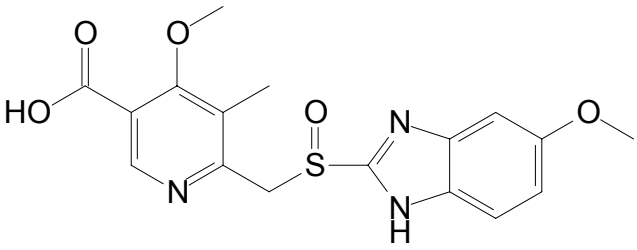


Figure 2. Structural formula of omeprazole acid (H 193/48).

The chemical name for omeprazole acid is: 5-methoxy-2-[[(5-carboxy-4-methoxy-3-methyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole.

CAS numbers: 120003-72-7 (neutral form)
120003-84-1 (di-sodium salt)

All other identified metabolites are equally or more hydrophilic (Appendix I - **Confidential**) than those tested in vitro, which means that they are not likely to pass through cell membranes and bind to intracellular receptors. Considering the hydrophilicity of the metabolites, and that they all are structurally related to those tested, their contribution to the antisecretory effect in vivo is expected to be insignificant.

In summary, esomeprazole sodium is almost completely metabolised in the body and the resulting metabolites are excreted in urine (80%) and faeces (20%). Two major metabolites are ~100 times less potent than the parent compound and other metabolites are equally or more hydrophilic. Most of the metabolites are predicted to enter the aquatic environment. Only a minor part of the used drug will be emitted as the parent compound.

6.1.2 Physical and Chemical Characterization

See 3.2.S.1.3 'General Properties' in Module 3.

Water solubility

300 mg/L (esomeprazole) at pH 7
Freely soluble (10^5-10^6 mg/L) (esomeprazole sodium)

Dissociation constants (pKa)

pKa = 8.8 (benzimidazole)
pKa = about 4 (pyridinium ion)

In a neutral aquatic environment, the drug substance exists as esomeprazole.

Octanol/Water Partition Coefficient

log K_{ow} (esomeprazole) = 2.2 at pH 7

Vapour pressure

Not determined. Esomeprazole is a solid and hence its vapour pressure is assumed to be very low ($<10^{-6}$ Pa).

6.1.3 Environmental Depletion Mechanisms

6.1.3.1 Aerobic biodegradation

The ready biodegradability of omeprazole has been investigated (OECD 301C) (Appendix IV - **Confidential**). In this test, aerobic microorganisms from a sewage treatment works are used to investigate their potential to easily degrade a substance. The results showed that omeprazole is:

Not readily biodegradable: $BOD_{28}/ThOD < 0.6$

Therefore, biodegradation can not be regarded as a rapid depletion mechanism for omeprazole. Since esomeprazole is an enantiomer of omeprazole, it can be assumed that esomeprazole is not readily biodegradable either. However, this does not necessarily indicate that omeprazole and esomeprazole are non-biodegradable, and further testing would be required to establish the potential of the compounds to degrade under more lenient conditions.

6.1.3.2 Chemical stability (acidic degradation)

The stability of esomeprazole in aqueous buffer solutions has been investigated. The sample solutions were protected from light. The half-life at 25°C (pH = 6.8) is about 20 hours, whereas the corresponding figure at 37°C is about 10 hours (Appendix V - **Confidential**). The half-life for the racemate omeprazole at 20°C (pH = 7) is about 30 hours (Appendix VI - **Confidential**). The degradation rate is assumed to be the same for the enantiomer and the racemate.

The data indicate that esomeprazole and omeprazole are rapidly degraded at 25°C, whereas the depletion process is somewhat slower at lower temperatures.

Adsorption to sludge

The adsorption and desorption to sludge was assessed according to the OPPTS guideline 835.1110 (Appendix VII- **Confidential**). The $K_{d(ads)}$ was 48, indicating that esomeprazole is likely to partition into the aqueous phase during wastewater treatment. The $K_{d(des)}$ was 242, however the variability was large (-1147 to 3444) due to the limited adsorption and desorption.

6.1.4 Environmental Concentrations

The Expected Introduction Concentration (EIC) is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole. See Appendix VIII – **Confidential.**

6.1.4.1 Summary

Esomeprazole sodium is almost completely metabolised after administration and the resulting metabolites are subsequently excreted in urine (~80%) and faeces (~20%). Based on the physico-chemical properties of esomeprazole, (Kow = 2.2, solubility = 300 mg/L, vapour pressure $<10^{-6}$ Pa), as well as the low measured adsorption to sludge, it is predicted that most of the parent compound (esomeprazole) will be partitioned into the aqueous phase during wastewater treatment. In a neutral aquatic environment, the drug substance exists as esomeprazole.

By analogy, since the major metabolites are equally or more hydrophilic than the parent compound it is expected that most of the metabolites will also be partitioned to the water phase and eventually target the aquatic environment.

In the aquatic environment, esomeprazole is likely to be rapidly degraded abiotically. Data indicate that both esomeprazole and omeprazole are rapidly degraded at 25°C in darkness, whereas the degradation rate is somewhat slower at lower temperatures. There is no evidence to suggest that biodegradation will be significant.

Only a small fraction is predicted to adsorb to sewage sludge and hence it is not expected that a significant amount will enter the terrestrial environment.

6.2 Environmental Effects of Released Substances

Ecotoxicological studies were performed with esomeprazole sodium and omeprazole sodium.

The following ecotoxicological studies were performed with esomeprazole sodium:

Green alga, *Selenastrum capricornutum*

The toxicity of esomeprazole sodium to green alga, (*S. capricornutum*) was assessed according to the OECD guideline 201 (Appendix IX - **Confidential**).

Based on the area under the growth curve (0 to 72 hours):

No observed effect (P=0.05) concentration (NOEC) = 3.9 mg/L
Median effective concentration, biomass (E_bC_{50}) = 19 mg/L

Based on the growth rate (0 to 72 hours):

NOEC (P=0.05) = 8.4 mg/L
Median effective concentration, growth rate (E_rC_{50}) = 85 mg/L

Water-flea, *Daphnia magna*

The long-term toxicity to *D. magna* was assessed according to the FDA EA Technical Assistance Document 4.09 (Appendix X - **Confidential**).

No observed effects on either reproduction or surviving adult length at 10 mg/L. Therefore, based on reproduction and length (21 days):

NOEC = 10 mg/L

Fathead minnow (*Pimephales promelas*)

The long-term toxicity to early life stages of fathead minnow was assessed according to OECD guideline 210 (Appendix XI - **Confidential**).

Based on hatch, survival, length and dry weight at 32 days, the following results were obtained:

NOEC (32 d) = 1.0 mg/L

Lowest observed effect concentration (LOEC) (32 d) = 3.2 mg/L

***Chironomus riparius* (freshwater midge)**

The long-term toxicity to the sediment dwelling organism *Chironomus riparius* was assessed according to the OECD guideline 218 (Appendix XII).

NOEC = 400 mg/kg (dry weight)

LOEC = 1000 mg/kg (dry weight)

The following ecotoxicological studies were performed with omeprazole sodium:

Activated sludge, respiration inhibition test

The respiration inhibition of activated sludge was assessed according to guideline OECD 209 (Appendix IV - **Confidential**).

3 h EC_{50} > 100 mg/L

No inhibition was observed at concentrations up to 100 mg/L.

Green alga, *Selenastrum capricornutum*

The toxicity of omeprazole sodium to green alga, (*S. capricornutum*) was assessed according to the OECD guideline 201 (Appendix XIII - **Confidential**).

Based on the area under the growth curve (0 to 72 hours):

No observed effect (P=0.05) concentration (NOEC)	< 1.81 mg/L
Median effective concentration, biomass (E_bC_{50})	= 30.1 mg/L

Based on the growth rate (0 to 72 hours):

NOEC (P=0.05)	= 1.81 mg/L
Median effective concentration, growth rate (E_rC_{50})	> 75.9 mg/L

Water-flea, *Daphnia magna*

The acute toxicity of omeprazole sodium to *Daphnia magna* was assessed according to guideline OECD 202, Part I (Appendix XIV- **Confidential**).

48 h EC_{50} >100 mg/L
48 h NOEC = 50 mg/L
48 h LOEC = 100 mg/L

Zebrafish (*Danio rerio*, former *Brachydanio rerio*)

The acute toxicity of omeprazole sodium to zebrafish was assessed according to OECD 203 (Appendix XV - **Confidential**).

96 h LC_{50} = 41.9 mg/L
96 h NOEC = 23.2 mg/L

6.2.1 Tiered Assessment

No rapid, complete depletion mechanism has been identified for esomeprazole and omeprazole. However, the result from the microbial inhibition test above indicates that the drug substances do not inhibit respiration of activated sludge microorganisms. Therefore, they are not thought to disrupt wastewater treatment processes. Furthermore, as the log K_{ow} is <3.5 (see 6.1.2 Physical and Chemical Characterization), the compounds are not likely to bioaccumulate in aquatic organisms, and Tier 1 is justified.

However, since chronic data are available for fish, *Daphnia magna* and microalga, a Tier 3 assessment has been undertaken, which means an assessment factor of 10 is justified. The most sensitive endpoint amongst the chronic test species was established in the fathead minnow test. However, since no EC_{50} was generated in this study, the LOEC has been used as a worst case.

32 days LOEC = 1000 µg/L

LOEC/EIC (Appendix VIII - **Confidential**) = 1000/EIC >10 (assessment factor), and no effects were observed at MEEC, i.e. no further testing is needed.

6.3 Summary of Environmental Fate and Effects

The intended use of esomeprazole (and omeprazole) will result mainly in metabolites entering the environment, since it is almost completely metabolised after administration. Approximately 80% of the metabolites are excreted in the urine and 20% in the faeces. The metabolites are predicted to partition to the aqueous phase and eventually target the aquatic environment via sewage treatment.

In the aquatic environment, both esomeprazole and omeprazole are likely to be rapidly degraded abiotically at a neutral pH, 25°C, whereas the degradation rate is somewhat slower at lower temperatures. There is no evidence to suggest that biodegradation will be significant.

Only a small fraction is predicted to adsorb to sewage sludge and hence exposure to the terrestrial environment is not expected to be significant.

In the risk assessment, the excreted metabolites were assumed to exhibit the same ecotoxicity as the parent compound, since the pharmacological effects for most of the metabolites are not known. This is considered to represent a pragmatic worst case.

The most sensitive endpoint (the LOEC for all endpoints in the fathead minnow study) in the chronic ecotoxicological tests, and an EIC taking no metabolism into account (Appendix VIII - **Confidential**), are used in the risk assessment

The EIC is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole.

LOEC/EIC = 1000/EIC >10 (assessment factor)

In conclusion, since the ratio of the LOEC for the most sensitive of the chronic test organisms, to the expected introduction concentration is larger than the assessment factor, no adverse environmental effects are anticipated as a consequence of the use of esomeprazole and omeprazole.

7. MITIGATION MEASURES

No adverse environmental effects are anticipated due to the use of esomeprazole and omeprazole. Therefore, no mitigation measures are needed.

8. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action. Therefore, no alternatives to the proposed action will be proposed.

9. LIST OF PREPARERS

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Persons consulted:

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Testing laboratory:

Brixham Environmental Laboratory, AstraZeneca, Brixham, UK

10. APPENDICES

10.1 Nonconfidential Appendices

10.1.1 Data Summary Table

DATA SUMMARY **TABLE** FOR ESOMEPRAZOLE, AND OMEPRAZOLE WHERE RELEVANT	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	300 mg/L (esomeprazole) at pH 7
Dissociation Constants	pKa = 8.8 (benzimidazole) pKa = about 4 (pyridinium ion)
Log Octanol/Water Partition Coefficient (log K_{ow})	log K_{ow} = 2.2 at pH 7
Vapour Pressure or Henry's Law Constant	No data. Presumed to be very low.
Sorption / Desorption (K_{oc})	No data
DEPLETION MECHANISMS	
Chemical stability (protected from light)	t½ at 25°C (pH = 6.8) approx. 20 hours
Adsorption/desorption to sludge	Kd (ads) = 48, Kd (des) = 242
Aerobic Biodegradation	Not readily biodegradable (BOD_{28}/ThOD <0.6)
Soil Biodegradation	No data
Photolysis	No data
Metabolism	Almost completely metabolised, <1% of the dose can be recovered in the urine as intact drug

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	No inhibition up to 100 mg/L (ppm) (omeprazole Na)
Acute Toxicity	**Water flea** (*D. magna*) (omeprazole Na): 48 h EC50 >100 mg/L 48 h NOEC = 50 mg/L **Zebrafish** (*D. rerio*) (omeprazole Na) 96 h LC50 = 41.9 mg/L 96 h NOEC = 23.2 mg/L
Chronic Toxicity	**Esomeprazole Na studies** **Green alga** (*S. capricornutum*) Biomass 72 h NOEC = 3.9 mg/L Biomass 72 h EC50 = 19 mg/L Growth rate 72 h NOEC = 8.4 mg/L Growth rate 72 h EC50 = 85 mg/L **Water flea** (*D. magna*) Reproduction and length, 21 d NOEC = 10 mg/L **Fathead minnow** (*P. promelas*) Hatch, survival, length and dry weight, 32 d NOEC = 1.0 mg/L 32 d LOEC = 3.2 mg/L ***Chironomus riparius*** (freshwater midge) Emergence 28 d NOEC = 400 mg/kg (dry weight) 28 d LOEC = 1000 mg/kg (dry weight) **Omeprazole Na study** **Green alga** (*S. capricornutum*) Biomass 72 h NOEC <1.81 mg/L Biomass 72 h EC50 = 30.1 mg/L Growth rate 72 h NOEC = 1.81 mg/L Growth rate 72 h EC50 >75.9 mg/L

10.2 Confidential Appendices

(b)(4)

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/s/

Jon E. Clark
11/18/2008 09:45:07 AM

Moheb Nasr
12/10/2008 02:41:29 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: October 14, 2008

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Teshara G. Bouie
OPS/ONDQA/DPM

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: **NDA 021-689 SE1-014: Nexium I.V. Supplement**

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Background

This environmental assessment (EA), dated April 18, 2008, supports a new drug application supplement for Nexium® I.V. (esomeprazole sodium) for Injection for (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers Nexium is currently approved for treatment of Gastroesophageal Reflux Disease (GERD), healing of erosive esophagitis, maintenance of healing of erosive esophagitis, symptomatic GERD; risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. Nexium for Injection use will primarily occur in hospitals throughout the United States. The EA was prepared in accordance with 21 CFR Part 25 by AstraZeneca LP.

Discussion

Esomeprazole is the S-enantiomer of the racemate omeprazole. Due to the similarities between esomeprazole and omeprazole, omeprazole is included in evaluating the environmental characteristics of esomeprazole.

Esomeprazole is extensively metabolized by humans. Esomeprazole and its metabolites are predicted to partition to the aqueous environment. Since the activity of many of the metabolites is unknown, the firm assumed the metabolites exhibit the same ecotoxicity as the parent compound. This is the worst case scenario, as the two studied metabolites showed activity 100 fold less than the parent compound, and the other known metabolites would be predicted to have a similarly low activity.

Environmental effects data submitted include ecotoxicological studies of fish, daphnia, and algae, and showed that the most sensitive species tested is the zebrafish. Chronic data are also submitted with this supplement. (b) (4) In addition, there are no observed effects at the MEEC.

Previous adequate EAs submitted for Nexium (NDA 21-153 and 22-101) did not provide chronic data. All other environmental fate and effects data are the same. Refer to the previous EA reviews for additional information.

With the availability of chronic data for fish, *Daphnia magna* and microalga, a Tier 3 assessment has been undertaken. The most sensitive endpoint for the chronic test species was established in the fathead minnow. However, since no EC_{50} was generated in this study, the NOEC has been used as a worst case value (32 days NOEC = (b) (4) µg /L): NOEC/EIC = (b) (4) (chronic toxicity data assessment factor) and effects were not observed at the MEEC; therefore, according to CDER guidance, no further testing is required. (Note: the EA erroneously states that the *LOEC* = (b) (4) µg /L. According to the tabular information provided this should be the NOEC = (b) (4) µg /L. This error does not change the conclusions of this review).

This assessment indicates that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

As reported in this EA, the total quantity of esomeprazole and omeprazole required for all products manufactured by AstraZeneca with the addition of this supplement in any of the next 5 years is expected to be (b) (4) kg/yr. The calculated EIC is (b) (4) µg/L (ppb). This is a slight increase from previous estimates (production volume: (b) (4) kg/yr; EIC = (b) (4) µg /L) provided in the September 1, 2006 EA (NDA 21-153)

A Finding of No Significant Impact (FONSI) is recommended.

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/s/

Raanan Bloom
10/14/2008 10:03:49 AM
ENV ASSESSMENT

Jon E. Clark
11/18/2008 09:44:49 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	21689
Supporting document/s:	0197 (S-014)
Applicant's letter date:	December 14, 2012 (Resubmission)
CDER stamp date:	December 14, 2012
Product:	Nexium (esomeprazole sodium) For Injection
Indication:	(b) (4) risk reduction of bleeding of bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer.
Applicant:	AstraZeneca, Wilmington, DE
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Sushanta K. Chakder, Ph.D.
Supervisor:	Sushanta K. Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Stacy Barley, RN.

Submission Contents: Response to the FDA Complete Response letter, dated June 16, 2011 for Nexium IV For Injection for a new indication - (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer.

Background:
Nexium IV, a proton pump inhibitor is currently approved for the treatment of gastroesophageal reflux disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate. The applicant submitted a Supplement to the NDA (dated May 29, 2008) for a new indication of Nexium I.V: (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer, (b) (4)

(b) (4) A complete response (CR) to the NDA supplement was issued on November 26, 2008 due to insufficient clinical information. A second CR was issued on June 16, 2011. In the current submission, the Applicant did not submit any nonclinical information for esomeprazole sodium. Intravenous toxicology studies conducted with esomeprazole sodium and reviewed in original NDA submission, were used to support the proposed dosing regimen.

Executive Summary:

The proposed dosing regimen for Nexium IV for this indication, (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer is 80 mg IV infusion over 30 minutes followed by 8 mg/h continuous IV infusion for the next 71.5 hours. Thus, the proposed i.v. dose is 4.5 mg/kg/24 hr on the first day. Esomeprazole sodium was studied in intravenous toxicity studies in rats and dogs. In rats, intravenous doses of 18 to 36 times (3-6 times the proposed clinical dose, based on body surface area) the proposed continuous i.v. infusion daily clinical dose, was well tolerated. In dogs, esomeprazole sodium was tolerated well following continuous intravenous infusion for 14 or 28 days at doses several fold higher than the proposed daily i.v. infusion dose.
In a 2-week continuous i.v. infusion study in dogs (Study #TDD1316), dose levels of 120 and 240 mg/kg was tolerated without any deaths or treatment-related adverse cardiovascular effects. The 120 and 240 mg/kg/doses are about 27 and 54 times (14 and 28 times the clinical dose, based on body surface area) the proposed daily clinical i.v. dose.

In a 1-month continuous infusion study in dogs (Study (b)(4) 56859/SR 01333-01), groups of animals were administered the vehicle or esomeprazole sodium at dose levels of 30, 86 and 170 mg/kg/day (10, 250 and 500 µmole/kg/day). There were a total of 8 mortalities in all groups including the control group (2, 1, 2 and 3 animals were sacrificed pre-terminally from the control, low, mid and high dose groups, respectively). Thus, the mortalities were not dose-related, and were also observed on the control group. No treatment-related effects on the QT or QTc parameters were observed in any group. A slight decrease in heart rate was observed in males in Week 4. The incidences of redness and inflammation at the site were similar for the control and low dose group, and higher in the mid and high dose groups. Thrombus formation in the lung along with pleural inflammation and fibrosis and hemorrhage was observed in 0, 1, 1 and 2 males and 1, 1, 3 and 2 females from the control, low, mid and high dose groups, respectively. The 35 mg/kg/day dose was the highest tolerable dose of esomeprazole in this continuous infusion study in dogs. The 35 mg/kg dose in dogs is about 8 times (4.2 times the clinical dose, based on body surface area) the proposed daily i.v. clinical dose.

Labeling:

No changes in the nonclinical sections (Section 8.1 and Section 13.1) of the existing label have been proposed. (b) (4)

(b) (4)

Summary of Nonclinical Toxicology Studies:

Intravenous toxicity studies in rats:

In a 28-day IV toxicity study in Sprague-Dawley rats (Study (b)(4) 56771), groups of male animals were administered IV doses of esomeprazole at 48, 86 or 160 mg/kg/day (140, 250 or 450 µmole/kg/day), and the female animals were administered 26, 52 or 100 mg/kg/day (75, 150 or 300 µmole/kg/day) doses. There were no mortalities in any group. The doses of 160 and 100 mg/kg/day were the tolerated doses in males and females, respectively. CNS depression, decreased motility, rigidity, ataxia and convulsions (only at the high dose) were observed at the mid and high doses. The target organs of toxicity were the CNS, stomach (Chief cell hypertrophy), Kidney (chronic nephropathy) and the site of injection. The 160 and 100 mg/kg doses in rats are approximately 36 and 22 times the proposed daily i.v. clinical dose, respectively.

In a second 28-day toxicity study in rats (Study #57465SR), esomeprazole sodium, at i.v. doses of 4 and 80 mg/kg/day (12 and 230 µmole/kg/day) was tolerated well. The target organs of toxicity were the stomach, kidney and the injection site, and the 4 mg/kg/day dose was the NOEL. The Cmax and AUC values at the 80 mg/kg dose were 224 µmole/L and 240 µmol. h/L, respectively. The 80 mg/kg dose in rats is about 18 times the proposed daily clinical dose.

Intravenous toxicity studies in dogs:

In a 28-day i.v. toxicity study in Beagle dogs (Study (b)(4) 56859), groups of animals were administered 4.8, 10 and 22 mg/kg/day (14, 30 and 65 µmole/kg) doses of esomeprazole sodium by slow injections (30 min/day) through an implanted catheter. Treatment-related excessive scratching and redness at the injection site occurred with higher incidences than the controls in animals administering the mid and high doses. There were no deaths in any group. In the stomach, reduced sized parietal cells within the fundic mucosa, interstitial edema and denser eosinophilic cytoplasm were observed. The NOAEL was not established because of the stomach effects at all doses, and the 10 mg/kg/day dose was the tolerated dose.

In a 2-week continuous i.v. infusion MTD study in dogs (Study #TDD1316), dose levels of 120 and 240 mg/kg was tolerated without any deaths or treatment-related adverse cardiovascular effects. Emesis, soft fluid feces, decreased activity, subdued behavior and ataxia were observed

at these doses. The 120 and 240 mg/kg/doses are about 27 and 54 times the proposed daily clinical i.v. dose.

In a 1-month continuous infusion study in dogs (Study (b)(4) 56859/SR 01333-01), groups of animals were administered the vehicle or esomeprazole sodium at dose levels of 30, 86 and 170 mg/kg/day (10, 250 and 500 µmole/kg/day). The EKG tracings of all dogs were recorded prior to start of dosing and 2 hr after the daily change of infusion bags on the second day and towards the end of Week 4 of dosing (Days 25, 26 or 27). One male each from the mid and high dose groups and one female from the high dose group showed decreased activity and sore wet lesions were observed in 1 and 2 animals at 86 and 170 mg/kg/day, respectively. There were a total of 8 mortalities in all groups including the control group (2, 1, 2 and 3 animals were sacrificed pre-terminally from the control, low, mid and high dose groups, respectively). The low dose animal showed bloody vomiting and decreased activity before sacrifice, and other animals were sacrificed because of infection and other welfare reasons. Thus, the mortalities were not dose-related, and were also observed on the control group. No treatment-related effects on the QT or QTc parameters were observed in any group. A slight decrease in heart rate was observed in males in Week 4. The incidences of redness and inflammation at the site were similar for the control and low dose group, and higher in the mid and high dose groups. Gastric Chief cell and parietal cell atrophy was observed at a similar incidence in male and female dog from all groups. Thrombus formation in the lung along with pleural inflammation and fibrosis and hemorrhage was observed in 0, 1, 1 and 2 males and 1, 1, 3 and 2 females from the control, low, mid and high dose groups, respectively. The mean plasma concentrations on days 2 to 28 were 6.04, 10.5 and 24.9 µmol/L in males and 6.43, 15.1 and 15.6 µmol/L in females, respectively. The AUC (days 1-28) were 6640, 6570 and 24600 µmo.hl/L in males, and 4220, 9900 and 10100 µmol.h/Lin females, respectively. The 35 mg/kg/day dose was the highest tolerable dose of esomeprazole in this continuous infusion study in dogs. The 35 mg/kg dose in dogs is about 8 times the proposed daily i.v. clinical dose.

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/s/

SUSHANTA K CHAKDER
07/22/2013

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21,689

SERIAL NUMBER: Efficacy supplement

DATE RECEIVED BY CENTER: June 19, 2008

DRUG NAME: Nexium / Esomeprazole sodium, infusion

INTENDED CLINICAL POPULATION: Re-bleeding patients following endoscopy for acute bleeding gastric or duodenal ulcers.

SPONSOR: AstraZeneca LP
Wayne, PA

DOCUMENTS REVIEWED: EDR – Module 4

REVIEW DIVISION: Division of Gastroenterology Products (HFD-180)

PHARM/TOX REVIEWER: Ke Zhang, Ph.D.

ACTING PHARMACOLOGY TEAM LEADER: David Joseph, Ph.D.

DIVISION DIRECTOR: Donna Griebel, M.D.

PROJECT MANAGER: Ms. Chantal Phillips

Date of review submission to Division File System (DFS):

November 12, 2008

TABLE OF CONTENTS

Executive Summary

1. Recommendations

1.1 Recommendation on approvability

From a preclinical standpoint, approval of Nexium is recommended for the proposed indications.

1.2 Recommendation for nonclinical studies: None.

1.3 Recommendation on labeling: None.

2. Summary of nonclinical findings:

In the 14-day intravenous toxicity study in rats, treatment with esomeprazole at 80 mg/kg/day with and without degradation products (b) (4) and (b) (4) induced clinical signs of toxicity including partly closed eyes, decreased activity, salivation, incoordination, and tremors and increased weights of the liver, stomach, adrenals and kidney. Similar changes were noted for esomeprazole with and without degradation products.

The degradation products (b) (4) and (b) (4) of esomeprazole were negative in the Ames tests. Esomeprazole with and without degradation products (b) (4) and (b) (4) were negative in the in vivo chromosomal aberration test in rats.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21,689
Review number: 01
Sequence number/date/type of submission:
Efficacy supplement / June 19, 2008

Information to sponsor: Yes () No (x)

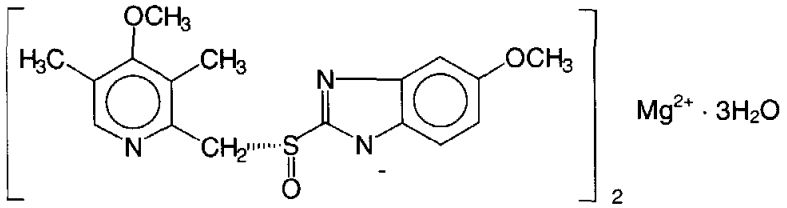
Reviewer name: Ke Zhang, Ph.D.
Division name: Division of Gastroenterology Products
HFD #: 180
Review completion date: November 12, 2008

Drug: Nexium, injection

Generic name: Esomeprazole sodium
Chemical name: Bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate.

Molecular formula/molecular weight: $C_{34}H_{36}N_6O_6S_2Mg\bullet 3H_2O$ / 767.2

Structure:



Relevant INDs/NDAs/DMFs: NDA 21,153 (Nexium oral capsule)

Drug class: Gastric parietal cell H^+/K^+-ATPase inhibitor.

Indication: Nexium injection is indicated for the (b) (4) (b) (4) risk reduction of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Clinical formulation: NEXIUM I.V. for Injection is supplied as a freeze-dried powder containing 20 mg or 40 mg of esomeprazole per single-use vial.

Route of administration: I.V. infusion.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Any information or data necessary for approval of NDA 21,689 that AstraZeneca LP does not own or has a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that AstraZeneca LP does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21,689.

Studies reviewed within this submission:

1. 14-day intravenous toxicity study in rats
2. Ames test with degradation product (b) (4)
3. Ames test with degradation product (b) (4)
4. In vivo chromosome aberration test with esomeprazole with and without degradation products

Studies not reviewed within this submission: None.

2.6.6 TOXICOLOGY

2.6.6.3 Repeat-dose toxicity

Study title: 14-day intravenous toxicity study of esomeprazole with and without degradation products in rats

Study no.: 502501
Conducting laboratory and location:
(b) (4)

Date of study initiation: December 4, 2007
GLP compliance: This study was conducted in compliance with OECD GLP principles.

QA report: yes (x) no ( )
Drug lot #: 113/01, 258212300/2301

Methods: To assess the repeat-dose toxicity of esomeprazole with and without degradation products, esomeprazole was given to Sprague-Dawley rats by intravenous infusion for 30 minutes at 0 and 80 mg/kg/day with and without degradation products (b) (4) (b) (4) and (b) (4) for 14 days. The i.v dose of 80 mg/kg/day was previously tested in rats. The study design is summarized in the sponsor's Table 2 and this table is attached below.

Table 2 Groups and dose levels

Group Number	Number and Sex	Animal Reference Number	Dose Rate (mL/kg*h)	Treatment	Formulation Concentration[a] (mg/mL)	Dose level (mg/kg)	Dose level (µmol/kg)
1	10 M	101-110	20	Saline	0	0	0
	10F	151-154, 165, 156-159, 170					
2	10 M	201-205, 207-210, 216	20	Esomeprazole plus: (b)(4)	7.4 plus :	80[b] plus :	230[b] plus :
	10F	251, 253-255, 262, 256-260					
3	10 M	301-306, 308, 310, 317, 329	20	Esomeprazole	7.9	80[b]	230[b]
	10F	352-355, 361, 356-360					

All doses and concentrations of the test compounds included in this report are expressed in terms of the parent compounds

a Given as the median concentrations during infusion, calculated from the mean concentrations analysed in the pre- and post infusion formulation samples (see Section 6.1), not the nominal concentrations

b The nominal dose of esomeprazole is given. It was not considered necessary to adjust this, as a deviation of ±10% of the intended concentration of the active compound is considered to be acceptable on formulation analysis (see Section 6.1)

c The concentration of the degradation products in the dosing formulation decreased notably (slightly for (b)(4) during infusion (as was expected), and thus these dose levels have been re-calculated using the median concentrations during infusion (see Section 6.1)

Clinical signs of toxicity were observed daily. Body weights and food consumption were determined weekly. Hematology, clinical chemistry, and urinalysis were conducted at termination. Ophthalmological examination was conducted before treatment and at termination. All animals were necropsied at

termination and organ weights were determined. Histopathologic examination was conducted in all animals in all groups. The following tissues or organs were collected, but only a small number of tissues were examined microscopically (see the sponsor's list below).

abnormal tissues
[a]animal identification
adrenals
[a]aorta (thoracic)
[a, b]bone and marrow (sternum)
[a, b]bone (femur)
[a]brain (forebrain, midbrain, cerebellum and medulla oblongata)
[a]cecum
[a]colon
[a]duodenum
[a, f]epididymides
esophagus
[a, c]eyes
[a]harderian gland
heart (including section of aorta)
[a]ileum
infusion site(s)including catheter tip(s)
[a]jejunum
kidneys
[a]lacrimal gland
liver (sample of 2 lobes)
[d]lungs (sample of 2 lobes)
lymph nodes (mandibular, unilateral; mesenteric)
[a, e]mammary gland (inguinal)
[a, c, e]optic nerves
[a]ovaries
[a]pancreas
pituitary
[a]prostate
[a]salivary gland (mandibular, unilateral)
[a]sciatic nerve
[a]seminal vesicles
[a]skeletal muscle
[a]skin (inguinal)
[a]spinal cord (cervical, thoracic and lumbar)
spleen
[g]stomach
[a, f]testes
thymus
[e]thyroid lobes (and parathyroids)
[a]tongue
[a]trachea
[a]urinary bladder
[a]uterus (horns, body and cervix)
[a]vagina

a Retained but not processed
b Bone decalcified prior to sectioning
c Fixed in Davidson's fluid
d Infused with neutral buffered 10% formalin (all animals)
e Examined histopathologically only when present in routine sections of eyes (optic nerves), or skin (mammary gland). At least one parathyroid was examined. One attempt to recut was performed to try to find missing tissues
f Fixed in Bouin's fluid.(all animals)
g At necropsy the stomach was removed, the eosophagus and duodenum cut off, the stomach opened along the greater curvature, rinsed well in saline and then weighed. The stomach was fastened to a paraffin block using pins and subsequently preserved in 10% buffered formalin

Plasma levels of esomeprazole were determined at 5 minutes, 1 or 2 hours after last infusion.

Results:

Mortality: One male from group 3 was found dead on day 14. No particular clinical signs were recorded prior to the death. Two other deaths were due to technical problem during dosing.

Clinical signs: The treatment-related clinical signs of toxicity are summarized in the sponsor's Table 8 and this table is attached below.

Table 8 Incidence of salient clinical signs during the 14-day dosing period

Clinical Sign	Group 1 Total Number days observed (in Total Number of Animals)	Group 2 Total Number Days Observed (in total Number of Animals)	Group 3 Total Number days Observed (in Total Number of Animals)
Males			
Number animals/group	10	10	10
Eye(s) partly closed	5 (3)	17 (7)	18 (7)
Females			
Number animals/group	10	10	10
Eye(s) partly closed	3 (2)	25 (9)	35 (10)
Activity decreased	2 (2)	5 (5)	6 (6)
Salivation	0 (0)	1 (1)	0 (0)
Weakness	0 (0)	2 (2)	1 (1)
Incoordination	0 (0)	1 (1)	1 (1)
Tremor	0 (0)	1 (1)	0 (0)

Body weights: There were no treatment-related changes. The body weights are summarized in the sponsor's Table 12 and this table is attached below.

Table 12 Summary of body weights (g)

Males

Group 1 - Saline
Group 2 - Esomeprazole with degradation products
Group 3 - Esomeprazole without degradation products

Group	Summary information	Day -8	Day -1	Day 7
1	Mean	285.6	298.4	328.8
	SD	10.5	13.7	16.8
	N	10	10	10
2	Mean	286.5	296.8	322.5
	SD	13.4	12.0	13.2
	N	10	10	10
3	Mean	287.7	297.4	328.1
	SD	13.7	9.3	12.4
	N	10	10	10

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 12 Summary of body weights (g)

Females

Group 1 - Saline
Group 2 - Esomeprazole with degradation products
Group 3 - Esomeprazole without degradation products

Group	Summary information	Day -8	Day -1	Day 7
1	Mean	208.8	213.2	230.8
	SD	4.8	8.6	6.6
	N	10	10	10
2	Mean	207.4	213.5	234.3
	SD	4.7	8.8	8.7
	N	10	10	10
3	Mean	205.2	211.0	235.7
	SD	10.8	6.0	10.2
	N	10	10	10

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Food consumption: There were no treatment-related changes.

Ophthalmoscopy: There were no treatment-related changes.

Hematology: There were no treatment-related changes.

Clinical chemistry: Slight increase in serum cholesterol level and decrease in chloride concentration were noted in the treatment groups. The results are summarized in the sponsor's Table 9 and this table is attached below.

Table 9 **Mean (±SD) serum cholesterol and chloride concentrations following 14 days' esomeprazole treatment**

Parameter	Males			Females		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Cholesterol (mg/dL)	86.4 ± 10.4	95.8 ± 7.7*	98.4 ± 5.9**	73.4 ± 13.1	92.1 ± 8.8**	90.6 ± 9.6**
Chloride (mmol/L)	103.2 ± 1.3	101.3 ± 1.1*	101.6 ± 1.8*	104.3 ± 1.5	99.5 ± 2.0***	100.0 ± 1.7***

* P≤0.05 ** P≤0.01 *** P≤0.001

Urinalysis: There were no treatment-related changes.

Gross pathology: There were no treatment-related changes.

Organ weights: Increased organ weights of the liver, stomach, adrenals, and kidney were noted in both esomeprazole groups. The results are summarized in the sponsor's Table 10 and this table is attached below.

Table 10 **Mean absolute and relative (to brain) weights of the stomach, liver, kidney and adrenals in esomeprazole-treated animals (groups 2 and 3)**

Organ[a]		ESO with Degradation Products (Group 2)		ESO without Degradation Products (Group 3)	
		Males	Females	Males	Females
	Number of animals	10	10	9	10
Body weight	Absolute (g)	310.86	219.50	317.96	221.52
Brain weight	Absolute (g)	1.80	1.69	1.82	1.69
Stomach weight	Absolute (g)	2.13	1.90	2.15	1.84
	% Diff (G1)	**20**	**22**	**21**	**18**
	Relative to brain weight (%)	118.01	111.96	117.85	109.24
	% Diff (G1)	**20**	**23**	**20**	**20**
Liver weight	Absolute (g)	8.88	6.27	9.20	6.27
	% Diff (G1)	**10**	**14**	**14**	**14**
	Relative to brain weight (%)	492.22	370.60	505.08	371.85
	% Diff (G1)	**10**	**15**	**12**	**16**
Kidney weight	Absolute (g)	2.25	1.58	2.36	1.64
	% Diff (G1)	5	**8**	**10**	**12**
	Relative to brain weight (%)	124.79	93.36	129.48	97.19
	% Diff (G1)	5	**10**	**8**	**14**
Adrenal weight	Absolute (g)	0.061	0.077	0.058	0.078
	% Diff (G1)	4	**11**	-1	**13**
	Relative to brain weight (%)	3.42	4.52	3.21	4.61
	% Diff (G1)	3	**13**	-3	**15**

a Based on statistical analysis of group means, values highlighted in bold are significantly different from the control group ($P \leq 0.05$); refer to data tables for actual significance levels and tests used.

Histopathology: There were no treatment-related changes.

Plasma levels of esomeprazole: It appears that the plasma level of esomeprazole was higher in females than in males. The plasma level of esomeprazole was similar between esomeprazole groups with and without degradation products. The results are summarized in the sponsor's Table 7 and this table is attached below.

Table 7 **Median (range) plasma concentrations of esomeprazole in rats after 30-minute intravenous infusion of esomeprazole for 14 days**

Group and Sex	Time after Dosing[a]	Plasma Concentrations of Esomeprazole (µmol/L)
2 M[b]	5 minutes	104 (92-125)
	1 hour	3.38 (1.9-3.6)
3 M[c]	5 minutes	101 (87.8-117)
	1 hour	2.17 (0.905-3.74)
2 F[b]	5 minutes	227 (193-282)
	2 hours	17.5 (4.52-44.4)
3 F[c]	5 minutes	223 (198-259)
	2 hours	25.7 (7.73-60.6)

a After the end of infusion
b Esomeprazole with degradation products
c Esomeprazole without degradation products

Conclusion: The treatment with esomeprazole induced clinical signs of toxicity including partly closed eyes, decreased activity, salivation, incoordination, and tremors. The incidence of treatment-related clinical signs was similar with and without degradation products. Weights of the liver, stomach, adrenals and kidney were increased in both esomeprazole groups. There were no treatment-related changes in body weight, food consumption, ophthalmology, urinalysis, gross pathology, or histopathology.

2.6.6.4 Genetic toxicology

Study title: Ames test with (b) (4) a degradation product of esomeprazole
Study report No: 1561BV
Testing Laboratory: Safety Assessment, AstraZeneca R&D Sodertalje, Sweden
Date of study initiation: October 31, 2007
Date of study report: May 13, 2008
GLP Compliance: This study was conducted in compliance with OECD GLP principles.
QA-report: Yes (x) No ()
Drug Batch No.: SN1075013805

Methods: To examine the potential mutagenic effects of (b) (4) the reverse mutation assay (Ames test) was conducted using the pre-incubation method and the plate incorporation method in four

strains of Salmonella typhimurium (TA98, TA100, TA1535, and TA1537) and one strain of E. Coli (WP2uvrA) in the presence and absence of a metabolic activator, S-9 mix from rat liver. The following concentrations were tested: 50, 169, 508, 1690, and 5080 µg/plate with and without S-9 for the plate incorporation method and 50, 100, 199, 299, and 499 µg/plate for the pre-incubation method. Following positive controls were tested (see sponsor's Table 4 below):

Table 4 Positive controls

Positive control chemical	Solvent	Dose per plate		Bacterial strain	Metabolic activation
		µg	µmol		
sodium azide	water	0.50	0.0077	TA1535	-
				TA100	-
2-nitrofluorene	dimethyl sulfoxide	0.50	0.0024	TA98	-
9-aminoacridine	dimethyl sulfoxide	70	0.30	TA1537	-
potassium dichromate	water	25	0.085	E.coli *uvrA*/pKM101	-
2-aminoanthracene	dimethyl sulfoxide	2.0	0.010	TA1535	+
				TA100	+
				TA98	+
		5.0	0.026	TA1537	+
				E.coli *uvrA*/pKM101	+

- Solvent: Acetonitril:HCl
- **Counting method**: The plates were examined and the revertant colony numbers were scored using a Sorcerer Colony Counter.
- **Cytotoxic endpoints**: The condition of the bacterial background lawn was evaluated for evidence of cytotoxicity.
- **Genetic toxicity endpoints/results**: Number of revertant colonies.

Criteria for positive results: The results should be considered positive if the test substance induced a two-fold increase in the mean revertant colonies as compared to the control. This increase should be dose-related and reproducible.

Results:

- Study validation: The positive controls significantly increased the revertant colonies compared to the solvent control.

Study outcome:

Plate incorporation method: Reduction of bacterial growth was noted at concentrations of (b)(4) g/plate and higher. A marginal

increase in revertant colonies occurred in the treatment group. This increase was within the range of historical control values except in TA98 and E.coli uvrA without S9. However, this increase was less than two-fold compared to the solvent control and not clearly dose-dependent. Therefore, the results are considered negative. The study results are presented in the sponsor's Tables 6 and 7 and these tables are attached below.

Table 6 Plate incorporation test - without metabolic activation

Study Number : 1561BV
Experiment : 1561BV_P1 Start date : 2007-11-06 End : 2007-11-09
Test compound : (b)(4) Batch: 006
Solvent : acetonitril/HCl 50/50% v/v

(b)(4)

(Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli uvrA/ pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control											(b) (4)
											(b) (4)
Positive control											(b) (4)

Pos. controls:
TA1535:sodium azide (b) (4) µg, TA100:sodium azide (b) (4) µg, E.coli uvrA/pKM101:potassium dichromate (b) (4) µg,
TA98:2-nitrofluorene (b) (4) µg, TA1537:9-aminoacridine (b) (4) µg
p = Precipitate formed on the plate t = Toxicity

Table 7 Plate incorporation test - with metabolic activation

Study Number : 1561BV
Experiment : 1561BV_P1 Start date : 2007-11-06 End : 2007-11-09
Test compound : (b)(4) Batch: 006
Solvent : acetonitril/HCl 50/50% v/v

(b)(4) (Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli uvrA/ pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control		(b) (4)									
		(b) (4)									
Positive control		(b) (4)									

Pos. controls:
TA1535:2-aminoanthracene (b)(4) µg, TA100:2-aminoanthracene (b)(4) µg, E.coli uvrA/pKM101:2-aminoanthracene (b)(4) µg,
TA98:2-aminoanthracene (b)(4) µg, TA1537:2-aminoanthracene (b)(4) µg
p = Precipitate formed on the plate t = Toxicity

Pre-incubation method: A marginal increase in revertant colonies occurred in the treatment group. The increase was within the range of historical control values except in TA100 with S9. However, the increase was less than two-fold compared to the solvent control and not clearly dose-dependent. The study results are presented in the following sponsor's tables.

Table 8 Liquid pre-incubation test 1 - without metabolic activation

Study Number : 1561BV
Experiment : 1561BV_L1 Start date : 2007-11-13 End : 2007-11-16
Test compound : (b)(4) Batch: 006
Solvent : acetonitril/HCl 50/50% v/v

(b)(4) (Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli uvrA/ pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control		(b)(4)									
		(b)(4)									
Positive control		(b)(4)									

Pos. controls:
TA1535:sodium azide (b)(4) µg, TA100:sodium azide (b)(4) µg, E.coli uvrA/pKM101:potassium dichromate (b)(4) µg,
TA98:2-nitrofluorene (b)(4) µg, TA1537:9-aminoacridine (b)(4) µg
t = Toxicity p = Precipitate formed on the plate

Table 9 Liquid pre-incubation test 1 - with metabolic activation

Study Number : 1561BV
Experiment : 1561BV_L1 Start date : 2007-11-13 End : 2007-11-16
Test compound : (b)(4) Batch: 006
Solvent : acetonitril/HCl 50/50% v/v

(b)(4) (Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli uvrA/ pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control		(b)(4)									
		(b)(4)									
Positive control		(b)(4)									

The historical data are summarized in the following sponsor's tables.

Table B1 Solvent controls Plate-incorporation method

Salmonella/E.coli strains	TA1535		TA100		E.coli *uvrA*/pKM101		TA98		TA1537	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Mean	14	13	103	114	120	151	26	39	10	14
SD	4	3	19	18	8	7	5	6	4	3
Range Min - Max	5 to 28	7 to 28	70 to 178	75 to 189	82 to 168	86 to 211	17 to 41	25 to 54	4 to 29	7 to 31
No. of experiments	207	207	237	237	89	85	232	232	205	204

Table B3 Solvent controls Liquid pre-incubation method

Salmonella/E.coli strains	TA1535		TA100		E.coli *uvrA*/pKM101		TA98		TA1537	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Mean	13	13	101	112	121	192	27	39	10	14
SD	4	3	18	18	7	7	6	6	4	3
Range Min - Max	5 to 26	6 to 24	66 to 154	77 to 151	73 to 180	124 to 269	16 to 52	27 to 56	4 to 28	8 to 25
No. of experiments	93	89	93	92	60	63	93	91	92	88

Similar results were obtained from another study (a non-GLP study #1840NV).

In conclusion, (b)(4) was not genotoxic under the study conditions.

Study title: Ames test with (b)(4), a degradation product of esomeprazole
Study report No: 1618BV
Testing Laboratory: Safety Assessment, AstraZeneca R&D Sodertalje, Sweden
Date of study initiation: October 31, 2007
Date of study report: May 19, 2008
GLP Compliance: This study was conducted in compliance with OECD GLP principles.
QA-report: Yes (x) No ()
Drug Batch No.: SN1076108519

Methods: To examine the potential mutagenic effects of (b)(4) (b)(4) the reverse mutation assay (Ames test) was conducted using the pre-incubation method and the plate incorporation method in four strains of Salmonella typhimurium (TA98, TA100, TA1535, and TA1537) and one strain of E. Coli (WP2uvrA) in the presence and absence of a metabolic activator, S-9 mix from rat liver. The following concentrations were tested: 50.7, 169, 507, 1690, and 5070 µg/plate with and without S-9 for the plate incorporation method and 47.5, 158, 475, 1580, and 4750 µg/plate for the pre-incubation method. The following positive controls were tested (see the sponsor's Table 3 below):

Table 3 Positive controls

Positive control chemical	Solvent	Dose per plate		Bacterial strain	Metabolic activation
		µg	µmol		
sodium azide	water	0.50	0.0077	TA1535	-
				TA100	-
2-nitrofluorene	dimethyl sulfoxide	0.50	0.0024	TA98	-
9-aminoacridine	dimethyl sulfoxide	70	0.30	TA1537	-
potassium dichromate	water	25	0.085	E.coli *uvrA*/pKM101	-
2-aminoanthracene	dimethyl sulfoxide	2.0	0.010	TA1535	+
				TA100	+
				TA98	+
		5.0	0.026	TA1537	+
				E.coli *uvrA*/pKM101	+

- **Negative control**: Dimethyl sulfoxide.
- **Counting method**: The plates were examined and the revertant colony numbers were scored using a Sorcerer Colony Counter.

- **Cytotoxic endpoints:** The condition of the bacterial background lawn was evaluated for evidence of cytotoxicity.
- **Genetic toxicity endpoints/results:** Number of revertant colonies.

Criteria for positive results: The results should be considered positive if the test substance induced a two-fold increase in the mean revertant colonies as compared to the control. This increase should be dose-related and reproducible.

Results:

- Study validation: The positive controls significantly increased the revertant colonies compared to the solvent controls.

Study outcome: The treatment did not significantly increase the number of revertant colonies as compared to the control.

Plate incorporation method: The study results are presented in the sponsor's Tables 5 and 6.

Table 5 Plate incorporation test - without metabolic activation

Study Number : 1618BV
Experiment : 1618BV P1 Start date : 2007-11-09 End : 2007-11-12
Test compound : (b)(4) Batch: SN1076108519
Solvent : dimethyl sulfoxide

(b)(4)

(Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli uvrA/ pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control											(b)(4)
											(b)(4)
Positive control											(b)(4)

Pos. controls:
TA1535:sodium azide (b)(4)µg, TA100:sodium azide (b)(4)µg, E.coli uvrA/pKM101:potassium dichromate (b)(4)µg,
TA98:2-nitrofluorene (b)(4)µg, TA1537:9-aminoacridine (b)(4)g
p = Precipitate formed on the plate

Table 6 Plate incorporation test - with metabolic activation

Study Number : 1618BV
Experiment : 1618BV_P1 Start date : 2007-11-09 End : 2007-11-12
Test compound : (b)(4) Batch: SN1076108519
Solvent : dimethyl sulfoxide

(b)(4) (Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli uvrA/ pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control		(b)(4)									
		(b)(4)									
Positive control		(b)(4)									

Pos. controls:
TA1535:2-aminoanthracene (b)(4) µg, TA100:2-aminoanthracene (b)(4) µg, E.coli uvrA/pKM101:2-aminoanthracene (b)(4) µg,
TA98:2-aminoanthracene (b)(4) µg, TA1537:2-aminoanthracene (b)(4) µg
p = Precipitate formed on the plate

Pre-incubation method: The study results are presented in the sponsor's Tables 7 and 8.

Table 7 Liquid pre-incubation test - without metabolic activation

Study Number : 1618BV
Experiment : 1618BV_L1 Start date : 2007-11-20 End : 2007-11-23
Test compound : (b)(4) Batch: SN1076108519
Solvent : dimethyl sulfoxide

(b)(4) (Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control		(b)(4)									
		(b)(4)									
Positive control		(b)(4)									

Pos. controls:
TA1535:sodium azide (b)(4) µg, TA100:sodium azide (b)(4) µg, E.coli pKM101:Mitomycin C (b)(4) µg, TA98:2-nitrofluorene (b)(4) µg,
TA1537:9-aminoacridine (b)(4) µg
t = Toxicity

Table 8 Liquid pre-incubation test - with metabolic activation

Study Number : 1618BV
Experiment : 1618BV L1 Start date : 2007-11-20 End : 2007-11-23
Test compound : (b)(4) Batch: SN1076108519
Solvent : dimethyl sulfoxide

(b)(4) (Dose/plate)		Bacterial strain and number of revertant colonies per plate									
		TA1535		TA100		E.coli pKM101		TA98		TA1537	
µg	µmol	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Solvent control											(b)(4)
											(b)(4)
Positive control											(b)(4)

Pos. controls:
TA1535:2-aminoanthracene (b)(4) µg, TA100:2-aminoanthracene (b)(4) µg, E.coli pKM101:2-aminoanthracene (b)(4) µg,
TA98:2-aminoanthracene (b)(4) µg, TA1537:2-aminoanthracene (b)(4) µg

In conclusion, (b)(4) was not genotoxic under the study testing conditions.

Study title: In vivo Chromosomal aberration test in rats with and without degradation products of Esomeprazole

Study No: 961721
Testing Laboratory: (b)(4)

GLP Compliance: This study was conducted in compliance with OECD GLP principles.
QA-report: Yes (x) No ()
Drug Batch No.: 113/01 and 258212300/2301

Methods: To examine the potential induction of chromosomal aberrations by the degradation products of esomeprazole, the in vivo chromosomal aberration test was conducted in female rats using esomeprazole with and without the degradation products. Esomeprazole was given by intravenous infusion at 160 mg/kg, with and without degradation products (b)(4) The dose of 160 mg/kg was given by two 30-minute infusions, approximately 3.5-4 hours apart. The following doses of the degradation products were given: 1.8 mg/kg for (b)(4), 0.74 mg/kg for (b)(4), and 2.8 mg/kg for (b)(4). The details of the study design were presented in the following sponsor's table.

Table 3 Groups and dose levels

Group Number	Number & Sex	Animal Ref. Number	Sampling Time[a] HAE2	Route/ Dose Rate (mL/kg*h)	Treatment	Form Conc[b] (mg/mL)	Dose Level[c, d] (mg/kg)	(µmol/kg)
1	7F	R1 1501-1507	42	Intra-venous /20	Saline	0	0 (2x0)	0 (2x0)
	7F	R2 1508-1514	18					
2	7F	R1 2501-2505,	42	Intra-venous /20	ESO plus:	7.4 plus:	160 (2x80) plus:	460 (2x230) plus:
	7F	2606, 2507 R2 2508-2514	18		(b)(4)			
3	7F	R1 3501-3507	42	Intra-venous /20	ESO	7.9	160 (2x80)	460 (2x230)
	7F	R2 3508-3514	18					
	4F[e]	R1 3515, 3616, 3517, 3618	NA					
	4F[e]	R2 3519-3521, 3722	NA					
	4F[e]	R3 3523-3526	NA					
	3F[e]	R4 3528-3530	NA					
	4F[e]	R5[f] 3531-3534	NA					
4	7F	R2 4515-4521	18	Oral/NA	Cyclophos-ph amide	2.0	20	NA

All doses and concentrations of the test compounds included in this report are expressed in terms of the parent compounds

Animal Ref Nos. = Animal reference numbers HAE2= Hours after the end of the 2nd infusion

Form conc = Formulation concentration R1/2/3/4/5= Replicate 1/2/3/4/5

ESO= Esomeprazole NA= Not applicable

a Colchicine was administered by intraperitoneal injection to all main study animals (not to the TK animals) at a dose of 4 mg/kg, 3 hours prior to scheduled euthanasia, using a dose volume of 10 mL/kg. The dose was approximately evenly split between 2 injection sites to ensure exposure.

b Given as the median concentrations during infusion, calculated from the mean concentrations analysed in the pre- and post infusion formulation samples (see Section 6.1), not the nominal concentrations

c The nominal dose of esomeprazole is given. It was not considered necessary to adjust this, as a deviation of ±10% of the intended concentration of the active compound is considered to be acceptable on formulation analysis (see Section 6.1)

d The concentration of the degradation products in the dosing formulation decreased notably during infusion (as was expected), and thus these dose levels have been re-calculated using the median concentrations during infusion (see Section 6.1)

e Animals used for blood sampling for TK evaluation, only

f Animals 3531 to 3534 (replicate 5) only received a single infusion, as blood sampling was only performed at 3h 25 min following the end of the 1st infusion in these animals.

The animals were sacrificed at 18 or 42 hours after the second infusion and bone marrow was collected for evaluation of cells with aberrations. Colchicine (4 mg/kg) was given to all animals 3 hours prior to termination. Cyclophosphamide was used as a positive control. The following observations were reported: clinical signs, body weight, necropsy, and plasma concentration of the test articles.

Criteria for positive results: The results should be considered positive if the test substance induced a significant increase in the incidence of aberrant cells as compared to the control. This increase should be dose-related and reproducible.

Results: Following clinical signs of toxicity were observed in both esomeprazole groups: decreased activity, partly closed eyes, convulsion, tremors, hunched posture, lying on side, weak, labored/shallow breathing and irregular respiratory rate. The results of examination of bone marrow are summarized in the sponsor's Table 11 and this table is attached below.

Table 11 Group mitotic index and % aberrant metaphase

Treatment	Dose (mg/kg/day)	Mean MI †	Mean % Aberrant †
18 Hour sampling time			
Saline	-	10.1	0.0
Eso+	2 x 80	8.8	0.0
Eso-	2 x 80	8.1	0.2
CP	20	2.2	7.3**
42 Hour sampling time			
Saline	-	8.6	0.3
Eso+	2 x 80	7.1	0.0
Eso-	2 x 80	9.6	0.1

Eso+ Esomeprazol with degradation products
Eso- Esomeprazol without degradation products
CP Cyclophosphamide
MI Mitotic index

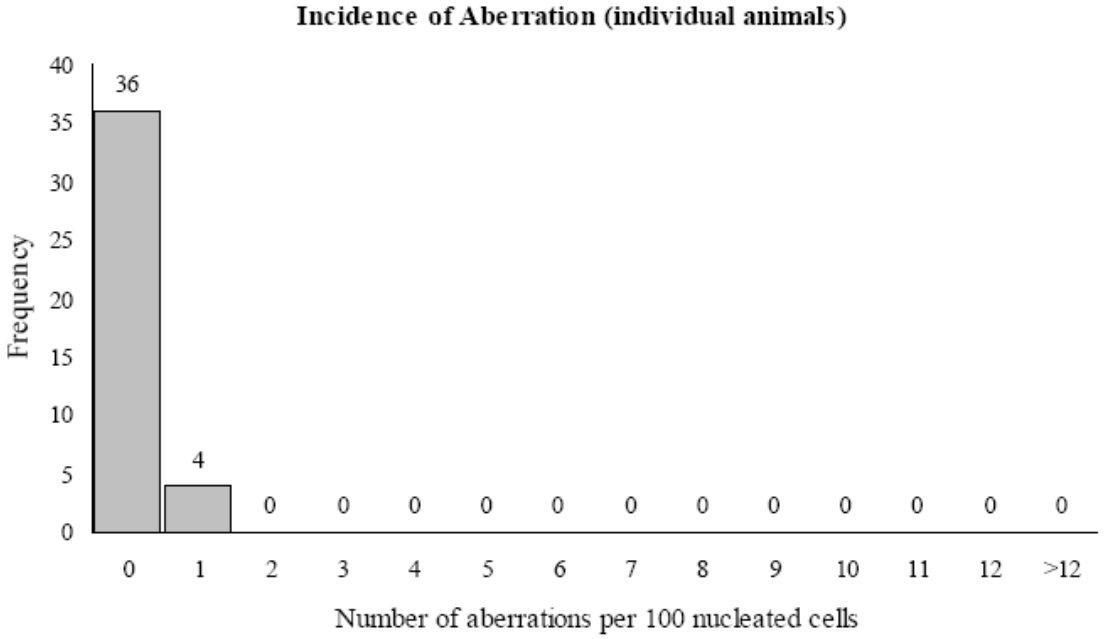
Results of statistical analysis (one-sided probabilities):

**	$P < 0.001$	(highly significant)
*	$P \leq 0.01$	(significant)
otherwise	$P > 0.01$	(not significant)

† Occasional apparent errors of ± 1% may occur due to rounding of values for presentation in the table.

The results indicated that treatment with esomeprazole had no effects on the incidence of chromosomal aberrations. The historical control data were presented in the following figure.

Figure 1 Historical vehicle/Negative control values



The individual animal mean aberration is 0.10%. These QA audited results are collected from GLP compliant studies performed between November 2004 and prior to the present study.

The plasma concentrations of esomeprazole are summarized in the sponsor's Tables 1 and 2. These tables are attached below.

Table 1 **Summary of plasma concentrations of esomeprazole in main study animals following two 30-minute intravenous infusions of esomeprazole, with and without degradation products**

Group	Dose Esomeprazole (mg/kg)	Time	Median (Range) Plasma Concentrations Esomeprazole (µmol/l)
2[a]	160 (2 x 80)	5 MAE 1	256 (217-310)
		5 MAE 2	312 (239-362)
3[b]	160 (2 x 80)	5 MAE 1	259 (205-307)
		5 MAE 2	320 (2.54-347)
3[c]	160 (2 x 80)	5 MAE 1	254 (130-280)
		5 MAE 2	283 (237-356)

MAE 1 or 2 = Minutes after the end of the 1st or 2nd infusion
a Esomeprazole with degradation products administered, main study animals
b Esomeprazole without degradation products administered, main study animals
c Esomeprazole without degradation products administered, TK satellite animals

Table 2 **Summary of C_{max} and AUC values for esomeprazole, based on median plasma concentrations in female rats following 30-minute intravenous infusions of 2 x 80 mg/kg esomeprazole, without degradation products**

Daily Dose (mg/kg)	C_{max1}[a] (µmol/L)	C_{max2}[a] (µmol/L)	AUC[a] (µmol*h/L)
160 (2 x 80)	NC [254]	283 [270, 296]	786 [749, 822]

Individual values in square brackets
NC = Not calculated
a Median of the exposure values for animals with 3.5 and 4 hours between the end of the 1st and start of the 2nd infusions (with 3 to 4 rats at each sampling time point)

In conclusion, esomeprazole was not clastogenic with or without degradation products in the study condition.

LABELING:

The sponsor's proposed labeling is consistent with the approved labeling for Nexium. The proposed labeling is adequate and thus no revision is needed.

OVERALL CONCLUSIONS AND RECOMMENDATIONS:

Esomeprazole magnesium is the S-enantiomer of the racemic proton pump inhibitor, omeprazole, which inhibits H^+/K^+-ATPase activity in the gastric parietal cells and thus blocks the final step of the gastric acid secretion. NEXIUM I.V. for Injection is indicated for the short-term treatment (up to 10 days) of GERD patients with a history of erosive esophagitis. Nexium is used as an alternative to oral therapy in patients when therapy with NEXIUM Delayed-Release Capsules is not possible or appropriate. The recommended adult dose is 20 or 40 mg/day.

The current submission is an efficacy supplement to NDA 21,689 for Nexium injection. The new proposed indication is (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. The proposed dose is 80 mg/day. Since the proposed daily dose of Nexium is higher than the approved daily dose of 20 or 40 mg, the sponsor conducted the following nonclinical studies to support approval of this efficacy supplement: a 14-day intravenous toxicity study in rats using esomeprazole with and without degradation products, and genotoxicity studies of esomeprazole degradation products including Ames tests and an in vivo chromosomal aberration test.

In the 14-day intravenous toxicity study, rats were treated by intravenous infusion of esomeprazole, with and without degradation products (b)(4) The dose of 80 mg/kg/day was tested. Esomeprazole increased organ weights of the liver, stomach, adrenals and kidney in both esomeprazole groups. The treatment with esomeprazole induced clinical signs of toxicity including partly closed eyes, decreased activity, incoordination, and tremors. The incidence of these clinical signs was similar with and without degradation products. These clinical signs were also noted in the previous 28-day i.v. toxicity study in rats (study (b)(4) 56771, 2002).

The degradation products of esomeprazole including (b)(4) and (b)(4) were negative in the Ames tests. The treatment with esomeprazole with and without degradation products (b)(4) (b)(4) and (b)(4) did not increase the incidence of chromosomal aberration in the in vivo chromosomal aberration test in rats. The current labeling for Nexium I.V. states that esomeprazole was negative in the Ames test, in the *in vivo* rat bone marrow

cell chromosomal aberration test, and in the *in vivo* mouse micronucleus test, but was positive in the *in vitro* human lymphocyte chromosomal aberration test.

There were 28-day i.v. toxicity studies with esomeprazole in rats and dogs submitted to the original NDA 21,689. These studies were reviewed on June 24, 2008. The highest tolerable doses were 48 and 24 mg/kg/day in male and female rats, respectively, and 35 mg/kg/day in dogs. The identified target organs of toxicity were the central nervous system, stomach, and site of injection in both rats and dogs.

Recommendations:

From a preclinical standpoint, approval of Nexium IV is recommended for the proposed indication.

_____ _____
Ke Zhang, Ph.D. Date
Pharmacologist, DGP

_____ _____
David Joseph, Ph.D. Date
Acting Supervisory Pharmacologist
DGP

CC:
NDA
DGP
DGP/CSO
DGP/Dr. Joseph
DGP/Dr. Zhang

R/D Init.: DJ/11/6/08
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/s/

Ke Zhang
11/13/2008 09:29:13 AM
PHARMACOLOGIST

David Joseph
11/13/2008 12:45:14 PM
PHARMACOLOGIST
I concur with Dr. Zhang's recommendation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-689/ 014
Drug Name:	Nexium IV (esomeprazole sodium 20 mg and 40 mg) for Injection)
Indication(s):	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Applicant:	AstraZeneca
Date(s):	Letter Date: December 14, 2012 Received Date: December 14, 2012 PDUFA Due Date: August 14, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Lisa A. Kammerman, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors
Clinical Team:	Aisha Peterson, M.D., Robert Fiorentino, M.D.
Project Manager:	Stacey Barley, RN, M.S.N., M.H.A.

Keywords: Clinical studies, NDA review

Table of Contents

Appendices

1. EXECUTIVE SUMMARY

The Applicant's submission is a response to a second Complete Response letter that FDA issued on June 16. 2011. The submission does not contain any new clinical studies. Rather, the submission relies primarily on data that were previously submitted. The medical review team will need to decide whether this submission's information along with the results from the original, single and adequate well-controlled esomeprazole study (D961C00001) are now sufficient to support approval.

Although I address the Applicant's responses to all seven items contained in the Complete Response letter, my review focuses on the clinical trial design and statistical analysis responses to Items 2 and 4 of the Complete Response letter. The response to Item 2 discusses FDA's choice of subjects who were included in the second review cycle analysis of two studies of omeprazole (I-840 and I-841). The response to Item 4 explores potential explanations for the inconsistent three day rebleeding rates among placebo-treated subjects observed in the original esomeprazole study (D961C00001, 10%) and the single-center, Hong Kong study of omeprazole (Lau et al, 20%).

The Applicant's response to Item 2 regarding who should be included in the analysis of the Day 3 rebleeding rates in the omeprazole studies (I-840 and I-841) appears to be more of a clinical review issue than a statistical review issue. During review cycle 2, the clinical team decided to align, to the extent possible, studies I-840 and I-841 with the original esomeprazole study (D961C00001). To achieve that goal, the team identified a group of omeprazole-treated subjects who would have met the entry criteria of D961C00001 and who received the same endoscopic treatments administered in D961C00001. As a result of these decisions, the sample size was reduced to 52 subjects and an exploratory analysis compared the two treatment groups; the observed treatment difference between omeprazole and placebo was statistically non-significant at α=0.05. Whether this exploratory analysis should be limited to the 52 subjects identified by the clinical review team in cycle 2 or should be expanded to the 137 subjects identified in the Applicant's response is a clinical decision. The difference in Day 3 rebleeding rates between the omeprazole and placebo treatment groups appears consistent across groups of subjects with different types of endoscopic treatments

Item 4 of the Complete Response letter noted the placebo Day 3 rebleeding rate for Lau et al (20%) was twice the placebo Day 3 rebleeding rate for D961C00001 (10%). Because the reasons for the difference in placebo response rates were unknown, the letter questioned whether the results of the Lau et al study could be generalized to the U.S. population. Although I do not agree with the Applicant's approach to identifying possible reasons for the differences in placebo rebleeding rates, I consider any type of cross-study analyses to be exploratory only. Therefore, the results of such analyses should not be given much weight in deciding whether the results of Lau can be generalized to a broader population.

Although the original esomeprazole study (D961C00001) showed a treatment effect of -4.4% (p=0.03), a major review issue in the first two cycles was whether the level of evidence coming

from this single study was sufficient to support the efficacy and, therefore, approval of the indication. This current submission does not contain any new data from clinical trials. The medical division will need to decide whether the analyses of I-840 and I-841 should be limited to the 52 subjects identified in the previous review cycle or should be expanded to the 137 subjects identified by the Applicant in this submission. Further, I view the results of the cross-study analyses identifying possible reasons for differences between D961C00001 and Lau et al to be exploratory only. This applies both to the Applicant's analyses and to mine.

2. INTRODUCTION

2.1 Overview

This submission is a response to a second Complete Response letter that FDA issued on June 16, 2011; Appendix 1 of this review contains a copy of the letter. The submission does not contain additional studies. Rather, to address the questions contained in the Complete Response letter, the submission interprets the results of previously submitted studies and provides the results of new analyses of those studies. My review addresses each of the seen items contained in the Complete Response letter

The following paragraphs provide a brief overview of the two previous review cycles.

On May 29, 2008, the FDA received a supplemental NDA for Nexium IV. The submission contained a single study, D961DC00001, which did not provide the level of evidence needed to support efficacy for the desired indication. As a result, the FDA issued a Complete Response on November 26, 2008.

On September 6, 2010, the Applicant submitted a response to the November 26, 2008 Complete Response letter. However, the information contained in the response did not provide substantial evidence of efficacy and a second Complete Response letter was issued on June 16, 2011. The Applicant's response contained results from a bridging study between omeprazole IV and esomeprazole IV, and data from randomized controlled clinical trials of omeprazole IV. The submission of the randomized trials with omeprazole IV substituted for an adequate and well-controlled study of esomeprazole, as recommended in the November 26, 2008 Complete Response letter. The submission also contained results from observational studies with omeprazole IV, meta-analyses, outcomes of treatment in clinical practice and a summary of published systematic reviews of available literature on clinical studies with PPIs.

2.2 Data Sources

This submission was submitted electronically and is located in the Electronic Document Room at \\cdsesub1\evsprod\NDA021689, starting with eCTD sequence number 111.

I also reviewed the following documents:

Statistical Review of the Cycle 2 submission, review dated 6/7/2011

Statistical Review (Addendum) of the Cycle 2 submission, review dated 6/15/2011

Complete Response Letter from FDA to Applicant, letter dated 6/16/2011

February 28, 2013 response to Information Request dated February 18, 2013

June 20, 2013 response to Information Request dated June 12, 2013

June 27, 2013 response to Information Request dated June 24, 2013

3. STATISTICAL EVALUATION

This section addresses the Applicant's responses to each of the items contained in the Compete Response Letter, with an emphasis on study design and statistical issues.

3.1 Complete Response Letter Item 1

The Complete Response Letter indicated trials I-840 and I-841 were not designed to support the proposed indication. The endoscopic treatments administered and the primary endpoints differed from those used in trial D961C00001.

The Applicant states the results from I-840 and I-841 indicate the beneficial effect of high-dose PPI treatment is very generalizable, because the effect of omeprazole is consistently shown regardless of the background endoscopic treatment regimen; see Table 1.

Because this is a clinical conclusion, I defer to the medical reviewer's evaluation of this answer.

3.2 Complete Response Letter Item 2

I view the Applicant's response regarding who should be included in the analysis of Studies 840 and 841 as a clinical review issue and not a statistical review issue. The following paragraphs describe my reasoning.

The Cycle 2 Complete Response Letter indicated only 52 subjects from trials I-840 and I-841 matched the enrollment criteria for trial D961C00001, which was the original efficacy trial. Based on this small group of subjects, although the 72 hour rebleeding rate was lower in the omeprazole-treated subjects (13.6%) than in the placebo-treated subjects (23.3%), the result was not statistically significant.

This submission states that a more relevant analysis is the 127 subjects who received the same treatment modalities as in study D961C00001, with or without additional endoscopic treatment. After stratifying by type of endoscopic treatment, the difference between the study treatments favored omeprazole (p=0.025).

Although on its face, the analysis of the 52 subjects appears to be a 'traditional' subgroup analysis because the number of subjects constitutes a small proportion of the subjects enrolled in

studies I-840 and I-841, I do not view this analysis to be a statistical issue. Rather, the Cycle 2 clinical review team believed it was important to align, to the extent possible, studies I-840 and I-841 with the original esomeprazole study (D961C00001). To achieve that goal, the clinical team identified a group of omeprazole-treated subjects who would have met the entry criteria of the original esomeprazole study (D961C00001) and who received the same endoscopic treatments administered in D961C00001. As a result of these decisions, the sample size was reduced to 52 subjects.

Whether this exploratory analysis should be limited to the 52 subjects identified by the clinical review team in the previous review cycle or should be expanded to the 137 subjects identified by the Applicant in this submission is a clinical decision. The following table shows the rebleeding rate for omeprazole-treated subjects is lower than the rebleeding rate for placebo-treated subjects, across four groups of subjects: (1) subjects with any type of endoscopic treatment (n=213), (2) subjects whose endoscopic treatment differed from the endoscopic treatments used in D961C00001 (n=76), (3) subjects whose endoscopic treatment was the same as the endoscopic treatment given in D961C00001, plus subjects who received additional endoscopic treatment (n=137), and (4) subjects with the same endoscopic treatment given in D961C00001 and who do not receive additional endoscopic treatment (n=52).

Table 1. Rates of rebleeding within 72 hours for Studies I-840 and I-841 combined, by type of endoscopic treatment

	Treatment Group		
Endoscopic treatment	Omeprazole	Placebo	Treatment Difference
Any type of endoscopic treatment (n=213)	16.7% (17/102)	30.6% (34/111)	-13.9%
Endoscopic treatment differed from endoscopic treatment used in D961C00001 (n=76)	23.8% (10/42)	38.2% (13/34)	-14.4%
Same endoscopic treatment used in D961C00001, plus additional endoscopic treatment (n=137)	11.7% (7/60)	23.3% (21/77)	-15.6%
Same endoscopic treatment used in D961C00001 (n=52)	13.6% (3/22)	23.3% (7/30)	-9.7%

Source: Adapted from Dr. Peterson's presentation, CDER Regulatory Briefing on April 19, 2013

3.3 Complete Response Letter Item 3

The Complete Response Letter noted "the ability to generalize the results of this [Lau et al] trial to the U.S. population is limited." Although the submission does not contain any new clinical trial data, the Applicant submitted results of a pharmacokinetics study and a literature review. The clinical team and the clinical pharmacologist are reviewing these. My statistical review (dated 6/7/2011) discussed the limitations of Lau et al and our ability to generalize the clinical study results to the U.S. population.

The results of the pharmacokinetics study and literature review need to be considered together with my review of the Lau et al study in order to determine whether the Applicant has successfully addressed Item 3 of the Complete Response Letter.

3.4 Complete Response Letter Item 4

The Complete Response Letter noted the placebo rebleeding rate for Lau et al (20%) was twice the placebo rebleeding rate for D961C00001 (10%). Because the reasons for the difference in placebo response rates were unknown, the letter questioned whether the results of the Lau et al study could be generalized to the U.S. population.

As I elaborate in the following paragraphs, I do not agree with the Applicant's approach to identifying possible reasons for the differences in placebo rebleeding rates. The Applicant implemented two Cox regression models. In each case, the dependent variable was the number of days from randomization until a rebleeding event within 72 hours of randomization; data were censored at Day 3. The first model contained two independent terms: Study (Lau or D961C00001) and Study Drug (Esomeprazole/omeprazole or Placebo). The second model included an additional 14 independent variables, plus Study and Study Drug. These additional variables represented age, sex, hospitalization for a rebleed, previous ulcer bleeding, ASA grade, presence of H. pylori (positive/trace or negative), Forrest class, NSAID (including aspirin) and warfarin use.

Because time to rebleeding is the focus of Cox regression models, the use of Cox regression models seems discordant with the primary endpoint of interest – whether a subject had any re-bleeding within 72 hours or had no re-bleeding within 72 hours. For that reason, categorical data analysis models are better suited than Cox regression models for assessments of Day 3 rebleeding rates.

In addition, the Cox regression models treated all the events as occurring at distinct times, even though this was not the case. The Lau study used interval-censored data while D961C00001 used actual dates and times for a rebleeding event. In other words, the events in the Lau study were recorded as Day 0, Day 1, Day 2 or Day 3, while events in D961C00001 were recorded at distinct times. Interval-censored data means that although the event time is recorded as Day 2, for example, the event actually occurred between Day 1 and Day 2. To illustrate how this affects the analysis, assume a subject has a rebleeding event at 30 hours. In Lau, the subject's rebleeding time was recorded as 2 days; in D961C00001, the subject's rebleeding time was recorded as 1.25 days. Despite these two types of data, the Cox regression models counted all events as occurring at distinct times. On its face, the use of Cox regression models with only

three possible times for events (excluding Day 0) in the Lau study does not seem very robust with respect to the proportional hazards assumption of Cox regression models and with respect to handling ties.

Because of the number of independent variables, applying any type of regression model to these data is a concern. The 6-to-1 ratio of the number of rebleeding events (91) to the number of independent variables (16) is somewhat low. Typically, higher ratios are necessary to ensure stable estimates of the regression model parameters. Second, multi-colinearity (i.e., linear dependence) among the variables, if present, could also affect the estimates of the parameters. The submission did not assess multi-colinearity; see the February 28, 2013 response to our Information Request dated February 18, 2013. Multi-colinearity is a lesser concern when the intent of a model is to predict an outcome without regard to the actual variables included as predictors. However, when the intent of a model is to identify variables that are most predictive an outcome, then multi-colinearity needs to be assessed. This latter goal appears to be the purpose of the Cox regression models contained in the submission.

The Cox regression analyses included data from subjects randomized to the active treatment groups in addition to data from subjects randomized to placebo. Possibly, the variables identified by the analyses may not have been the correct ones for explaining the differences in placebo rebleeding rates. A different approach is to focus only on the placebo-treated subjects. This might be useful because although the placebo rebleeding rate in the Lau study (20%) was about twice that of D961C00001 (10%), the treatment rebleeding rates were similar (Lau: 4%, D961C00001: 6%). It was this difference in placebo rates that accounted, primarily, for a larger observed treatment difference for Lau (-16%) than the treatment difference observed in D961C00001 (-4%).

The results of my exploratory analyses suggest the distributions of the following variables differed between D961C00001 and Lau. The distributions for sex, warfarin and NSAIDs appeared similar across the two studies.

- History of peptic ulcer bleeding (yes)
  9% (D961C00001) vs. 30% (Lau)
- Hospitalized at sign of GI bleeding (yes)
  9% (D961C00001) vs. 19% (Lau)
- Forrest Class:
  Ia: 9% (D961C00001) vs. 10% (Lau)
  Ib: 43% (D961C00001) vs. 41% (Lau)
  IIa: 38% (D961C00001) vs. 31% (Lau)
  IIb: 10% (D961C00001) vs 18% (Lau)
- ASA Grade:
  I: 39% (D961C00001) vs. 34% (Lau)
  II: 48% (D961C00001) vs. 22% (Lau)
  III: 13% (D961C00001) vs. 28% (Lau)
  IV: 0% (D961C00001) vs 16% (Lau)
- Acetylsalicyclic acid (ASA) medication (yes):
  27% (D961C00001) vs. 17% (Lau)

- H. pylori laboratory Assessment – Positive or trace
  71% (D961C00001) vs. 60% (Lau)

Because D961C00001 did not enroll anyone with ASA Grade IV, any differences in placebo rebleeding rates attributed to differences in ASA Grade IV is confounded with study. Thus, the submission's assertion that differences between the studies in re-bleeding rates is explained by ASA grade IV needs to be viewed with caution. Potentially, other characteristics unique to the Lau study could also explain the differences.

Among the placebo-treated subjects, regardless of study, Day 3 rebleeding rates appeared to be related to:

- Hospitalized at sign of GI bleeding, 3.5% (among those hospitalized) vs. 14% (not hospitalized)
- Forrest Class: 22% (Ia), 7% (Ib), 14% (IIa), 22% (IIb)
- ASA Grade: 9% (I), 12% (II), 20% (III or IV)

Results from my exploratory logistic regression models suggest the relationships between each of the variables and Day 3 rebleeding (yes/no) are consistent across studies. These models used Day 3 rebleeding (yes/no) as the dependent variable. A separate model was fit for each of the predictor variables. Each of these models also contained an interaction term between the predictor and study (D961C00001 or Lau). In each case the interaction terms were non-significant.

3.5 Complete Response Letter Item 5

The Complete Response Letter noted "substantive differences in the efficacy outcomes within important subgroups in the clinical trial reported by Lau, et al. compared to D961DC00001." The letter cited the subgroups of patients 65 years of age and older, and the subgroup of patients with Forrest Ib classification.

To address the differences for these two subgroups, the submission cites the results of their exploratory analyses that were included in their response to Item 4 of the Complete Response Letter. My review of Item 4 describes the weaknesses of these analyses; see 3.4 Complete Response Letter Item 4.

In addition, the submission offers possible clinical reasons for the differences in the subgroup of patients with Forrest Ib classification. I defer to the medical reviewer for a review of this aspect of the Applicant's response.

3.6 Complete Response Letter Item 6

The Complete Response Letter noted "the information from observational studies and literature reviews of intravenous esomeprazole and omeprazole were not considered adequate to constitute primary evidence of the efficacy of the product for the proposed indication." In response, the Applicant discusses results from observational studies and a literature review.

I defer to the medical reviewer for a review of this item.

3.7 Complete Response Letter Item 7

Item 7 of the Complete Response Letter describes why FDA's review concluded study D961DC00001 could not serve as a single and adequate well-controlled trial to support approval of the proposed indication. Item 7 identifies three issues related to the use of a Breslow-Day test to support homogeneity of the treatment effect across study centers, influence of Site 0012 (the Netherlands) on the overall results, and the relationship between PK/PD outcomes and *H. pylori* status.

Although I generally agree with the Applicant's response that the Breslow-Day test was inconclusive regarding the presence or absence of heterogeneity of treatment effect, and the influence of Site 0012, the Complete Response letter noted these deficiencies because of the Division's reliance on a single and adequate well-controlled study to support the proposed indication. The medical team needs to decide whether the information contained in this submission combined with the results of a single and adequate well-controlled study that was not deemed sufficient to stand on its own are sufficient to support the efficacy of esomeprazole for the proposed indication.

4. CONCLUSIONS

The Applicant's response regarding who should be included in the analysis of the three day rebleeding rates in the omeprazole studies (I-840 and I-841) appears to be more of a clinical review issue than a statistical review issue. During review cycle 2, the clinical team decided to align, to the extent possible, studies I-840 and I-841 with the original esomeprazole study (D961C00001). To achieve that goal, the team identified a group of omeprazole-treated subjects who would have met the entry criteria of D961C00001 and who received the same endoscopic treatments administered in D961C00001. As a result of these decisions, the sample size was reduced to 52 subjects. The observed treatment difference between omeprazole and placebo for these subjects was statistically non-significant at α=0.05. Whether this exploratory analysis should be limited to the 52 subjects identified by the clinical review team in cycle 2 or should be expanded to the 137 subjects identified in the Applicant's response is a clinical decision. The difference in three day rebleeding rates between the omeprazole and placebo treatment groups appears consistent across groups of subjects with different types of endoscopic treatments

The Complete Response letter noted the placebo three day rebleeding rate for Lau et al (20%) was twice the placebo three day rebleeding rate for D961C00001 (10%). Because the reasons for the difference in placebo response rates were unknown, the letter questioned whether the results of the Lau et al study could be generalized to the U.S. population. Although I do not agree with the Applicant's approach to identifying possible reasons for the differences in placebo rebleeding rates, I consider any type of cross-study analyses to be exploratory only. Therefore, the results of such analyses should not be given much weight in deciding whether the results of Lau can be generalized to a broader population. This comment applies equally to my exploratory analyses.

Appendix 1 Complete Response Letter dated 6/16/2011

APPEARS THIS WAY ON ORIGINAL

6 pages have been withheld as Duplicate. See page 11 of this Approval Package for the Complete Response Letter dated 6/16/2011 .

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

/s/

LISA A KAMMERMAN
08/27/2013

MICHAEL E WELCH
08/27/2013
Concur with review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION ADDENDUM

CLINICAL STUDIES

NDA/Serial Number:	21-689/ 014
Drug Name:	Nexium IV (esomeprazole sodium 20 mg and 40 mg) for Injection)
Indication(s):	[redacted] (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Applicant:	AstraZeneca
Date(s):	Letter Date: September 15, 2010 Received Date: September 16, 2010 PDUFA Due Date: June 16, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Lisa A. Kammerman, Ph.D.
Concurring Reviewers:	Michael Welch, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors
Clinical Team:	Erica Wynn, M.D.
Project Manager:	Stacey Barley, RN, M.S.N., M.H.A.

Keywords: Clinical studies

Table of Contents

1. EXECUTIVE SUMMARY

In this addendum to my review (dated 6/7/2011), I address certain statistical issues raised by the Applicant's response to the Complete Response letter that was dated November 26, 2008. The establishment of efficacy of esomeprazole in this complete response relies on (1) a study that bridges esomeprazole and omeprazole, and (2) placebo-controlled studies of omeprazole.

The statistical issues contained in the Complete Response letter arose because a single study was being used to establish the efficacy of esomeprazole. A series of sensitivity analyses were done by the statistical reviewer to assess the robustness of the study results; see statistical review dated 11/13/2008. The analyses included an investigation of the contribution of country to the overall results. Because the study did not enroll sites from the United States, the clinical team was concerned about the variation in physician expertise and standard of care across countries. Country variation was not accounted for in the Applicant's analyses of the single study. Moreover, many of the study sites were small, precluding analyses that adjusted for study center.

In their response to the letter, the Applicant maintains the study results are consistent across subgroups, secondary endpoints and study centers.

The Applicant's assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers is not persuasive. Because the Breslow-Day test is not a very powerful test for detecting lack of homogeneity, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables in the original study further limits the usefulness of the test. Additionally, the test assesses the consistency of odds ratios, whereas the estimate of interest was the difference between two treatment groups.

Center 0102, located in the Netherlands, enrolled 21 subjects and was one of the largest centers in the study of 767 subjects. Despite accounting for just less than 3% of the overall enrollment, a sensitivity analysis that excluded this center resulted in a smaller and statistically non-significant treatment effect. This suggests treatment effect was not consistent across study centers and highlights the potential lack of robustness of the treatment effect, an important consideration when relying on a single study.

I agree with the Applicant that the results did not appear to vary among subgroups defined by race, age, and gender.

The results regarding secondary endpoints are inconclusive. The rate of surgery did not differ between treatment groups (p=0.31). The number of blood units transfused was lower for the esomeprazole treatment group (492) relative to placebo (738), although the result was not persuasive (p=0.05). However, the endoscopic retreatment rate was lower for esomeprazole (4.3%) relative to placebo (8.2%); p=0.02. Looked at in the context of the reliance on a single study to support efficacy, the results for surgery and blood units transfused are not persuasive. The treatment effect for endoscopic retreatment was -3.9%, which is comparable to the treatment

effect of -4.4% for the primary endpoint. This finding may have more clinical relevance than the findings for the other two secondary endpoints, although the p-value (p=0.02) is not of the magnitude usually required for a single study.

Although the original study showed a treatment effect of -4.4% (p=0.03), a major review issue was whether the level of evidence coming from this single study was sufficient to support the efficacy and, therefore, approval of the indication. The statistical and clinical concerns resulted in the comments that I have reviewed in this document. The Applicant's responses, from my perspective, do not dispel concerns regarding the level of evidence, and issues with the distribution of the treatment effect across study center and country.

From my perspective, the review question of interest is whether the original study can be considered one of two studies to support the efficacy of esomeprazole, where the other studies are the omeprazole studies contained in the resubmission. As I reported in my statistical review (dated 6/7/2011), one set of omeprazole studies (I-840 and I-841) had too few subjects to make any meaningful conclusions regarding efficacy. The other study was conducted solely in Hong Kong. While the study's results appeared persuasive, the issue is whether the results can be generalized to the United States. Thus, the approval of the desired indication seems to rest on the original study.

2. INTRODUCTION

On May 29, 2008, the Food and Drug Administration received a supplemental NDA for Nexium IV. The submission contained a single study, D961DC00001, which did not provide the level of evidence needed to support efficacy for the desired indication. As a result, the FDA issued a Complete Response letter that was dated November 26, 2008.

In this resubmission, although the Applicant acknowledges the level of significance in the single study did not reach the level of significance needed for a single study to support efficacy, the Applicant does not agree with all the reasons cited in the Completer Response letter. For instance, the Applicant disagrees with the FDA finding of a non-significant result when the primary analysis was adjusted for country through the use of a Mantel-Haenszel test, claiming the test resulted in a decreased sample size because the test eliminated 29 (of 64) strata which did not have any observations and that more rebleeding events were eliminated from the placebo group than from the treatment group. They also claim the results are consistent across study centers and subgroups defined by age (≥65 years, <65 years), based on what would be expected from chance alone. They also address the concern that a site from the Netherlands appeared to disproportionately influence the size of the overall treatment effect and its statistical significance. They also assert results are consistent among secondary endpoints.

In the next section, I address each of the responses related to these statistical.

3. STATISTICAL EVALUATION

The statistical issues contained in the Complete Response letter arose because a single study was being used to establish the efficacy of esomeprazole. A series of sensitivity analyses were done by the statistical reviewer to assess the robustness of the study results; see statistical review dated 11/13/2008. The analyses included an investigation of the contribution of country to the overall results. Because the study did not enroll sites from the United States, the clinical team was concerned about the variation in physician expertise and standard of care across countries. Country variation was not accounted for in the Applicant's analyses of the single study. Moreover, many of the study sites were small, precluding analyses that adjusted for study center.

In order to facilitate the discussion, the following headings and their numbers correspond to those used by the Applicant in their complete response.

2.1 Statistical significance of results

The Applicant acknowledges the level of significance did not meet the FDA's recommendation regarding the level of significance needed for a single study submission.

On its face, the Applicant's point regarding the FDA's use of the Mantel-Haenszel test, stratified by country, seems valid. Within each country (16 countries), a 2x2 table for the cross-classification of treatment (esomeprazole or placebo) and response (rebleed, no rebleed) was created and combined across countries. The Applicant states 29 of 64 tables were excluded because of the absence of observations in many of the table cells.

However, this was not the case. The statistical reviewer used PROC FREQ, a SAS procedure, to implement the Mantel-Haenszel test. The procedure adds a value of 0.5 to cells with no observations. Consequently, no tables were excluded from her analysis.

It should be noted the analysis was the protocol-specified Mantel-Haenszel test stratified by Forest class (I vs. II), type of endoscopic hemostatic treatment used (single vs. combination treatment) and country. The Applicant's response seems to suggest they believe that country was the only stratification variable.

The statistical reviewer noted that none of the countries demonstrated a statistically significant treatment effect favoring either drug or placebo (see following table). This finding could mean either that country is an effect modifier and the analyses should be stratified by country, or that because the treatment effect is modest the enrollments within countries were not large enough to detect a statistically significant treatment effect.

Table 3.7
Study D961DC00001: Treatment Effect and 95% Confidence Interval for Clinically Significant Rebleeding within 72 hours by Country

Country	$n_{Esomeprazole}$ / $n_{Placebo}$	Treatment Effect (%) (Esomeprazole - Placebo)	95% C.I.* (Exact)
Spain	8 / 8	12.5	(-31.4, 54.5)
South Africa	20 / 22	5.4	(-14.0, 27.5)
Sweden	52 / 49	3.5	(-8.4, 15.6)
Denmark	35 / 36	0.2	(-15.0, 15.6)
France	27 / 31	0.0	(-11.2, 12.8)
UK	4 / 1	0.0	(-97.5, 67.2)
Austria	19 / 24	-3.1	(-22.4, 18.3)
Hong Kong	25 / 25	-4.0	(-22.2, 13.5)
Turkey	24 / 24	-4.2	(-22.9, 13.6)
Netherlands	26 / 27	-7.0	(-28.3, 14.6)
Russia	52 / 59	-8.2	(-19.4, 1.1)
Romania	26 / 24	-8.3	(-27.0, 5.9)
Germany	27 / 26	-11.8	(-33.5, 8.1)
Norway	15 / 16	-18.3	(-46.2, 9.9)
Greece	12 / 13	-23.1	(-53.8, 7.2)
Finland	3 / 4	-25.0	(-81.0, 49.4)
OVERALL	**375 / 389**	**-4.4**	**(-8.4, -0.5)**

Source: Statistical Reviewer's listing.

* Exact confidence interval calculated using StatXact.

Source: Table 3.7 from statistical review dated 11/13/2008

2.2 Internal consistency across study centers

The Complete Response letter indicated the study lacked internal consistency across study centers. The letter emphasized the range in point estimates, both by center and by country (see table below).

To address this concern, the Applicant used a Breslow-Day test to examine the homogeneity of odds ratios across all centers (p=0.6) and for the larger centers (p=0.4) and concluded there was insufficient evidence to conclude heterogeneity in the odds ratios.

Curiously, the Applicant's response does not address how the 29 tables without observations were handled. Presumably, PROC FREQ was used and a value of 0.5 was added to the cells that did not have any observations.

The Breslow-Day test is not a very powerful test for detecting lack of homogeneity. So the lack of a statistically significant finding is not necessarily meaningful. Moreover, according to the SAS documentation of PROC FREQ's implementation of the test, "the sample size should be relatively large in each stratum, and at least 80% of the expected cell counts should be greater than 5. Note that this is a stricter sample size requirement than the requirement for the Cochran-Mantel-Haenszel test for qx2x2 tables, in that each stratum sample size (not just the overall

sample size) must be relatively large. Even when the Breslow-Day test is valid, it might not be very powerful against certain alternatives, as discussed in Breslow and Day (1980)."

Finally, the treatment effect described in the clinical study reports is the difference between esomeprazole and placebo – not the odds ratio. The appropriateness of using a test to assess the homogeneity of the odds ratio instead of a test to assess the homogeneity of the difference between treatment groups is not clear. When event rates are low, the odds ratio is a good estimate of the relative risk. In this study, the rebleed rates were 5.9% for esomeprazole and 10.3% for placebo. The rates may be small enough to permit the use of the odds ratio.

Table A.1
Study D961DC00001: Treatment Effect and 95% Confidence Interval by Center
(ITT Population)

Center Number	n_{Nexium} / $n_{Placebo}$	Esomeprazole – Placebo (%)	95% C.I.
11	1 / 3	**66.67**	
12	6 / 6	-16.67	
23	3 / 3	**16.67**	
41	3 / 4	-25.00	
76	7 / 5	**14.29**	
82	3 / 4	-25.00	
84	3 / 3	-33.33	
98	7 / 8	-25.00	
99	5 / 5	-20.00	
105	5 / 5	**20.00**	
106	1 / 2	**100.00**	
110	1 / 2	-50.00	
121	1 / 2	-100.00	
122	5 / 7	-8.57	
133	1 / 1	-100.00	
138	7 / 6	-16.67	
143	2 / 1	**50.00**	
144	3 / 4	-50.00	
160	2 / 4	**25.00**	
163	3 / 2	**33.33**	
174	2 / 2	-50.00	
175	3 / 5	-20.00	
176	4 / 4	**50.00**	
177	7 / 11	**14.29**	
180	7 / 3	-19.04	
183	7 / 6	**14.29**	
186	3 / 3	-33.00	
201	5 / 3	**20.00**	
215	8 / 8	-12.50	
21 (Denmark)	13 / 16	-6.25	(-30.23, 18.60)
53 (France)	13 / 13	0.0	(-26.17, 26.17)
78 (Germany)	10 / 10	-20.00	(-56.67, 19.04)
101 (Hong Kong)	25 / 25	-4.00	(-22.22, 13.51)
102 (the Netherlands)	**11 / 10**	**-30.91**	**(-66.10, 7.99)**
127 (Romania)	12 / 12	-8.33	(-38.48, 18.85)
145 (Russia)	12 / 16	-12.50	(-38.48, 14.43)
149 (South Africa)	14 / 15	7.62	(-20.12, 35.97)
184 (Turkey)	12 / 13	-7.69	(-37.57, 18.91)

Source: Statistical Reviewer's Listing

Source: Table A.1 from statistical review dated 11/13/2008

2.3 Internal consistency in demonstrating treatment effect in important subgroups such as age ≥65 years

I agree with the Applicant that the treatment effect does not appear to differ between the two age groups, although I base my conclusion on observation rather than a formal test.

The statistical reviewer noted:

> Table A.2 presents descriptive results by race, age and gender. In the larger subgroups numerical differences favor esomeprazole over placebo. The rate of clinically significant rebleeding within 72 hours is less in the esomeprazole group compared to the placebo group for the following subgroups:
>
> - Caucasian (5.5% for esomeprozole vs. 10.8% for placebo)
> - Oriental (3.7% for esomeprozole vs. 7.4% for placebo)
> - less than 65 years of age (5.5% for esomeprozole vs. 11.9% for placebo)
> - at least 65 years of age (6.2% for esomeprozole vs. 8.4% for placebo)
> - males (5.9% for esomeprozole vs. 10.4% for placebo)
> - females (5.8% for esomeprozole vs. 9.9% for placebo)

Source: Statistical review dated 11/13/2008

2.4 Internal consistency in demonstrating the treatment effect in important secondary efficacy outcomes in the first 72 hours

The Complete Response letter notes the proportion of patients who underwent surgery did not differ between the two treatment groups (p=0.31), the esomeprazole treatment group had a lower number of blood units transfused (492) relative to placebo (738), p=0.05; and the endoscopic retreatment rate was lower for esomeprazole (4.3%) relative to placebo (8.2%, p=0.02). The letter also indicates these comparisons required adjustments for multiple comparisons and cites the results of a Bonferroni adjustment. Note, in her review, the statistical reviewer considered the Applicant's analyses exploratory because the protocol did not specify adjustments for multiplicity.

In their response, the Applicant acknowledges the lack of statistical significance for some of the secondary endpoints, but maintains they are supportive of the primary endpoint. They all favor esomeprazole and, therefore, support the findings for the primary endpoint. Because they are being used to support the primary findings, the Applicant indicates adjustments are not needed.

If the sole purpose of the secondary endpoints is to provide supportive evidence, then I do not believe adjustments are needed. If the intent was to gain labeling claims, then adjustments would be needed. The larger issue is the reliance on a single study to support efficacy. In that context, the results for surgery and blood units transfused are not persuasive. The treatment effect for endoscopic retreatment was -3.9% and this result may have more clinical relevance than the results for the other two secondary endpoints, despite the p-value (p=0.02) not being of the magnitude usually required of a single study.

2.5 Regarding Site 0102 in the Netherlands

Center 0102, located in the Netherlands, reported the largest treatment effect of all centers that participated in the study: -31% rebleeding events. The investigator at the site received significant payments from AstraZeneca. When the center was excluded from the analysis, the

treatment effect for the entire study decreased from -4.4% to -3.7% (95% CI: -7.7, 0.1), and the p-value increased to 0.06.

The Applicant maintains the data generated from the site are of high quality and should be retained. Their response indicates this site recruited higher-risk patients more frequently compared with the study overall as assessed by reasons for hospitalization, Forrest classification, physical status classification and shock at admission.

As shown in the table above, this site enrolled 21 subjects out of a total of 767 enrolled in the study. It is of interest that sensitivity analysis, which excludes a site that enrolled less than 3% of subjects, would result in a treatment effect that is not only smaller but also statistically non-significant. This finding points up concerns with the robustness of a single study that is being used to support efficacy.

4. CONCLUSIONS

The Applicant's assertion that the Breslow-Day test supports the homogeneity of the treatment effect across study centers is not persuasive. Because the Breslow-Day test is not a very powerful test for detecting lack of homogeneity, the lack of a statistically significant finding is not necessarily meaningful. Moreover, the small sample sizes when considering stratification variables further limits the usefulness of the test. Additionally, the test assesses the consistency of odds ratios, whereas the estimate of interest was the difference between two treatment groups.

Center 0102, located in the Netherlands, enrolled 21 subjects and was one of the largest centers in the study of 767 subjects. Despite accounting for just less than 3% of the overall enrollment, a sensitivity analysis that excluded this center resulted in a smaller and statistically non-significant treatment effect. This suggests treatment effect was not consistent across study centers.

Although the original study showed a treatment effect of -4.4% (p=0.03), a major review issue was whether the level of evidence coming from this single study was sufficient to support the efficacy and, therefore, approval of the indication. The statistical and clinical concerns resulted in the comments that I have reviewed in this document. The Applicant's responses, from my perspective, do not dispel concerns regarding the level of statistical significance, and issues with the distribution of the treatment effect across study center and country.

From my perspective, the review question of interest is whether the original study can be considered one of two studies to support the efficacy of esomeprazole, where the other studies are the omeprazole studies contained in the resubmission. As I reported in my statistical review (dated 6/7/2011), one set of omeprazole studies (I-840 and I-841) had too few subjects to make any meaningful conclusions regarding efficacy. The other study was conducted solely in Hong Kong. While the study's results appeared persuasive, the issue is whether the results can be generalized to the United States. Thus, the approval of the desired indication seems to rest on the original study.

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LISA A KAMMERMAN
06/15/2011

MICHAEL E WELCH
06/15/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-689/ 014
Drug Name:	Nexium IV (esomeprazole sodium 20 mg and 40 mg) for Injection)
Indication(s):	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Applicant:	AstraZeneca
Date(s):	Letter Date: September 15, 2010 Received Date: September 16, 2010 PDUFA Due Date: June 16, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Lisa A. Kammerman, Ph.D.
Concurring Reviewers:	Michael Welch, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors
Clinical Team:	Erica Wynn, M.D.
Project Manager:	Stacey Barley, RN, M.S.N., M.H.A.

Keywords: Clinical studies

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The establishment of efficacy of esomeprazole in this complete response relies on (1) a study that bridges esomeprazole and omeprazole, and (2) placebo-controlled studies of omeprazole. The bridging study is being reviewed by the clinical pharmacology team. The statistical question of interest is whether the results of the placebo-controlled studies of omeprazole establish the superiority of omeprazole in reducing rebleeding events.

Only one of the two sets of omeprazole studies support the superiority of omeprazole. The Lau study, conducted entirely in Hong Kong, showed a reduction in rebleeding within 30 days, from 22.5% (27/120) in the placebo treatment group to 6.7% (8/120) in the omeprazole treatment group ($p<0.001$). A major issue is whether these results can be generalized from an Asian population to a more diverse population. The medical team will need to decide this question.

The other set of studies – I-840 and I-841, contained only 52 subjects who would have met the entry criteria for D961DC00001 and who received the same treatment as did the subjects who enrolled in D961DC00001. Although the treatment effect favored omeprazole for the endpoint of rebleeding within 72 hours, the difference was not statistically significant: omeprazole – 13.6% (3/22) vs. placebo – 23.3% (7/30); $p=0.49$, Fisher's Exact Test.

2. INTRODUCTION

2.1 Overview

On May 29, 2008, the Food and Drug Administration received a supplemental NDA for Nexium IV. The submission contained a single study, D961DC00001, which did not provide the level of evidence needed to support efficacy for the desired indication. As a result, the FDA issued a Complete Response letter that was dated November 26, 2008. The letter recommended at least one additional, adequate and well-controlled study that should include some centers from the United States, a dose-finding study in the target population, an assessment of a study site in the Netherlands that reported the greatest treatment effect, a pharmacokinetic study in patients with hepatic impairment and a plan for studying Nexium IV in pediatric patients. The Complete Response letter also raised issues regarding the generalizability of the results to the United States because over one-third of the subjects were treated with endoscopic epinephrine injection as a single therapy, which is not an acceptable standard of treatment as single therapy for upper gastrointestinal bleeding from gastric or duodenal ulcers.

In this resubmission, although the Applicant acknowledges the level of significance in the single study did not reach the level of significance needed for a single study to support efficacy, the Applicant does not agree with all the reasons cited in the Completer Response letter. For instance, the Applicant disagrees with the FDA finding of a non-significant result when the

primary analysis was adjusted for country through the use of a Mantel-Haenszel test, claiming the test resulted in a decreased sample size because the test eliminated 29 (of 64) strata which did not have any observations and that more rebleeding events were eliminated from the placebo group than from the treatment group. They also claim the results are consistent across study centers and subgroups defined by age (≥65 years, <65 years), based on what would be expected from chance alone. They also assert results are consistent among secondary endpoints.

Nonetheless, to address the issues identified in the Complete Response letter, this resubmission consists of results from a bridging study between omeprazole IV and esomeprazole IV and data from randomized controlled clinical trials of omeprazole IV. The submission of the randomized trials with omeprazole IV substitutes for an adequate and well-controlled study of esomeprazole, as recommended in the Complete Response letter. The submission also contains results from observational studies with omeprazole IV, meta-analyses, outcomes of treatment in clinical practice and a summary of published systematic reviews of available literature on clinical studies with PPIs.

The data from the randomized controlled clinical trials with omeprazole IV are the focus of this statistical review. These studies include:

- A study reported by Lau JYW, Sung JJY, Lee KKC, et al: "Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers", New England Journal of Medicine, 2000, 343:310-316.

- Study I-840: "The effect of omeprazole on endoscopically treated bleeding peptic ulcers – a multicentre study"

- Study I-841: "Continuous omeprazole infusion therapy in patients with bleeding peptic ulceration of the upper gastrointestinal tract"

The Lau study was conducted between May 1998 and July 1999 at the Prince of Wales Hospital in Hong Kong. Eligible subjects were at least 16 years old and ran a high risk of rebleeding in whom endoscopic treatment of actively bleeding ulcers or ulcers with non-bleeding vessels had been successful after admission to the hospital. Subjects had to undergo endoscopic treatment within 24 hours of admission. After successful endoscopic treatment, a total of 240 subjects were randomized equally to either omeprazole (80 mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours) or placebo. At the end of infusion, all subjects were given 20 mg of omeprazole orally per day for eight weeks. The primary endpoint was bleeding recurrence within 30 days after. The study was terminated after the third interim analysis because of the significant difference between the treatment groups in the rate of recurrent bleeding satisfied the Peto-Haybittle rule. Among subjects randomized to omeprazole, the rebleeding rate was 6.7% (n=8) compared to 22.5% (n=27) among subjects randomized to placebo (p=0.0008, Fisher's exact test).

Studies I-840 and I-841 were conducted by the Applicant in the early 1990s in subjects with peptic ulcer bleeding (PUB). The objective was to compare omeprazole IV with placebo on

overall outcome assessed by a composite endpoint. The studies had similar study designs. Study I-840 was conducted in Denmark, the Netherlands and France; Study I-841 was conducted in Sweden and Norway. Together, the two studies enrolled 607 subjects. To make the study populations similar to that in D961DC00001, in which all subjects received endoscopic treatment, the data analyses of I-840 and I-841 excluded subjects who did not receive endoscopic treatment. As a result, Study I-840 contributed 192 subjects (omeprazole – 93, placebo – 99) and Study I-841 contributed 21 subjects (omeprazole – 9, placebo – 12). The exclusion of 394 subjects from the total enrollment of 607 subjects reflects the limited use of endoscopic treatment at the time these studies were conducted.

2.2 Data Sources

The study report and additional information for this submission were submitted electronically. These items are located in the Electronic Document Room at \\cdsesub1\evsprod\NDA021689 , starting with Folder 034.

I also considered the Statistical Review of NDA 21-689/014; review dated November 13, 2008.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

An objective of the review of Studies I-840 and I-841, and the study conducted by Lau et al was to ensure the comparability of the study populations and study endpoints with that of Study D961DC00001.

Study D961DC00001 was the single study contained in the original submission. The primary endpoint for the study was significant rebleeding within 72 hours of endoscopic treatment. Eligible subjects had a single bleeding source that was confirmed by endoscopy and treated successfully, defined to be the stopping of bleeding achieved by endoscopic treatment and with epinephrine injection therapy and/or one of the following coagulation treatments: heater probe, electrocautery, or hemoclips. Subjects were randomized equally to esomeprazole IV or placebo IV.

3.1.1 Studies I-840 and I-841

Studies I-840 and I-841 were conducted by the Applicant in the early 1990s in subjects with peptic ulcer bleeding (PUB). The objective was to compare omeprazole IV with placebo on overall outcome assessed by a composite endpoint. The studies had similar study designs. Study I-840 was conducted in Denmark, the Netherlands and France; Study I-841 was conducted in Sweden and Norway. Together, the two studies enrolled 607 subjects. To make the study populations similar to that in D961DC00001, in which all subjects received endoscopic treatment, the data analyses of I-840 and I-841 excluded subjects who did not receive endoscopic treatment. As a result, Study I-840 contributed 192 subjects (omeprazole – 93, placebo – 99) and

Study I-841 contributed 21 subjects (omeprazole – 9, placebo – 12) to the analyses. The exclusion of 394 subjects from the total enrollment of 607 subjects reflects the limited use of endoscopic treatment at the time these studies were conducted.

The Applicant concludes that omeprazole IV significantly reduced the number of rebleeding events within 72 hours and within 21 days compared with placebo (p=0.0173 and p= 0.0043, respectively); see Table 1.

However, the resubmission notes endoscopic treatment given to subjects in these two studies was not standardized, unlike Study D961DC00001 in which all subjects received epinephrine injection therapy and/or one of the following coagulation treatments: heater probe, electrocautery, or hemoclips. The resubmission contains an additional analysis that is stratified by the type of endoscopic treatment (same as treatment used in D961DC00001, or different type of treatment compared with D961DC00001); see Table 2. The conclusion is the treatment effect remains statistically significant.

We requested detailed information on the types treatments administered concomitantly with endoscopic treatment, because the resubmission did not contain the level of detail needed for a review of the results. The responses dated 2/14/2011, 2/18/2011 and 4/6/2011 clarified that the subset of 137 subjects identified in Table 2 as "same type of endoscopy treatment as used in D961DC00001" were subjects who fulfilled the entry criteria for study D961DC00001. Of these 137 subjects, however, only 52 subjects received endoscopic treatment that was actually used in D961DC00001. Of these 52 subjects, 38 received epinephrine as a single injection therapy.

Among the 52 subjects, a smaller proportion 13.6% (3/22) of omeprazole-treated subjects had a rebleeding event within 72 hours as compared to placebo-treated subjects: 13.6% (3/22) vs. 23.3% (7/30). However, this difference was not statistically significant (p=0.4882, Fisher's Exact Test). The sample size was too small to permit meaningful analyses of subgroups.

Table 1. Summary of efficacy results for endoscopically treated patients, pooled results from studies I-840 and I-841

Variable	Omeprazole (n=102)	Placebo (n=111)
Rebleeding within 24 hours[a], n (%)		
No rebleed	88 (86.3%)	87 (78.4%)
Rebleed	14 (13.7%)	24 (21.6%)
Rebleeding within 48 hours[a], n (%)		
No rebleed	85 (83.3%)	77 (69.4%)
Rebleed	17 (16.7%)	34 (30.6%)
Rebleeding within 72 hours[a], n (%)		
No rebleed	85 (83.3%)	77 (69.4%)
Rebleed	17 (16.7%)	34 (30.6%)
Rebleeding within 21 days[a], n (%)		
No rebleed	91 (89.2%)	82 (73.9%)
Rebleed	11 (10.8%)	29 (26.1%)
Death within 72 hours, n (%)		
No death	101 (99.0%)	110 (99.1%)
Death	1 (1.0%)	1 (0.9%)
Death within 21 days, n (%)		
No death	95 (93.1%)	104 (93.7%)
Death	7 (6.9%)	7 (6.3%)
Endoscopic retreatment within 72 hours, n (%)		
No endoscopic retreatment	97 (95.1%)	99 (89.2%)
Endoscopic retreatment	5 (4.9%)	12 (10.8%)
Endoscopic retreatment within 21 days, n (%)		
No endoscopic retreatment	96 (94.1%)	96 (86.5%)
Endoscopic retreatment	6 (5.9%)	15 (13.5%)
Surgery due to rebleeding within 72 hours, n (%)		
No surgery	97 (95.1%)	99 (89.2%)
Surgery	5 (4.9%)	12 (10.8%)
Surgery due to rebleeding within 21 days, n (%)		
No surgery	90 (88.2%)	96 (86.5%)
Surgery	12 (11.8%)	15 (13.5%)
Number of blood units transfused within 72 hours		
Mean (SD)	3.2 (2.4)	3.6 (2.9)
Min-Max	0-16	0-14

SD standard deviation

[a] Moderate plus severe rebleedings are reported during the 72 hour iv treatment period while only severe rebleeding is reported within 21 days. For definitions of rebleeding used in the studies see "Outcome variables" in Section 3.1.2.

I840_I841_efficacy

Source: Table 7, 'Summary of efficacy results for endoscopically treated patients, pooled results from studies I-840 and I-841', Supporting Documentation

Table 2. Analysis of rebleeding within 72 hours, endoscopically treated subjects in I-840 and I-841, pooled data

Endoscopy treatments	Rebleed status	Omeprazole n=102	Placebo n=111	p-value[a]	p-value[b]
All types	No rebleed	85 (83.3%)	77 (69.4%)	0.0173	0.0098
	Rebleed	17 (16.7%)	34 (30.6%)		
Different type of endoscopy treatment compared with D961DC00001	No rebleed	32 (76.2%)	21 (61.8%)		
	Rebleed	10 (23.8%)	13 (38.2%)		
Same type of endoscopy treatment as used in D961DC00001	No rebleed	53 (88.3%)	56 (72.7%)		
	Rebleed	7 (11.7%)	21 (27.3%)		

a Mantel-Haenszel test
b Cochran-Mantel-Haenszel test stratified by endoscopic treatment (injection technique/ electrocoagulation)

Source: Table 8, 'Analysis of rebleeding within 72 hours, endoscopically treated patients in I-840 and I-841, pooled data', Supporting Documentation

3.1.2 Lau Study

The materials available for review included:

- An article published by Lau and colleagues in the NEJM in 2006.
- A research proposal (dated 9/1/1998) that provides additional information on the study. This appears to be the equivalent of a study protocol.
- Datasets containing raw data and derived data

A detailed statistical analysis plan was not available for review. Minutes of meetings conducted by the data monitoring committee, which stopped the study after the third interim analysis, are no longer available and could not be reviewed. Although the NEJM article indicates the Peto-Haybittle rule was used, interim analyses are not mentioned in the research proposal.

The study was conducted between May 1998 and July 1999 at the Prince of Wales Hospital in Hong Kong. Eligible subjects were at least 16 years old and ran a high risk of rebleeding in whom endoscopic treatment of actively bleeding ulcers or ulcers with non-bleeding vessels had been successful after admission to the hospital. Subjects had to undergo endoscopic treatment within 24 hours of admission. After successful endoscopic treatment, a total of 240 subjects were randomized equally to either omeprazole (80 mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours) or placebo. At the end of infusion, all subjects were given 20 mg of omeprazole orally per day for eight weeks.

The study was designed to detect a reduction of 10% in the rate of rebleeding – from 15% to 5%, with 80% power at α=0.05 (two-sided). The primary endpoint was bleeding recurrence within 30 days after endoscopy and was analyzed using the intent-to-treat principle. The NEJM publication indicates "the Kaplan-Meier method was used to analyze the primary end point of recurrent bleeding within 30 days after endoscopy." The article contains a graphical presentation of Kaplan-Meier estimates. However, it appears the actual analyses were done on crude rates.

The study was terminated after the third interim analysis because the significant difference between the treatment groups in the rate of recurrent bleeding satisfied the Peto-Haybittle stopping rule. Among subjects randomized to omeprazole, the rebleeding rate was 6.7% (n=8) compared to 22.5% (n=27) among subjects randomized to placebo (p=0.0008, Fisher's exact test).

Results of analyses of subgroups defined by Forrest Classification suggest the treatment effect is fairly consistent across the subgroups, with the exception of '1A' (Table 3). The subgroup of subjects with Forrest Classification '1A' had the smallest observed treatment effect – -7.9%, but also had relatively few subjects.

Results of analyses of subgroups defined by age (≥65 years, <65 years) suggested older subjects accounted for most of the overall treatment effect. However, this could be due to the relatively few rebleeding events observed for younger subjects. The treatment effect for males was consistent with that for females.

Table 3. Recurrent bleeding within 30 days, overall and by Forrest Classification

	Omeprazole	Placebo	Treatment Difference	p-value (Fisher's Exact Test)
Overall	8/120 (6.7%)	27/120 (22.5%)	-15.8%	<0.001
Forrest Classification				
1A	2/14 (14.3%)	2/9 (22.2%)	-7.9%	1.00
1B	1/49 (2.0%)	8/49 (16.3%)	-14.3%	0.02
2A	3/38 (7.9%)	9/36 (25.0%)	-17.1%	0.06
2B	2/18 (11.1%)	8/26 (30.8%)	-19.7%	0.17
Age				
≥65 years	6/76 (7.9%)	24/80 (30.0%)	-22.1%	<0.001
<65 years	2/44 (4.6%)	3/40 (7.5%)	- 2.9%	0.67
Gender				
Male	5/80 (6.3%)	17/80 (21.3%)	-15.0%	<0.001
Female	3/40 (7.5%)	10/40 (25.0%)	-17.5%	0.06

Source: Statistical reviewer's analysis

3.2 Evaluation of Safety

Please refer to the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

In the Lau study, the treatment effect for those ≥65 years was much greater than that for those <65 years: -22.1% vs. -2.9% (Table 3). However, this difference may simply be a function of the relatively few events that occurred in the younger subjects. Among those <65 years, 5/84 experienced a rebleed compared with 30/156 among those ≥65 years. Results did not appear to differ by gender.

Analyses by race could not be evaluated because all subjects enrolled were Asian. This must be considered when a determination is made regarding the generalizability of the results to the United States. To illustrate, an editorial[1] that accompanied the Lau publication states the following:

> "Lau et al. did not measure intragastric pH. They indicate that because Asian subjects generally have lower acid output than white subjects, they were confident that the doses chosen would suppress acid adequately. Whether their clinical findings can be extrapolated to groups of people with higher acid output remains uncertain, however."

The 52 subjects enrolled in I-840 and I-841 who were most comparable to the population enrolled in Study D961DC00001 were too few to allow meaningful analyses of subgroups.

4.2 Other Special/Subgroup Populations

For the Lau study, I estimated the treatment effect according to Forrest Classification at baseline (Table 3). The treatment effect appeared fairly consistent across classifications 1B, 2A and 2B. The treatment effect for classification 1A was smaller than for the other classifications. However, this could be due to the relatively small number of subjects (n=23) who fell into this group.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

To address the Complete Response, the Applicant submitted studies that compared omeprazole and placebo: Studies I-840 and I-841, pooled; and Lau. A placebo-controlled study with esomeprazole was not conducted because of ethical considerations. To justify a decision to

[1] Libby ED. Editorial: Omeprazole to prevent recurrent bleeding after endoscopic treatment of ulcers. N Engl J Med 2000;343:358-359.

generalize the omeprazole study results to esomeprazole, the submission contains a bridging study for esomeprazole and omeprazole, which is being reviewed by the clinical pharmacology team. An important objective of the statistical and medical reviews of the omeprazole studies is to ensure the comparability of the study populations with the population of the original esomeprazole study, D961DC00001.

Of the original 607 subjects enrolled in 840/841, the Applicant identified 212 who would have met the entry criteria for D961DC00001. However, of these 212 subjects, only 52 received the same type of endoscopic treatments that were used in D961DC00001. Among these 52 subjects, a smaller proportion 13.6% (3/22) of omeprazole-treated subjects had a rebleeding event within 72 hours as compared to placebo-treated subjects: 13.6% (3/22) vs. 23.3% (7/30). However, this difference was not statistically significant (p=0.4882, Fisher's Exact Test).

The Lau study, which enrolled 240 subjects, had a statistically significant finding ($p<0.001$) in favor of omeprazole for reducing rebleeding events within 30 days: omeprazole – 6.7% (8/120), placebo – 22.5% (27/120). Because the study was not designed for drug approval, certain documentation was not available for review. For example, I did not review a statistical analysis plan, protocol, a charter for the data monitoring committee or committee meeting minutes.

A major issue with the Lau study is the entire study population comprised Asian subjects. Whether these results can be generalized to a more diverse population is unknown.

5.2 Conclusions and Recommendations

The establishment of efficacy of esomeprazole in this complete response relies on (1) a study that bridges esomeprazole and omeprazole, and (2) placebo-controlled studies of omeprazole. The bridging study is being reviewed by the clinical pharmacology team. The statistical question of interest is whether the results of the placebo-controlled studies of omeprazole establish the superiority of omeprazole in reducing rebleeding events.

Only one of the two sets of omeprazole studies support the superiority of omeprazole. The Lau study, conducted entirely in Hong Kong, showed a reduction in rebleeding within 30 days from 22.5% (27/120) in the placebo treatment group to 6.7% (8/120) in the omeprazole treatment group ($p<0.001$). A major issue is whether these results can be generalized from an Asian population to a more diverse population.

The other set of studies – I-840 and I-841, contained only 52 subjects who would have met the entry criteria for D961DC00001 and who received the same treatment as did the subjects who enrolled in D961DC00001. Although the treatment effect favored omeprazole for the endpoint of rebleeding within 72 hours, the difference was not statistically significant: omeprazole – 13.6% (3/22) vs. placebo – 23.3% (7/30); p=0.49, Fisher's Exact Test.

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06/06/2011

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06/07/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number:	21-689 / 014
Drug Name:	Nexium IV (esomeprazole sodium 20 mg and 40 mg) for Injection
Indication(s):	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Applicant:	GlaxoSmithKline
Date(s):	Letter Date: May 29, 2008 PDUFA Date: Nov. 28, 2008
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology Products
Clinical Team:	Anil Nayyar, M.D., Clinical Reviewer Hugo Gallo-Torres, M.D., Clinical Team Leader
Project Manager:	Chantal Phillips

Key Words: Clinical studies, NDA review, CMH model strata specification, Single Study, Non-U.S. study, Multinational Study

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The one submitted study does not provide substantial statistical evidence demonstrating the efficacy of Nexium IV (esomeprazole sodium) for Injection for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Although the study demonstrated a reduction in rebleeds for Nexium compared to placebo using the protocol-specified analysis model ($p = 0.03$) this result is not statistically persuasive. Moreover, the efficacy comparisons do not remain consistent when adjustments are made for country and physician expertise/standard of care. From a statistical perspective, I would recommend the Applicant conduct a second clinical trial that is deemed appropriate by the Clinical Team.

1.2 Background

Nexium (esomeprazole sodium) is a proton pump inhibitor (PPI) approved for GERD. This single study submission is a labeling supplement for Nexium i.v. This is an international (non-U.S.), randomized, multicentre, prospective, double-blind, parallel-group, placebo controlled study comparing the efficacy and safety of esomeprazole i.v. and placebo i.v. given for 72 hours after therapeutic endoscopic treatment in patients with acute bleeding gastric or duodenal ulcers. After the 72-hour i.v. treatment period, all patients received active treatment with 40 mg oral esomeprazole once daily for 27 days. This review focuses on the 72-hour i.v. treatment period.

The Applicant's proposed indication is:

> *NEXIUM I.V. for Injection is indicated for* (b) (4) *risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.*

1.3 Statistical Issues and Findings

This reviewer found two statistical issues in this submission. They are: 1) After study completion, the final analysis model was revised in the SAP with no protocol amendment; and 2) the clinical concern about country variation in physician expertise and standard of care were not accounted for in the analyses. To address these statistical issues, I conducted the primary efficacy analysis with the pre-specified model and performed various sensitivity analyses addressing country effects. These results did not provide consistent efficacy conclusions.

From a statistical perspective, Study D961DC00001 does not provide consistent or robust evidence of efficacy. Although the study demonstrated a reduction in rebleeds for Nexium compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted to investigate the country variation in physician expertise and standard of care did not give consistent results to the protocol specified analyses. Interpretation of these findings with respect to their clinical relevance is left to the clinical team.

2. INTRODUCTION

2.1 Overview

The Applicant has submitted one clinical study (D961DC00001) designed to demonstrate the safety and efficacy of Nexium IV (esomeprazole sodium) for Injection for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. Table 2.1 presents a brief summary of this study.

Table 2.1
Brief Summary of Clinical Study for Nexium I.V.

Study Number (No. of Centers / Countries) Dates of Study Conduct	Treatment	Number Randomized	Design[1]
D961DC00001 (91 / Austria, Denmark, Finland, France, Germany, Greece, Hong Kong, Netherlands, Norway, Romania, Russia, South Africa, Spain, Sweden, Turkey, and UK) 10-30-05 to 12-14-07	Esomeprazole i.v. Placebo i.v. **Total**	376 391 **767**	R, DB, PG, PC, MC, 3 day i.v.

Source: Statistical reviewer's listing.
[1] R = Randomized, DB = Double-blind, PG = Parallel Group, PC = Placebo Controlled, MC = Multicenter

According to the Applicant:

> The study was conducted in patients with bleeding from a gastric or a duodenal ulcer and in whom there was a high risk of a clinically significant rebleeding after the initial bleeding was successfully treated endoscopically.
>
> Such a relapse of bleeding may be life threatening and result in prolonged hospital stay and additional diagnostic and therapeutic interventions. The rate of clinically significant rebleeding during the first 72 hours after initial endoscopic treatment was therefore a relevant primary outcome variable. …
>
> The rationale for using high dose iv PPIs was based on *in vitro* studies indicating that the blood coagulation system is highly sensitive to the lowering of pH. Clotting time is prolonged and platelet disaggregation is increased at lower pH, and it has therefore been suggested that an early and pronounced reduction of intragastric acidity may reduce the frequency of rebleeding from peptic ulcers. (Section 5.2, page 39 of study report)

2.2 Data Sources

The study report and additional information for this study were submitted electronically. The submitted SAS data sets for the study were complete and well documented. These items are located in the Electronic Document Room at \\CDSESUB1\evsprod\NDA021689\021689.enx under various submissions starting with date 5-29-2008.

3. STATISTICAL EVALUATION

3.1 Design of Study D961DC00001

This is an international (non-U.S.), randomized, multi-center, prospective, double-blind, parallel-group, placebo controlled study comparing the efficacy and safety of esomeprazole i.v. and placebo iv given for 72 hours (a bolus infusion of 80 mg followed by a continuous infusion of 8 mg per hour) after therapeutic endoscopic treatment in patients with acute bleeding gastric or duodenal ulcers.

The Applicant has submitted one clinical study (D961DC00001) designed to demonstrate the safety and efficacy of Nexium i.v. (esomeprazole i.v.) for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

The target population was male and female, at least 18 years of age, who had undergone successful endoscopic hemostatic treatment of a bleeding gastric or duodenal ulcer. Subjects were recruited at 91 centers in 16 countries, not including the United States. Eligible subjects had a single bleeding source, within the last 24 hours, that was endoscopically confirmed from either a gastric or duodenal ulcer classified as Forrest Ia (arterial bleeding), Ib (oozing bleeding), IIa (non-bleeding visible vessel), or IIb (adherent clot). The source of bleeding was treated successfully if bleeding was stopped and was achieved by endoscopic treatment with epinephrine injection therapy and/or one of the following coagulation treatments: heater probe, electrocautery, or hemoclips. Eligible subjects were equally randomized to esomeprazole or placebo using a block randomization schedule and started on study treatment as soon as possible after the endoscopic hemostatic treatment.

Patients were studied who had been treated for peptic ulcer bleeding with successful endoscopic hemostasis, The primary efficacy objective was to compare the efficacy of 72 hours continuous i.v. infusion of either esomeprazole or placebo based on the rate of clinically significant rebleeding during the i.v. treatment period. The primary endpoint is the rate of clinically significant rebleeding within 72 hours of continuous infusion of esomeprazole or placebo.

Secondary efficacy objectives included the comparison of 72-hour i.v. infusion of either esomeprazole or placebo for the following seven endpoints:

1. The rate of clinically significant rebleeding within 7 days and 30 days
2. Proportion of mortalities within 72 hours and 30 days
3. Rate of "bleed-related" mortalities within 30 days, based on the assessments by the Endpoint Committee
4. Proportion of patients who, within 72 hours and 30 days, had surgery due to rebleeding
5. Proportion of patients who within 72 hours and 30 days, had endoscopic re-treatment due to rebleeding
6. Number of blood units transfused within 72 hours and 30 days
7. Number of days hospitalized due to rebleeding within 30 days

The primary analysis for the rate of clinically significant rebleeding within 72 hours was based on a Mantel-Haenszel test, stratified for type of endoscopic treatment at baseline. A two-sided chi-square test with significance level of 5% was used. The final primary efficacy test significance level is adjusted, to account for two interim analyses done, and is equal to 0.0489. The estimated treatment difference along with a 95% confidence interval and p-value for testing the superiority of esomeprazole to placebo were presented. A Breslow-Day test was used to evaluate the country-treatment interactions.

The primary efficacy population was the ITT population, defined as all patients randomized with at least 1 data point after randomization, except those who did not receive any infusion of esomeprazole or placebo.

Included in the ITT analysis were patients who had no endoscopic treatment as well as patients who had more than 2 types of endoscopic treatment performed. Patients with no endoscopic treatment were classified as having single treatment, and patients with more than 2 endoscopic treatments were classified as having combination treatment for type of endoscopic treatment at baseline.

The primary endpoint was also analyzed descriptively in subgroups based on race, age (up to 65 years or 65 years and above) and gender.

All secondary endpoints were tested for efficacy claims using the specific statistical methodology. A Mantel-Haenszel test was used for rate of rebleeding within 7 days, need for surgery, and need for endoscopic retreatment within 72 hours. Mortality and bleed related mortality were analyzed with Fisher's exact test. A log rank test was used for rate of rebleeding within 30 days, need for surgery within 30 days, and need for endoscopic retreatment within 30 days. Blood transfusion (number of blood units) and hospitalization (number of days hospitalized) were analyzed by a Wilcoxon two-sample test. No adjustments for multiplicity and no ordering of importance for the endpoints were prespecified in the protocol.

The study sample size of 760 subjects (380 subjects per treatment group) was based on assuming 7% (esomeprazole) and 15% (placebo) rebleeding rates within the first 72 hours, a 2-sided chi-square test with 5% significance level and 90% power and 10% of the subjects excluded from the per-protocol analysis.

The study was monitored for efficacy and safety by a Data and Safety Monitoring Board (DSMB) with access to all study data as defined in a Charter. Different statistical thresholds were applied to assess safety and efficacy. The DSMB conducted and interpreted the findings of two pre-specified interim analyses, conducted after approximately 33% and 67% of the subjects had completed the study, based on procedures and recommendations described in a *Guideline for Interim Analyses*. The DSMB made recommendations to the Applicant on whether to continue, modify, or prematurely terminate the study.

The interim analyses used asymmetric group sequential procedures with boundaries to monitor a positive trend (less rebleed with esomeprazole) in rebleeding rate. Interim analyses were conducted by a statistician who was independent of the DSMB and Applicant. The alphas for stopping for benefit are as follow: α=0.0001 at the first interim look and α=0.001 at the second interim look. The stopping rule was based on the total number of expected events and analyzed on an ITT principle.

3.2 Evaluation of Efficacy

There are two statistical issues in this submission. They are: 1) the final analysis model was revised in the SAP after study completion, with no protocol amendment and 2) the clinical concern about country variation in physician expertise and standard of care were not accounted for in the analyses. To address these statistical issues, I conducted the primary efficacy analysis with the pre-specified model and sensitivity analyses for the country issues.

In the initial protocol dated June 1, 2005, the baseline factors of endoscopic treatment (single vs. combination) and Forrest class (I vs. II) were assumed by the Applicant to influence the probability of rebleeding and that they should be included in the analysis. According to the Applicant, after a blinded review of the data, no difference was seen in rebleed rate between the Forrest groups. The analysis was therefore changed in the Statistical Analysis Plan (dated Dec. 17, 2007) to only be stratified for endoscopic treatment (single vs. combination). No protocol amendment documenting this change was issued. The Applicant stated that: "All changes were made prior to unblinding of study data" (Section 5.8.2 on page 74 of study report).

The DSMB reviewed unblinded data at formal interim analysis meetings on 21 November 2006 and on 13 March 2007. Recommendations to continue the study were communicated to the Applicant after those meetings.

3.2.1 Subject Disposition and Baseline Characteristics

Table 3.1 presents the number of randomized subjects and their disposition. A total of 767 subjects were randomized, 376 subjects to the esomeprazole group and 391 to the placebo group. For the primary efficacy endpoint, 764 of the 767 randomized subjects were included in the ITT analysis. One patient in the esomeprazole group did not take any study medication and 2 subjects in the placebo group did not sign the informed consent form and they were therefore excluded from the ITT analysis.

Discontinuation rates were similar in both treatment groups (10.4% for esomeprazole and 10.7% for placebo). The primary reasons for study discontinuation are adverse events (2.7% for esomeprazole and 3.8% for placebo), subject request to be withdrawn (3.5% for esomeprazole and 1.8% for placebo), and lost to follow-up (2.1% for esomeprazole and 1.5% for placebo).

Table 3.1
Study D961DC00001: Randomization and Disposition of All Subjects

	Esomeprazole	**Placebo**
Number Randomized (ITT)	376	391
Number Analyzed for Efficacy n(%)*	375 (99.7)	389 (99.5%)
Completed n(%)*	337 (89.6)	349 (89.3)
Discontinued n(%)*	39 (10.4)	42 (10.7)
Primary Reason for Discontinuation n (%)*:		
Adverse Event	10 (2.7)	15 (3.8)
Subject Request to be Withdrawn	13 (3.5)	7 (1.8)
Lost to Follow-up	8 (2.1)	6 (1.5)
Non-compliant	2 (0.5)	2 (0.5)
Death	3 (0.8)	5 (1.3)
Safety Reasons	1 (0.3)	2 (0.5)
Other	2 (0.5)	5 (1.3)

Source: Table 11, page 78, Study D961DC00001 report.
* With respect to number of randomized subjects.

Both groups were similar in baseline and demographic characteristics. The majority of the subjects were male (68% for esomeprazole and 69% for placebo), Caucasian (87% for esomeprazole and 88% for placebo), had combination endoscopic treatment (51% for esomeprazole and 51% for placebo), and had a mean age of about 61 years (62 years for esomeprazole group and 60 years for placebo). There were small differences between treatment groups in the proportion of subjects in each of the four Forrest class categories (see Table 3.2).

Table 3.2
Study D961DC00001: Forrest Class of All Subjects in the ITT Analysis

Forrest Class	**Esomeprazole (n=375)**	**Placebo (n=389)**
Ia	28 (7.5)	40 (10.3)
Ib	166 (44.2)	163 (41.9)
IIa	136 (36.3)	151 (38.8)
IIb	42 (11.2)	34 (8.7)
Missing	3 (0.8)	1 (0.3)

Source: Table 14, page 83, Study D961DC00001 report.

3.2.2 Applicant Efficacy Results

The Applicant's result for the primary efficacy endpoint of rate of clinical significant rebleedings within 72 hours is presented in Table 3.3. The rate of clinical significant rebleedings within 72 hours of i.v. treatment after hemostasis decreases by a mean of 4.4% with esomeprazole compared to placebo (p=0.026). Also, no significant country-by-treatment interactions were found based on the Breslow-Day test.

Table 3.3

Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for ITT Population

	Esomeprazole (N=375)	Placebo (N=389)	Esomeprazole - Placebo
% No Rebleed (n)[1]	94.1% (353)	89.7% (349)	
% Rebleed (n)[1]	5.9% (22)	10.3% (40)	
Treatment Difference vs. Placebo (95% C.I.)[1]			-4.4% (-8.3%, -0.6%)
p-value for Treatment Difference[2]			0.0256

Source: Table 21 on page 88 and Table 54 on page 135 of Study D961DC00001 report.
[1] Percentages and 95% confidence interval are sample based.
[2] p-value based on Mantel-Haenszel test stratified by type of endoscopic hemostatic treatment used (single vs. combination treatment)

The Applicant's results for the 72 hour secondary efficacy endpoints are presented in Table 3.4. The secondary endpoints after 72 hours are not clinically meaningful for evaluating i.v. esomeprazole because after 72 hours, all subjects receive only oral esomeprazole 40 mg daily up to day 30. In addition, these results are considered exploratory because no adjustments for multiplicity were prespecified in the protocol. The results are as follows:

- the proportion of mortalities within 72 hours increased by a mean of 0.3% with esomeprazole compared to placebo
- the proportion of subjects who had surgery due to rebleeding within 72 hours decreased by a mean of 1.0% with esomeprazole compared to placebo
- the proportion of subjects who had endoscopic re-treatment due to rebleeding within 72 hours decreased by a mean of 3.9% with esomeprazole compared to placebo
- the number of blood units transfused within 72 hours deceased by a mean of 246 units with esomeprazole compared to placebo

Table 3.4

Study D961DC00001: Efficacy Results for Secondary Endpoints for ITT Population

	Esomeprazole (N=375)	Placebo (N=389)	Treatment Difference
Proportion of mortalities within 72 hours % (n)	0.3% (1)	0% (0)	0.3%
Proportion who had surgery due to rebleeding within 72 hours % (n)	1.3% (5)	2.3% (9)	-1.0%
Proportion who had endoscopic re-treatment due to rebleeding within 72 hours % (n)	4.3% (16)	8.2% (32)	-3.9%
Number of blood units transfused within 72 hours	492	738	-246

Source: Table 24 on page 92, Table 25 on page 92, Table 26 on page 94, Table 27 on page 95 of Study D961DC00001 report.

3.2.3 Reviewer Sensitivity Analyses

Sensitivity analyses for the primary efficacy endpoint of rate of rebleeding were performed to evaluate how the pre-specified study findings compared to those from alternative analyses.

First, the original, protocol-specified Mantel-Haentzsel analysis included Forrest class (I vs. II) and type of endoscopic treatment (single vs. combination) as stratification variables. Using this model, the results are similar to those presented in Table 3.3 (p=0.0274).

To provide a more meaningful analysis of the data, the Clinical Reviewer has noted issues with the protocol definition of the stratification variables of Forrest class and the type endoscopic treatment. (b) (4) Second, single endoscopic epinephrine injection (see Section 3.1) is not an acceptable current standard of treatment to stop bleeding ulcers. Given this information, the Clinical Reviewer and I decided that it would be best to adjust for all four Forrest class categories and to analyze the subgroup of patients who received single endoscopic injection treatment.

The Clinical Reviewer and I had other concerns about the study design, namely, the non-inclusion of U.S. centers and variations across centers/countries with respect to physician expertise and standard of care. Not accounting for center or country variations could result in misleading results, especially in the absence of U.S. data.

A model based examination of treatment effect by center was not feasible because only 19 of the 91 centers (21%) had greater than 12 randomized subjects. Below are a few descriptive center details that are of interest:

- 29 centers (32%) had fewer than 20 subjects with a non-zero treatment effect
- 9 centers (10%) had at least 20 subjects with a non-zero treatment effect
- 1 center (1%) had at least 20 subjects with a treatment effect of zero
- 41 centers (45%) had fewer than 20 subjects and a treatment effect of zero
- 12 centers (13%) had a treatment effect that could be estimated

So the majority of the centers (54 ÷ 91 = 59%) either had a treatment effect of zero or a treatment effect that could not be estimated. Most of these details can be seen in Table A.1 in the Appendix, which presents center information for those centers that had a non-zero treatment effect.

Also of note is that all eight of the French centers had a treatment effect of zero; and of the three UK centers, one had a treatment effect of zero and the other two had a treatment effect that could not be estimated. In addition, of the nine centers with at least 20 subjects with a non-zero treatment effect (see shaded part of Table A.1), one center from the Netherlands (#102) had the largest treatment effect, in favor of esomeprazole, of -30.9%. Table 3.4 presents treatment effect information for center #102 from the Netherlands. Note that the 95% confidence interval includes zero.

Table 3.5
Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for the Netherlands Center #102

	Esomeprazole (N=11)	Placebo (N=10)	Esomeprazole - Placebo
% No Rebleed (n)	90.9% (10)	60% (6)	
% Rebleed (n)	9.1% (1)	40% (4)	
Treatment Difference vs. Placebo			-30.9% (-66.10, 7.99)

Source: Statistical Reviewer's Listing

To investigate the influence of the Netherlands center #102 on the protocol specified model results, I removed this center from the analysis. The results are presented in Table 3.5 below. Excluding center 102, with 21 subjects, changed the results. The treatment effect for the rate of clinically significant rebleedings within 72 hours changed from -4.4% with a significant p-value of 0.0274 to -3.7% with a non-significant p-value of 0.0596.

Table 3.6
Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours Excluding Netherlands Center #102

	Esomeprazole	Placebo	Esomeprazole – Placebo
N	364	379	
% No Rebleed (n)	94.23% (343)	90.50% (343)	
% Rebleed (n)	5.77% (21)	9.50% (36)	
Treatment Difference vs. Placebo (95% C.I.)			-3.73% (-7.67%, 0.10%)
p-value			0.0596

Source: Statistical Reviewer's Listing
* p-value based on the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II) and type of endoscopic hemostatic treatment used (single vs. combination treatment)

Since it was not feasible to include center as a stratification factor in the formal analysis, we decided that a way to account for variations with respect to physician expertise and standard of care was to include country as a stratification factor in our analyses and to explore treatment effect by country.

Table 3.6 presents the treatment effects and 95% confidence intervals for the 16 countries participating in the study. The treatment effect has a wide range from a minimum of -25.0% (esomeprazole better than placebo) to a maximum of 12.5% (placebo better then esomeprazole). Recall that the overall treatment effect is -4.4% with a 95% C.I. interval of (-8.3%, -0.6%). Note that all the country confidence intervals include zero. With an overall treatment effect of -4.4%, I would expect there to be at least a few countries that show a treatment effect in favor of esomeprazole, based on the upper bound of the 95% confidence interval being less than zero.

Analysis using the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II) and type of endoscopic hemostatic treatment used (single vs. combination treatment) and now adding country as a factor resulted in a non-significant p-value of 0.0582. A similar analysis using Forrest class as four separate categories instead of two resulted in a non-significant p-value of 0.1069. For both analyses, the treatment effect for the rate of clinically significant rebleedings within 72 hours is still -4.4%.

Table 3.7
Study D961DC00001: Treatment Effect and 95% Confidence Interval for Clinically Significant Rebleeding within 72 hours by Country

Country	$n_{Esomeprazole}$ / $n_{Placebo}$	Treatment Effect (%) (Esomeprazole - Placebo)	95% C.I.* (Exact)
Spain	8 / 8	12.5	(-31.4, 54.5)
South Africa	20 / 22	5.4	(-14.0, 27.5)
Sweden	52 / 49	3.5	(-8.4, 15.6)
Denmark	35 / 36	0.2	(-15.0, 15.6)
France	27 / 31	0.0	(-11.2, 12.8)
UK	4 / 1	0.0	(-97.5, 67.2)
Austria	19 / 24	-3.1	(-22.4, 18.3)
Hong Kong	25 / 25	-4.0	(-22.2, 13.5)
Turkey	24 / 24	-4.2	(-22.9, 13.6)
Netherlands	26 / 27	-7.0	(-28.3, 14.6)
Russia	52 / 59	-8.2	(-19.4, 1.1)
Romania	26 / 24	-8.3	(-27.0, 5.9)
Germany	27 / 26	-11.8	(-33.5, 8.1)
Norway	15 / 16	-18.3	(-46.2, 9.9)
Greece	12 / 13	-23.1	(-53.8, 7.2)
Finland	3 / 4	-25.0	(-81.0, 49.4)
OVERALL	**375 / 389**	**-4.4**	**(-8.4, -0.5)**

Source: Statistical Reviewer's listing.

* Exact confidence interval calculated using StatXact.

As mentioned at the beginning of this section, according to the Clinical Reviewer, single endoscopic injection therapy is not an acceptable current standard of treatment to stop bleeding ulcers. Table 3.7 below presents results after excluding those subjects who received single endoscopic injection therapy. The treatment effect for the rate of clinically significant rebleedings within 72 hours is -4.5% with a non-significant p-value of 0.0667 using the protocol specified model and a non-significant p-value of 0.3270 using my model (see bottom of Table 3.7 for model description).

Table 3.8
Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for Subjects Not Receiving Single Endoscopic Injection Therapy

	Esomeprazole (N=232)	Placebo (N=247)	Esomeprazole - Placebo
% No Rebleed (n)	94.4% (219)	89.88% (222)	
% Rebleed (n)	5.6% (13)	10.12% (25)	
Treatment Difference vs. Placebo (95% C.I.)			-4.52% (-9.55%, 0.35%)
p-value based on the protocol-specified model[1]			0.0667
p-value based on this Reviewer's model[2]			0.3270

Source: Statistical Reviewer's Listing

[1] p-value based on the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II) and type of endoscopic hemostatic treatment used (single vs. combination treatment)

[2] p-value based on the Mantel-Haenszel test stratified by country, Forrest class (Ia, Ib, IIa, IIb), and type of endoscopic hemostatic treatment used (single vs. combination treatment)

For comparison, the results of an analysis using those subjects who did receive single endoscopic injection therapy are presented in Table 3.8. The treatment effect for the rate of clinically significant rebleedings within 72 hours is -4.3% with a non-significant p-value of 0.2039 using the protocol specified model and a non-significant p-value of 0.2699 using my model (see bottom of Table 3.8 for model description).

Table 3.9
Study D961DC00001: Percent of Subjects with Clinically Significant Rebleeding within 72 hours for Subjects Receiving Single Endoscopic Injection Therapy

	Esomeprazole (N=143)	Placebo (N=142)	Esomeprazole - Placebo
% No Rebleed (n)	93.7% (134)	89.4% (127)	
% Rebleed (n)	6.3% (9)	10.6% (15)	
Treatment Difference vs. Placebo (95% C.I.)			-4.27% (-11.2%, 2.3%)
p-value based on the protocol-specified model			0.2039
p-value based on this Reviewer's model			0.2699

Source: Statistical Reviewer's Listing.
[1] p-value based on the protocol-specified Mantel-Haenszel test stratified by Forrest class (I vs. II)
[2] p-value based on the Mantel-Haenszel test stratified by country and Forrest class (Ia, Ib, IIa, IIb)

All the above alternative analyses do not provide clear, supportive evidence for the overall treatment effect and the protocol-specified model results. With an overall treatment effect of -4.4%, one would expect there to be at least a few countries that show a treatment effect in favor of esomeprazole, based on the upper bound of the 95% confidence interval being less than zero. Also, all p-values for alternative analyses are not significant, a change from the protocol-specified model p-value of 0.0274.

From a statistical perspective, the above alternative analyses of Study D961DC00001 do not provide consistent evidence of efficacy. Although the study demonstrated a reduction in rebleeds for esomeprazole compared to placebo using the protocol-specified analysis model, the sensitivity analyses conducted to investigate the country variation in physician expertise and standard of care did not give results consistent with protocol-specified analyses. Given that this is a single study whose results are not statistically persuasive, i.e., with a very small p-value, and are not supported by alternative analyses, careful consideration should be given to interpreting these results. Therefore, interpretation of these findings with respect to their clinical relevance should be left to the clinical team.

3.3 Evaluation of Safety

There are no statistical issues with evaluation of safety. Refer to the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

Table A.2 presents descriptive results by race, age and gender. In the larger subgroups numerical differences favor esomeprazole over placebo. The rate of clinically significant rebleeding within 72 hours is less in the esomeprazole group compared to the placebo group for the following subgroups:

- Caucasian (5.5% for esomeprozole vs. 10.8% for placebo)
- Oriental (3.7% for esomeprozole vs. 7.4% for placebo)
- less than 65 years of age (5.5% for esomeprozole vs. 11.9% for placebo)
- at least 65 years of age (6.2% for esomeprozole vs. 8.4% for placebo)
- males (5.9% for esomeprozole vs. 10.4% for placebo)
- females (5.8% for esomeprozole vs. 9.9% for placebo)

5. CONCLUSIONS

For the primary efficacy analysis based on the rate of clinically significant rebleeding within 72 hours of i.v. treatment after hemostasis, the one submitted study does not provides statistically persuasive evidence demonstrating the efficacy of Nexium IV (esomeprazole sodium) for Injection for (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

6. APPENDIX

Table A.1
Study D961DC00001: Treatment Effect and 95% Confidence Interval by Center
(ITT Population)

Center Number	n_{Nexium} / $n_{Placebo}$	Esomeprazole – Placebo (%)	95% C.I.
11	1 / 3	**66.67**	
12	6 / 6	-16.67	
23	3 / 3	**16.67**	
41	3 / 4	-25.00	
76	7 / 5	**14.29**	
82	3 / 4	-25.00	
84	3 / 3	-33.33	
98	7 / 8	-25.00	
99	5 / 5	-20.00	
105	5 / 5	**20.00**	
106	1 / 2	**100.00**	
110	1 / 2	-50.00	
121	1 / 2	-100.00	
122	5 / 7	-8.57	
133	1 / 1	-100.00	
138	7 / 6	-16.67	
143	2 / 1	**50.00**	
144	3 / 4	-50.00	
160	2 / 4	**25.00**	
163	3 / 2	**33.33**	
174	2 / 2	-50.00	
175	3 / 5	-20.00	
176	4 / 4	**50.00**	
177	7 / 11	**14.29**	
180	7 / 3	-19.04	
183	7 / 6	**14.29**	
186	3 / 3	-33.00	
201	5 / 3	**20.00**	
215	8 / 8	-12.50	
21 (Denmark)	13 / 16	-6.25	(-30.23, 18.60)
53 (France)	13 / 13	0.0	(-26.17, 26.17)
78 (Germany)	10 / 10	-20.00	(-56.67, 19.04)
101 (Hong Kong)	25 / 25	-4.00	(-22.22, 13.51)
102 (the Netherlands)	**11 / 10**	**-30.91**	**(-66.10, 7.99)**
127 (Romania)	12 / 12	-8.33	(-38.48, 18.85)
145 (Russia)	12 / 16	-12.50	(-38.48, 14.43)
149 (South Africa)	14 / 15	7.62	(-20,12, 35.97)
184 (Turkey)	12 / 13	-7.69	(-37.57, 18.91)

Source: Statistical Reviewer's Listing

Table A.2

Table 22 Proportion of patients with clinically significant rebleeding within 72 h by race, age and gender, ITT population

Subgroup		Rebleed status	Eso[a] (n=375)	Placebo[b] (n=389)
Race	Caucasian	No rebleed	307(94.5%)	305(89.2%)
		Rebleed	18(5.5%)	37(10.8%)
	Black	No rebleed	3(75.0%)	5(100.0%)
		Rebleed	1(25.0%)	0(0.0%)
	Oriental	No rebleed	26(96.3%)	25(92.6%)
		Rebleed	1(3.7%)	2(7.4%)
	Other	No rebleed	17(89.5%)	14(93.3%)
		Rebleed	2(10.5%)	1(6.7%)
Age	<65	No rebleed	172(94.5%)	185(88.1%)
		Rebleed	10(5.5%)	25(11.9%)
	≥ 65	No rebleed	181(93.8%)	164(91.6%)
		Rebleed	12(6.2%)	15(8.4%)
Gender	Male	No rebleed	239(94.1%)	240(89.6%)
		Rebleed	15(5.9%)	28(10.4%)
	Female	No rebleed	114(94.2%)	109(90.1%)
		Rebleed	7(5.8%)	12(9.9%)

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

Source: Table 22, page 89 of Study D961DC00001 report

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/s/

Sonia Castillo
11/13/2008 03:39:16 PM
BIOMETRICS

Mike Welch
11/13/2008 04:49:10 PM
BIOMETRICS
Concur with review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21689/S-014

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

4 MAY 2011

NDA: 21-689/S-014 and /S-017

Drug Product Name
Proprietary: Nexium I.V.
Non-proprietary: esomeprazole sodium for injection

Review Number: 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
18 April 2011 (S-017)	18 April 2011	19 April 2011	19 April 2011
19 April 2011 (S-014)	19 April 2011	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
15 September 2010 16 November 2010	2 (S-014)	23 March 2011

Applicant/Sponsor
Name: AstraZeneca LP
Address: 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
Representative: Mark A. DeSiato, Executive Director, Regulatory Affairs
Telephone: (302) 885-1386

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Amendments to Efficacy Supplements

2. SUBMISSION PROVIDES FOR: New indications for the drug product

3. MANUFACTURING SITES:
AstraZeneca LP
Westborough MA 01581-4500
USA

AstraZeneca AB
SE-151 85 Södertälje
SWEDEN

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile powder for injection in a glass vial for intravenous injection/infusion, 20 mg/vial or 40 m/vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Proton Pump Inhibitor

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: This was an eCTD submission. A product quality microbiology deficiency was identified in Product Quality Microbiology review #2 of NDA 21-689/S-014 (review dated 23 March 2011). This deficiency was conveyed to the applicant as part of the labeling edits/comments process. The applicant responded with a statement that the information needed to address this deficiency had been provided in the original submission for the drug product (NDA 21-689 dated 10 September 2003). However, the data needed to address the deficiency was not in the original submission. Therefore an information request was sent to the applicant requesting the required data (IR in email dated 15 April 2011). The amendments that are the subject of this review contain the response to the information request. Supplements 14 and 17 are both included in this review because the same labeling issue was in each of those supplements.

filename: N021689S014R3.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – These submissions are recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – N/A

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Bryan S. Riley, Ph.D.
Senior Review Microbiologist, OPS/NDMS

B. Endorsement Block _____

Stephen E. Langille, Ph.D.
Senior Review Microbiologist, OPS/NDMS

C. CC Block

N/A

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/s/

BRYAN S RILEY
05/06/2011

STEPHEN E LANGILLE
05/09/2011

Product Quality Microbiology Review

23 MARCH 2011

NDA: 21-689/S-014

Drug Product Name
Proprietary: Nexium I.V.
Non-proprietary: esomeprazole injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
15 September 2010	16 September 2010	16 October 2010	18 October 2010
16 November 2010	16 November 2010	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
29 May 2008	1	8 July 2008

Applicant/Sponsor
Name: AstraZeneca LP
Address: 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
Representative: Mark A. DeSiato, Executive Director, Regulatory Affairs
Telephone: (302) 885-1386

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Approvable pending resolution of Product Quality Microbiology Labeling issues (see List of Microbiology Deficiencies at the end of this review)

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Efficacy Supplement (Class 2 Resubmission)

2. SUBMISSION PROVIDES FOR: A new indication (Peptic Ulcer Bleed) for the drug product

3. MANUFACTURING SITES:
AstraZeneca LP
Westborough MA 01581-4500
USA

AstraZeneca AB
SE-151 85 Södertälje
SWEDEN

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile powder for injection in a glass vial for intravenous injection/infusion, 20 mg/vial or 40 m/vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Proton Pump Inhibitor

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: This was an eCTD submission. This resubmission is a complete response to an FDA Complete Response Letter (dated 26 November 2008). The submission contains clinical studies and labeling for the new indication. There were no manufacturing process changes related to this supplement and this review addresses only the drug product labeling.

filename: N021689S014R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is approvable pending resolution of product quality microbiology deficiencies (see List of Microbiology Deficiencies on the last page of this review).

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies – The drug product labeling provides for extended room temperature holding periods for the drug product admixtures. However, no microbiology stability data was provided to support the holding conditions. Growth of microorganisms inadvertently introduced into the admixture during dilution of the drug product could potentially harm the patient.

C. Assessment of Risk Due to Microbiology Deficiencies – The labeling deficiency provides a moderate risk to the patient due to the unknown ability of the admixtures to support microbial growth.

III. Administrative

A. Reviewer's Signature _____

Bryan S. Riley, Ph.D.
Senior Review Microbiologist, OPS/NDMS

B. Endorsement Block _____

Stephen E. Langille, Ph.D.
Senior Review Microbiologist, OPS/NDMS

C. CC Block

N/A

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/s/

BRYAN S RILEY
03/24/2011

STEPHEN E LANGILLE
03/24/2011

M E M O R A N D U M

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

DATE **July 8, 2008**

TO: NDA 21-689 SE1 014
Nexium IV (esomeprazole sodium) for Injection.

FROM: James L. McVey

cc: David Hussong, PhD

SUBJECT: Addition of treatment for bleeding post endoscopy (Peptic Ulcer Bleed).

Summary. A study is proposed for effectiveness evaluation of the treatment of patients with an 80 mg dose within a 30 minute span followed by 8 mg/hour for 71.5 hours. The maximum dose per hour is 84 mg. The approved endotoxin limit is (b)(4) EU/mg (in Sept 10, 2003 submission). The applicant states that there are no changes to the CMC section. An electronic document was reviewed.

(b)(4) the endotoxin limit is calculated to be (b)(4) EU/mg., well above the approved endotoxin limit.

Acceptable

END

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/s/

James McVey
7/10/2008 03:10:30 PM
MICROBIOLOGIST

David Hussong
7/10/2008 03:14:03 PM
MICROBIOLOGIST
I concur with the reviewer's endotoxins safety assessment and recommendations to APPROVE the supplement.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21689/S-014 (Cycle 3 Resubmission)	Submission Date(s): 12/14/2012; 02/19/2013; 03/12/2013; 06/20/2013; 07/16/2013
Brand Name	Nexium IV
Generic Name	Esomeprazole Sodium
Clinical Pharmacology Reviewer	Sandhya Apparaju, Ph.D.
Clinical Pharmacology Team Leader	Sue Chih Lee, Ph.D.
Pharmacometrics Reviewer	Kevin Krudys, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.
OCP Divisions	Division of Clinical Pharmacology 3 Division of Pharmacometrics
OND Division	DGIEP
Sponsor	AstraZeneca
Submission Type	Cycle 3 Resubmission of Supplemental NDA
Formulation; Strength(s)	Intravenous Injection; Supplied as freeze-dried powder containing 20 mg or 40 mg of esomeprazole per single-use vial
Indication	(b)(4) re-bleeding in patients following therapeutic endoscopy for bleeding gastric or duodenal ulcers

A CDER regulatory briefing was held on April 19, 2013 for this NDA. Data was presented by Clinical (Dr. Aisha Peterson- Johnson) and Clinical Pharmacology (Dr. Sandhya Apparaju) disciplines. Please refer to the clinical review of this resubmission for the details and outcomes of this regulatory briefing.

Table of Contents

1 Executive Summary

Regulatory Background: In the Complete Response letter issued to the sponsor at the end of cycle 2 review (June 16, 2011), DGIEP expressed concern that although the clinical trial reported by Lau et al (2000) is comparable to the design of D961DC00001 and provides evidence of efficacy of intravenous omeprazole for the proposed indication [prevention of Peptic Ulcer Bleeding, PUB], due to the ethnically homogenous population (Asian) of this study, the ability to generalize the results to the U.S. population may be limited. In particular, the Division expressed concern that Asian populations may have a lower parietal cell mass, a higher prevalence of *H. pylori* infection, and a higher prevalence of the CYP2C19 polymorphism, all of which could have contributed to the larger treatment effect observed in the Lau et al trial. The Division therefore asked for at least one additional, adequate, well controlled clinical trial to demonstrate the clinical benefit of Nexium IV in PUB patients. During subsequent communications, the sponsor voiced ethical concerns of conducting another controlled trial in the target population. This was in light of the published clinical guidelines (American College of Gastroenterology Guidelines; 2012 and the International Consensus Upper GI Bleeding Conference Group; 2010) that strongly advocate the use of intravenous PPI drugs in preventing peptic ulcer re-bleeding after a successful endoscopic hemostasis. Instead sponsor proposed to submit available pharmacokinetic/ pharmacodynamic (PK/PD) evidence to bridge the two populations (Asians and Caucasians) in order to support the applicability of Lau et al data to U.S. population.

Introduction to Cycle 3 Resubmission: The resubmission addresses various issues raised at the end of Cycle 2 review. One of the items addressed is the submission of PK/PD rationale to bridge the Chinese vs. Caucasian populations, in order to support the applicability of Lau et al clinical trial data (generated in Asian population) to the U.S. population. In this regard, the sponsor has submitted their findings from a PK/PD study involving various esomeprazole regimens conducted in Chinese volunteers (Study D961500007), as well as findings from the previously reviewed dose-ranging PK/PD study in Caucasians (Study D961500015). The Clinical Pharmacology review of Cycle 3 thus focuses on the review of PK and PD outcomes from these two studies as well as cross-study comparisons of data in the overall populations as well as subgroups when possible (*H. pylori* status, CYP2C19 status). The ultimate goal is to determine whether there is sufficient PK/PD information to address the issue whether findings from Lau study which included only Chinese patients can be generalized to U.S. population.
It should be noted that PK/PD data presented here were generated in healthy volunteers and involve cross-study comparisons from a small sample size, especially when subjects are further stratified into disease or genotypic subgroups. Applicability to the target PUB population is therefore unclear. However, trends observed for PK and PD across populations and subgroups, when evaluated along with the available clinical trial information can improve our understanding of the role of *H. pylori* status and CYP2C19 polymorphism on clinical outcomes. In addition, this submission addresses dosing recommendations in hepatic impairment subgroups, an issue pending from earlier review cycles.

1.1 Recommendation

NDA 21689 Supplement 14 is acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Overall conclusions: Based on the available PK and PD data among Chinese and Caucasian populations, there is no strong evidence to conclude that the ethnicity factor could contribute to differences in clinical outcomes between the pivotal phase 3 trial 001 and the Lau et al trial, 2000:

- **The impact of *H. pylori* status on clinical outcomes**: Better PD response (i.e. intragastric pH) was noted in subjects of Chinese PK/PD study 007 who were *H. pylori* positive, compared to *H. pylori* negative Chinese subjects. Although it is not certain that this PD difference translates into better clinical outcomes, the Phase 3 pivotal trial 001 and Lau et al trial did show better efficacy in *H. pylori* positive patients. Overall, we do not consider that *H. pylori* status contributed to differences in efficacy outcomes between the two trials because the proportion of *H. pylori* positive patients was similar between the two trials (approximately 65 % in the active treatment groups, and ~ 55% in the placebo groups).

- **The impact of CYP2C19 polymorphism on outcomes**: Differences in CYP2C19 polymorphism across Chinese and Caucasian subjects are unlikely to be an issue, as PK differences between genotypes were modest (17 %) and in addition an exposure-response (E-R) correlation was absent at the high intravenous doses evaluated for this indication.

- **The impact of parietal cell mass differences**: While we do not have concrete data to conclude one way or the other regarding the impact of parietal cell mass differences across ethnicities, the PD response was generally similar between the two PK/PD studies (007 in Chinese and 015 in Caucasians). There were however, some differences in few of the secondary PD outcomes assessed including % time during the first 3 hrs when pH was > 6 or % time over 24 hours with pH>7 which appeared to be better in the Chinese population compared to Caucasians.

Dosing recommendations in hepatic impairment subgroups: (b)(4) Instead, intravenous dosing recommendations in this population are based on i.v. omeprazole data in patients with hepatic impairment as well as a PK/PD bridge between these two drugs (study 004) and are as follows:

Mild hepatic impairment (C-P, A): 80 mg over 30 min + 6 mg/h over 71.5 h

Moderate hepatic impairment (C-P, B): 80 mg over 30 min + 6 mg/h over 71.5 h

Severe hepatic impairment (C-P, C): 80 mg over 30 min + 4 mg/h over 71.5 h

Summary of PK/PD review findings in Cycle 3 resubmission: A review of available PK and PD (gastric pH) information was conducted from two studies of esomeprazole infusion regimens in healthy Chinese and Caucasian volunteers to understand whether suitable bridging of clinical trial data for pivotal trial D961DC00001 (Cycle 1) and Lau et al (Cycle 2) can be achieved (pending issue from Cycle 2). The study in Chinese subjects included both *H. pylori* positive and negative subjects while the study with Caucasians included only *H. pylori* negative subjects. Both studies included subjects of various CYP2C19 genotypes. Data suggests the following:

- Within each of the two studies, no concentration-response relationship was observed.
- Data reviewed is limited by small sample sizes, particularly when evaluating subgroups.
- *H. pylori* status: A trend of larger PD outcomes was observed in the *H. pylori* positive subjects. In particular, the percent time with pH > 6 over the first 3 hours of treatment appeared most sensitive to the presence of *H. pylori* infection (Summary Table 1). Whether or not these differences in PD due to *H. pylori* infection noted in healthy volunteers would translate to meaningful differences in clinical outcomes is not conclusively understood. However, in the two clinical trials for Nexium IV in PUB indication (Study D961DC00001 and Lau, et al), there appears to be a similar incidence of *H. pylori* infection at baseline (65 % in the active treatment groups, and ~ 55% in the placebo groups). A summary of the re-bleeding rates by *H. pylori* status suggested lower incidence of re-bleeding in *H. pylori* positive patients compared to *H. pylori* negative patients. Please refer to the clinical and statistical reviews for further information in this regard.
- *H. pylori* negative subjects - Chinese vs. Caucasians: The PD outcome (% time over 24 h with pH >7) in *H. pylori* negative subjects was higher in Chinese subjects compared to Caucasians (11 % vs. 4 %; Table 1).
- CYP2C19 genotypes: The effect of genotype on PK was minimal at the proposed doses of esomeprazole in both studies (~17 % higher AUC in IMs). There were too few poor metabolizers (PMs) in each of these studies (n = 2 in 007, and n = 1 in 015) to make reasonable interpretations on this genotypic subgroup; nevertheless the systemic exposures in the PM subjects appeared generally comparable to that in IMs. Since the *H. pylori* status could impact the PD outcome, and the Caucasian study lacked *H. pylori* positive subjects, we compared only the *H. pylori* –ve populations across studies. As the Chinese study has a very small sample size (N=5 each for EM & IM), comparison of the PD outcomes between genotypes (Table 2A vs. 2B) is challenging. Since there is no apparent exposure-response relationship, effect of CYP2C19 genotype on PD outcomes (% time when pH> 6 over 24 h and over first 3 h), if any, cannot be explained by concentration differences between EMs and IMs.

Summary Table 1: Cross study comparisons of PD outcomes

PD outcome	**Chinese - *Overall* (*H. pylori* +ve, -ve) (n = 20)**	**Chinese *H. pylori* +ve (n = 9)**	**Chinese *H. pylori* –ve (n = 11)**	**Caucasian-*Overall* (*H. pylori* –ve) (n= 24)**
% time when pH >6 over 24 h	48 ± 17.4	59.12 ± 9.56	46.7 ± 20.4	46.6 ± 26.5

% time when pH> 6 over first 3 h	65 ± 28.6	82.77 ± 5.01	49.4 ± 33.6	43.4 ± 26.1
% time when pH>7 over 24 h	13.3 ± 10.6	18.75 ± 9.26	11.14 ± 8.56	4.0 ± 7.5

Summary Table 2. PD outcomes by genotypes in *H. pylori* (-) subjects: Chinese vs. Caucasians

A: CYP2C19 EMs/ *H. pylori* -ve	**Chinese (n = 5)**	**Caucasians (n = 17)**
% time when pH >6 over 24 h	44 ± 19.78	45.2 ± 28.5
% time when pH> 6 over first 3 h	42.9 ± 26.2	42.6 ± 24
% time when pH>7 over 24 h	7.48 ± 4.68	4.4 ± 8.5
B: CYP2C19 IMs/ *H. pylori* -ve	**Chinese (n = 5)**	**Caucasians (n = 6)**
% time when pH >6 over 24 h	50.1 ± 25.1	56.9 ± 13.9
% time when pH> 6 over first 3 h	52.7 ± 44.8	53 ± 28.3
% time when pH>7 over 24 h	16.1 ± 10.1	3.4 ± 4.9

Dosing recommendations in hepatic impairment subgroups: Sponsor provided modeling and simulation results to support dosing recommendations in patients with varying degrees of hepatic impairment. The sponsor's simulations do not support their proposed dosing regimen for the following reasons:

- The model assumes (b) (4) (b) (4) This assumption is not supported by the data.
- (b) (4) It is possible that bioavailability is also increased in patients with hepatic impairment. If this is the case, the sponsor is likely to over-estimate the impact of hepatic impairment on steady-state exposure.
- The sponsor has not provided data to support (b) (4) Exposure-response analysis in healthy subjects suggests that additional benefit in terms of pH is not achieved at higher exposures.

The final dosing recommendations in the hepatic impairment population are instead based on i.v. omeprazole data in patients with hepatic impairment, due to a previously established PK/PD bridge between the two drugs (Study 004; reviewed in Cycle 2). The steady-state concentrations (Css) and clearance estimates from the hepatic impairment subgroups (Child-Pugh A, B or C) in study I-1226 dosed with 80 mg/h over 30 minutes, followed by 8 mg/h over 24.5 h, were compared to the data from control subjects of study 004 receiving the same dose regimen and constant infusion rates that will achieve steady-state concentrations similar to those of control subjects were estimated. The constant infusion regimen in patients with mild, moderate and severe hepatic impairment should be 6 mg/h, 6 mg/h and 4 mg/h.

2 Question-Based Review

2.1 General Clinical Pharmacology

What is the relevant Clinical Pharmacology information for Esomeprazole?

The subject of the current resubmission is esomeprazole, the S-isomer portion of omeprazole (approved as Prilosec®). Esomeprazole is currently approved as Nexium® IV for the short-term treatment of GERD with EE in adults and pediatric patients, as an alternative to oral therapy. Omeprazole is a racemic mixture of S- and R-isomers. Both isomers are protonated in the acidic environment of the parietal cell to an achiral active moiety that inhibits the proton pump. Both are thus considered equipotent.

Both isomers are cleared by CYP2C19 and CYP3A4. The contribution of CYP2C19 to the metabolism of the S-isomer appears to be lesser compared to the R-isomer. Both isomers can inhibit CYP2C19 (also CYP3A4). At high doses of esomeprazole, the extent of inhibition is such that it almost totally shuts down the enzyme system.

At the 40 mg dose, the fold-differences in systemic exposure between extensive metabolizers (EMs) vs. poor metabolizers (PMs) of CYP2C19 were 5.3 fold for omeprazole (racemate), and 2.9-fold for esomeprazole (S-isomer) *[Source: Clinical Pharmacology and Biopharmaceutics review of NDA 21-153 by Dr. Suliman Al-Fayoumi, and Dr. Suresh Doddapaneni*] . This indicates differences in clearance possibly due to lower contribution and/or more potent inhibition of CYP2C19 (and hence a lower influence of CYP2C19 polymorphism) for the S-isomer (esomeprazole).

What is the proposed indication, mechanism of action and dosing regimen for intravenous esomeprazole in the current NDA supplement?

The proposed indication for Nexium IV in this NDA is (b) (4) (b) (4) re-bleeding in patients following therapeutic endoscopy for bleeding gastric or duodenal ulcers". For bleeding ulcers, a platelet plug generally secures hemostasis for several hours. However, the plug disintegrates unless it has been reinforced by a fibrin clot. The risk of re-bleeding appears highest within the first 72 hours post-endoscopic hemostasis. Presence of acid (i.e. pH effects) however, can cause profound alterations in the coagulation cascade. The proposed mechanism of action of proton-pump inhibitor (PPI) use in PUB is that increased intragastric pH caused by these drugs is favorable for clot stabilization and prevention of re-bleeding.

Available in vitro data suggests that target pH for optimal clot stabilization occurs at pH 6.4- 6.8 (Green et al, Gastroenterology 1978). The target pH in the studies conducted by the sponsor for the current indication was 6.0 (% time during 24 h when intragastric pH was ≥ 6), is lower than that indicated by in vitro information. However, sponsor also has separately documented the % of time over 24 h with pH ≥ 7.0 in these studies as seen further in the review below.

The proposed dosing regimen for Nexium IV in this indication is 80 mg IV infusion over 30 minutes followed by 8 mg/h continuous IV infusion for the next 71.5 hours. (b) (4)

(b) (4)

2.2 Key Clinical Pharmacology Review Findings for Cycle 3

What are the relevant findings from the review of the Chinese PK/PD study 007?

Study D961500007 ("Chinese PK/PD Study"): This was a single-dose, randomized, crossover study in 'healthy' Chinese subjects. Study enrolled 20 subjects, of whom 9 were *H. pylori* positive and 11 were *H. pylori* negative. The CYP2C19 genotype was assessed and included 7 extensive metabolizers (EM), 11 intermediate metabolizers (IM) and 2 poor metabolizers (PM).

The esomeprazole intravenous dose regimens assessed in this study were as follows:

A. 40 mg bolus administered over 3 minutes
B. 40 mg administered over 30 min; two doses separated by 12 h
C. 40 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
D. 80 mg over 30 min, followed by 4 mg/h infusion for 23.5 h
E* 80 mg over 30 min, followed by 8 mg/h infusion for 23.5 h

*The proposed dosing regimen for the target PUB indication is similar to Regimen E.

PK parameters evaluated included Cmax, Css, AUC24 and clearance. PD parameters evaluated included % time over 24 h with pH > 4, >5, >6, and >7; as well as % time over the first 3 h of dosing with pH > 6.

Overall PK: The Cmax values for the 40 mg (A, B, C) and 80 mg (D, E) esomeprazole bolus regimens demonstrated dose proportional characteristics. The AUC0-24h was ~ 60 % greater with the 8 mg/h infusions (e.g. regimen E), compared to the 4 mg/h (regimen D) infusion. Clearance values were comparable across the regimens. Average steady-state (Css) concentrations for the 4 mg/h regimen were roughly 50 % of that seen in the 8 mg/h infusion regimens.

Dose GROUP	Cmax (ng/mL)	Css (ng/mL)	AUC_{0-12h} (hr*ng/mL)	AUC_{0-24h} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	CL (L/hr)
A	3730.1 (3526.7, 3945.3)		5045.2[a] (4725.7, 5386.2)		5041.0 (4282.7, 5799.3)	7.9[b] (7.3, 8.6)
B	3149.8 (2977.6, 3332.0)		4913.2 (4601.3, 5246.3)		5011.9 (3939.0, 6084.8)	8.0[b] (7.3, 8.7)
C	3268.9 (3090.6, 3457.5)	1206.9 (1145.1, 12□2.0)		32970.1 (30882.4, 35199.0)		6.6 (6.3, 7.0)
D	6632.5 (6270.9, 7015.1)	633.3 (600.9, 667.5)		25036.3 (23451.0, 26728.7)		6.3 (6.0, 6.7)
E	6513.0 (6157.9, 6888.7)	1253.4 (1189.3, 1321.1)		39967.3 (37436.5, 42669.1)		6.4 (6.1, 6.7)

A: Esomeprazole 40 mg 3 minute intravenous injection

B: Esomeprazole 40 mg 30 minute intravenous infusion q12h

C: Esomeprazole 40 mg 30 minutes + 8 mg/hour intravenous infusion (23.5 hours

D: Esomeprazole 80 mg 30 minutes + 4 mg/hour intravenous infusion (23.5 hours)

E: Esomeprazole 80 mg 30 minutes + 8 mg/hour intravenous infusion (23.5 hours)

Overall PD: Based on the PD information, all regimens were successful in increasing gastric pH to above 4.0 for most of the 24 h duration. There was a trend for progressively smaller % of time over 24 hours when pH values were at or above 4, 5, 6 or 7, respectively. The goal of PPI therapy in peptic ulcer bleed patients (as claimed by the sponsor) is to maintain pH at or above 6.0 to stabilize the clot and prevent re-bleeding episodes. In this regard, the three regimens that included an initial 30 minute loading dose and a longer duration infusion regimen (C, D, E) were comparable in this population with respect to % time when pH > 6.0 in the first 3 hours of treatment (~ 60 %) and the % time over 24 hours when pH was above 6.0 (~ 50 %). Data suggests lack of dose-response relationship at the higher (LD + infusion) regimens evaluated (C, D, E).

Parameter	Drug administration regimen	Number of subjects	Time percentage %	95% CI
pH >4 (0-24h)	A	18	77.8	73.4, 82.2
	B	19	91.4	87.1, 95.7
	C	18	95.4	91.0, 99.8
	D	19	95.5	91.3, 99.8
	E	19	95.7	91.4, 100.0
pH >5 (0-24h)	A	18	64.7	57.2, 72.2
	B	19	75.4	68.1, 82.8
	C	18	81.0	73.5, 88.5
	D	19	77.2	69.9, 84.5
	E	19	79.0	71.6, 86.3
pH >6 (0-3h)	A	18	49.4	36.6, 62.1
	B	19	56.6	44.1, 69.1
	C	18	62.7	50.0, 75.5
	D	19	66.3	53.9, 78.7
	E	19	64.0	51.5, 76.5
pH >6 (0-24h)	A	18	41.1	33.6, 48.6
	B	19	49.4	42.1, 56.8
	C	18	57.2	49.7, 64.7
	D	19	49.9	42.6, 57.1
	E	19	53.0	45.6, 60.3
pH >7 (0-24h)	A	18	9.3	3.6, 14.9
	B	19	16.0	10.4, 21.6
	C	18	16.7	11.0, 22.4
	D	19	15.0	9.4, 20.5
	E	19	15.1	9.5, 20.7
pH median value (0-24h)	A	18	5.4	5.1, 5.7
	B	19	5.9	5.6, 6.2
	C	18	6.2	5.9, 6.5
	D	19	6.0	5.7, 6.3
	E	19	6.1	5.8, 6.3

PK and PD in subgroups: The following subgroup comparisons were of further interest to understand whether *H. pylori* status or CYP2C19 polymorphic status had independent effects on PK and PD of esomeprazole, particularly at the proposed dosing regimen E:

- PK by *H. pylori* status (+ve vs. –ve) in Chinese
- PD by *H. pylori* status (+ve vs. –ve) in Chinese
- PK by CYP2C19 genotype (EM, IM, PM) in Chinese
- PD by CYP2C19 genotype (EM, IM, PM) in Chinese; Small N for PMs (2)

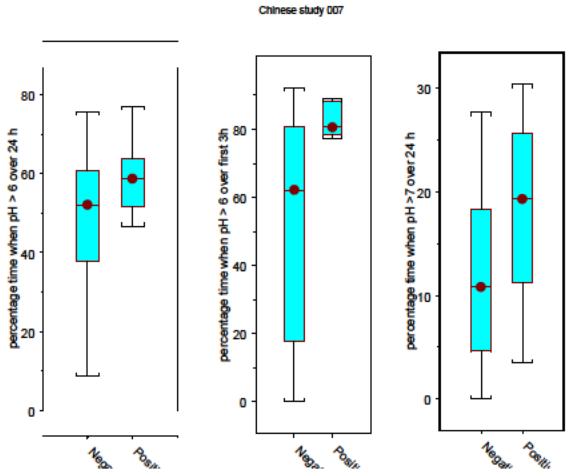
***H. pylori* status**: Study included similar numbers of *H. pylori* +ve (n = 9) and -ve (n = 11) subjects. No PK differences were noted by *H. pylori* status. At baseline, pH was somewhat higher in the *H. pylori* +ve group compared to the –ve group (1.67 vs. 1.47).

PD data for the proposed regimen E is shown below by *H. pylori* status. A trend for larger PD outcomes was noted in *H. pylori* positive Chinese subjects as shown below (primary PD outcome- % time over 24 h when pH >6, is highlighted).

Variability in PD data appeared larger with the *H. pylori* negative group, as seen from the standard deviation values:

Proposed Regimen E	*H. pylori* Positive (n = 9)	*H. pylori* Negative (n = 11)
% time when pH >4 over 24 h	98.37 ± 0.54	93.69 ± 5.05
% time when pH >6 over 24 h	**59.12 ± 9.56**	**46.7 ± 20.4**
% time when pH> 6 over first 3 h	82.77 ± 5.01	49.4 ± 33.6
% time when pH>7 over 24 h	18.75 ± 9.26	11.14 ± 8.56
Mean pH over 24 h	6.25 ± 0.23	5.84 ± 0.61

The box plots below provide a visual representation of some key PD outcomes:



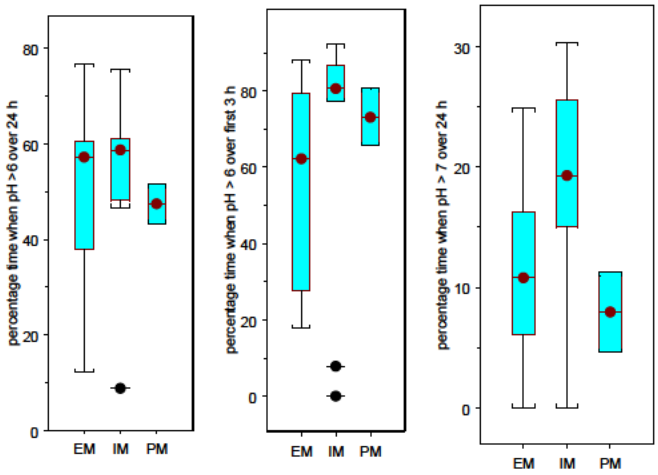
CYP2C19 polymorphism: Systemic exposure was modestly higher (~ 17 %) in the IMs compared to EMs (sample size for PMs is small to make inferences):

PK- Study 007	EMs (n = 7)	IMs (n = 10)	PMs (n = 2)
Cmax (ng/mL)	5953 ± 1257	7225 ± 1815	7846 ± 270
Css (ng/mL)	1199 ± 315	1354 ± 303	1320 ± 203
AUC24 (ng h/mL)	36573 ± 8058	43032 ± 8790	46784 ± 887
CL (L/h)	6.98 ± 1.44	6.3 ± 2.1	6.1 ± 0.94

The primary PD outcome (% time with pH > 6 over 24 h) was comparable across CYP2C19 genotypes. Differences were noted in few other PD outcomes, some of which were minimized when further stratified by *H. pylori* status (e.g. % time over 3 h when pH>6):

PD	Extensive Metabolizers (EM) [n = 7]	Intermediate Metabolizers (IM) [n = 10]	Poor Metabolizers (PM) [n = 2]
% Time pH >4 over 24 h	94.9 ± 4.0	95.8 ± 5.3	97.6 ± 2.0
% Time pH >6 over 3 h	54.6 ± 29.4	67.9 ± 34.1	73.1 ± 10.6
% Time pH > 6 over 24h	50.6 ± 20.5	53.4 ± 17.7	47.5 ± 5.9
% Time pH > 7 over 24h	11.2 ± 7.8	16.4 ± 10.6	7.9 ± 4.7
Median pH over 24h	5.9 ± 0.7	6.1 ± 0.5	5.9 ± 0.1

The box plots below provide visual representation of PD data by genotype status in Chinese subjects of study 007:



What are the relevant findings from the Caucasian volunteer PK/PD study 015?

Study D961500015 ("Caucasian PK/PD Study"): This was a randomized, cross-over PK and PD study of esomeprazole given as five different intravenous regimens in healthy Caucasian subjects. 26 subjects were enrolled in this study, all of whom were documented *H. pylori* negative. Subjects included 17 EMs, 8 IMs and 1 PM.

The esomeprazole intravenous dose regimens assessed in this study were as follows:

1. 40 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
2. 80 mg over 30 min, followed by 4 mg/h infusion for 23.5 h
3. **80 mg over 30 min, followed by 8 mg/h infusion for 23.5 h***
4. 120 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
5. 120 mg over 2 h, followed by 8 mg/h infusion for 23.5 h

* Proposed dosing regimen for target PUB patients is similar to regimen 3 above
PK parameters evaluated included Cmax, Css, AUC24 and clearance. PD parameters evaluated included % time over 24 h when pH was > 4, >5, >6, and >7; as well as % time over the first 3 h of dosing when pH was > 6.

Overall PK: Estimated geometric means with 95% confidence intervals for AUC0-24, Cmax, Css and CL of esomeprazole following the five investigated doses are presented in the table below. A trend for dose proportional increases in Cmax and AUC were noted which were further influenced by the infusion rates for the loading infusion (short-term) as well as longer-term infusions. Clearance values were similar across regimens.

Parameter	Unit	Treatment	N	Estimate	95% CI	
					Lower	Upper
AUC_{0-24}	µmol*h/L	40mg (0.5h)+8mg/h	22	89.69	81.31	98.93
		80mg (0.5h)+4mg/h	24	73.68	66.75	81.33
		80mg (0.5h)+8mg/h	23	111.05	100.51	122.69
		120mg (0.5h)+8mg/h	22	134.66	121.54	149.20
		120mg (2h)+8mg/h	20	126.23	113.80	140.01
CL	L/h	40mg (0.5h)+8mg/h	23	6.70	5.93	7.58
		80mg (0.5h)+4mg/h	24	5.51	4.86	6.24
		80mg (0.5h)+8mg/h	24	5.89	5.20	6.67
		120mg (0.5h)+8mg/h	22	5.40	4.74	6.14
		120mg (2h)+8mg/h	21	5.45	4.78	6.20
C_{max}	µmol/L	40mg (0.5h)+8mg/h	23	7.11	6.44	7.84
		80mg (0.5h)+4mg/h	24	16.01	14.48	17.71
		80mg (0.5h)+8mg/h	24	14.97	13.53	16.56
		120mg (0.5h)+8mg/h	22	23.12	20.81	25.68
		120mg (2h)+8mg/h	21	14.33	12.90	15.93
C_{ss}	µmol/L	40mg (0.5h)+8mg/h	23	3.46	3.06	3.92
		80mg (0.5h)+4mg/h	24	2.10	1.86	2.38
		80mg (0.5h)+8mg/h	24	3.94	3.48	4.46
		120mg (0.5h)+8mg/h	22	4.30	3.78	4.90
		120mg (2h)+8mg/h	21	4.26	3.74	4.85

Overall PD: All doses increased gastric pH significantly above the baseline. The proposed dosing regimen (80 mg/30 min + 8 mg/h infusion) appears to have larger benefit over the two lower dose regimens. The increase in doses beyond this did not afford additional benefit. Based on this information sponsor selected this dose regimen for further evaluation (this study was submitted and reviewed as a dose-finding study during Cycle 1 for NDA 21689/S014).

Variable	Treatment	N	Estimate	95% CI	
				Lower	Upper
pH>4 (0-24h)	Baseline	25	6.0	3.5	8.5
	40mg (0.5h)+8mg/h	23	82.0	74.4	89.7
	80mg (0.5h)+4mg/h	24	80.2	72.4	88.0
	80mg (0.5h)+8mg/h	24	89.5	81.7	97.3
	120mg (0.5h)+8mg/h	22	84.2	76.0	92.4
	120mg (2h)+8mg/h	20	89.5	81.2	97.8
pH>6 (0-3h)	Baseline	25	2.0	0.1	3.8
	40mg (0.5h)+8mg/h	23	24.6	12.4	36.9
	80mg (0.5h)+4mg/h	24	35.2	22.8	47.7
	80mg (0.5h)+8mg/h	24	45.8	33.3	58.3
	120mg (0.5h)+8mg/h	22	45.7	32.6	58.7
	120mg (2h)+8mg/h	20	44.6	31.3	57.9
pH>6 (0-24h)	Baseline	25	1.7	0.5	2.8
	40mg (0.5h)+8mg/h	23	46.0	34.1	57.8
	80mg (0.5h)+4mg/h	24	44.4	32.4	56.5
	80mg (0.5h)+8mg/h	24	52.3	40.3	64.4
	120mg (0.5h)+8mg/h	22	49.0	36.5	61.6
	120mg (2h)+8mg/h	20	56.3	43.5	69.0
pH>7 (0-24h)	Baseline	25	0.1	0.0	0.3
	40mg (0.5h)+8mg/h	23	2.4	0.0	5.3
	80mg (0.5h)+4mg/h	24	4.0	1.0	6.9
	80mg (0.5h)+8mg/h	24	4.8	1.8	7.8
	120mg (0.5h)+8mg/h	22	3.5	0.4	6.7
	120mg (2h)+8mg/h	20	3.6	0.4	6.8

PK and PD in subgroups: All subjects were negative for *H. pylori*. Therefore CYP2C19 polymorphism was a subgroup comparison of interest in study 015 in Caucasians.

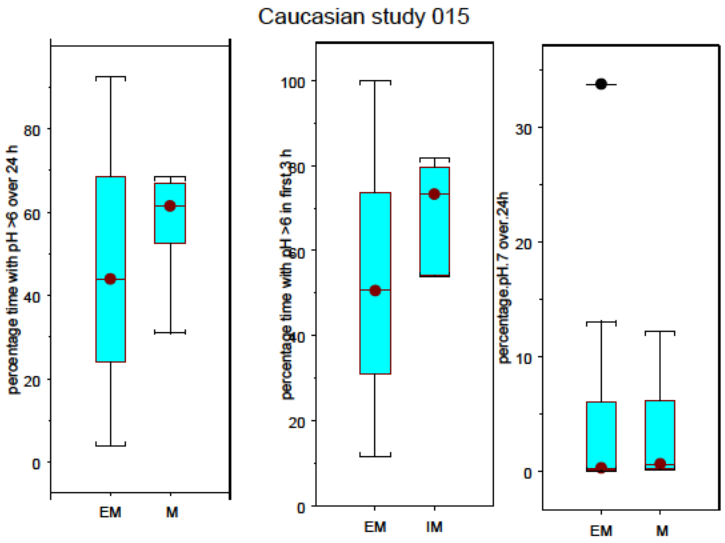
CYP2C19 polymorphism: Systemic exposures were modestly higher (~ 17 %) in the CYP2C19 IMs compared to EMs in this Caucasian study. Data below is for the proposed dose regimen:

Proposed Regimen	Overall	EM (n = 14 -17)	IEM (n = 6)	PM (n =1)
Cmax (umol/L)	14.2 ± 2.6	13.9 ± 3.0	14.5 ± 1.2	17.0
AUC24 (umol.h/L)	109 ± 23.1	105.1 ± 18.8	123 ± 31.5	105.4
Css (umol/L)	4.0± 1.0	3.9 ± 0.9	4.4 ± 1.5	3.7
80 mg over 30 minutes plus 8 mg/h over 23.5 h				

Some PD differences were noted across the genotypes. The relevance of these differences is unclear as data was associated with large variability and sample sizes were different across subgroups (17 EMs vs. 6 IMs) in this study. In addition, *H. pylori* status was not a confounding factor here, since all subjects were documented negative. The modest increases in PK are not anticipated to have a significant impact on PD, particularly since there was a lack of dose/exposure-response correlation *(see Pharmacometrics review)* across the infusion dose ranges evaluated in the present study, as well as in the Chinese study.

	EMs [n = 17]	**IMs [n = 6]**	**PMs [n = 1]**
% Time pH >4 over 24 h	86.3 ± 10.9	89.6 ± 7.5	59.9
% Time pH >6 over 3 h	42.6 ± 24	53 ± 28.3	0.0
% Time pH > 6 over 24h	45.2 ± 28.5	56.9 ± 13.9	7.4
% Time pH > 7 over 24h	4.4 ± 8.5	3.4 ± 4.9	0.0

The box plots below provide a visual representation of the PD data in Caucasians:



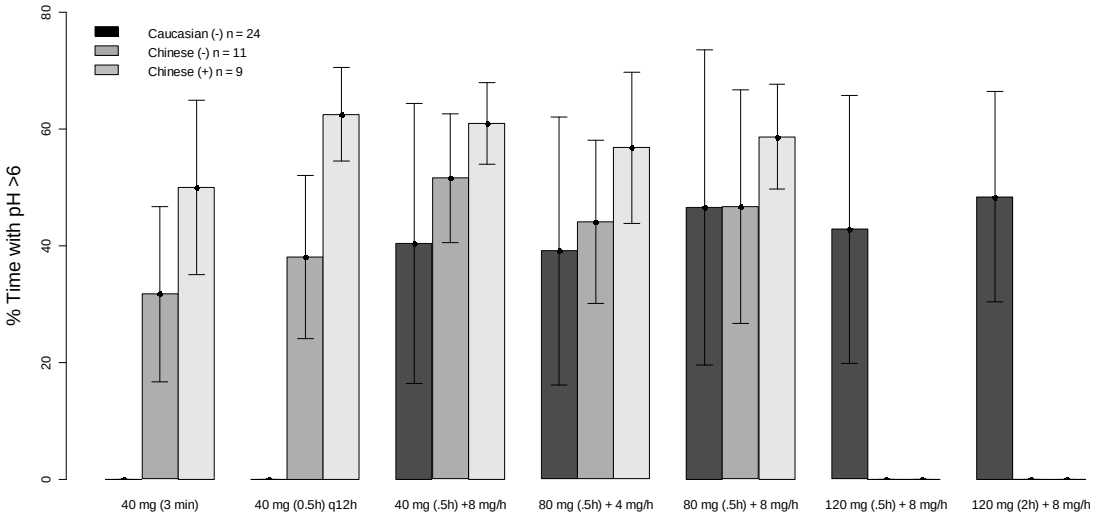
What are the relevant findings from cross-study comparisons of PK and PD (intragastric pH) across populations and subgroups of PK/PD studies 007 and 015?

PK comparisons: When comparing the overall populations of the two studies, there were only modest differences and PK in general appeared comparable. Cmax was higher in the Chinese population compared to Caucasians in general. Data is shown for the proposed regimen only:

PK in Overall Population	Chinese (n = 20)	Caucasians (n = 24)
Cmax (ng/mL)	6842 ± 1648	4899 ± 897
Css (ng/mL)	1297 ± 296	1380 ± 345
AUC24 (ng.h/mL)	41147 ± 8621	37950 ± 7935
CL (L/h)	6.5 ± 1.8	6.1 ± 1.4

PD comparisons: The primary PD outcome (% time over 24 h with pH > 6) was similar across populations (Chinese vs. Caucasians) and even when further stratified by *H. pylori* status (-ve only, as there were no *H. pylori* +ve subjects in study 015). A clear dose-response relationship was not established for % time over 24 h with pH >6 in Chinese or Caucasian subjects. Likewise, there was no relationship between exposure parameters (AUC, Css, C_{max}) and % time over 24 h with pH >6. Some of the differences noted for other PD outcomes were minimized when only *H. pylori* –ve subjects were compared across ethnicities, thus supporting that a *H. pylori* positive status renders larger PD effect in these outcomes (e.g. % time over 3 h with pH >6). The PD outcome % time over 24 h with pH >7 remained higher in Chinese subjects regardless of genotype or *H. pylori* status.

PD outcome	Chinese (n = 19) *Overall (+, -)*	Chinese (n = 11) *H. pylori* –ve	Caucasian(n= 24) *Overall (*–ve)
% time when pH >4 over 24 h	95 ± 4.6	93.69 ± 5.05	86.1 ± 11.3
% time when pH >6 over 24 h	48 ± 17.4	46.7 ± 20.4	46.6 ± 26.5
% time when pH> 6 over first 3 h	65 ± 28.6	49.4 ± 33.6	43.4 ± 26.1
% time when pH>7 over 24 h	13.3 ± 10.6	11.14 ± 8.56	4.0 ± 7.5



PD outcomes across Chinese and Caucasian volunteers were also compared within EMs and within IMs (*H. pylori* –ve only) and appeared generally comparable. A trend for higher % time with pH > 7 in Chinese subjects was noted. Across genotypes (EM vs. IM) some PD differences were apparent, although PK concentrations may not explain the PD differences due to general lack of E-R correlation; in addition, the data available is limited by small sample size and large variability.

CYP2C19 EMs/ *H. pylori* -ve	**Chinese (n = 5)**	**Caucasians (n = 17)**
% time when pH >4 over 24 h	93.6 ± 4.00	86.3 ± 10.9
% time when pH >6 over 24 h	44 ± 19.78	45.2 ± 28.5
% time when pH> 6 over first 3 h	42.9 ± 26.2	42.6 ± 24
% time when pH>7 over 24 h	7.48 ± 4.68	4.4 ± 8.5

CYP2C19 IMs/ *H. pylori* -ve	**Chinese (n = 5)**	**Caucasians (n = 6)**
% time when pH >4 over 24 h	93.3 ± 6.8	89.6 ± 7.5
% time when pH >6 over 24 h	50.1 ± 25.1	56.9 ± 13.9
% time when pH> 6 over first 3 h	52.7 ± 44.8	53 ± 28.3
% time when pH>7 over 24 h	16.1 ± 10.1	3.4 ± 4.9

What other information is useful to conclude comparability of PK and PD outcomes in subgroups of interest?

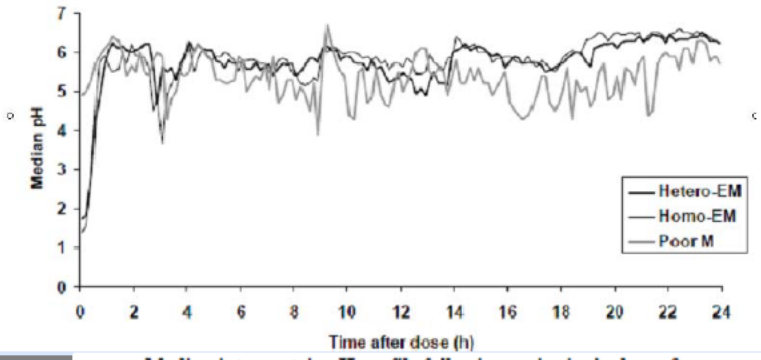
Study 004 was a bridging study evaluating PK/PD of omeprazole and esomeprazole in healthy Caucasian volunteers (*H. pylori* negative; Dose: 80 mg/30 minutes followed by 8 mg/h over 23.5 h). Information was previously used in Cycle 2 to support the use of omeprazole clinical trial data generated from the Lau et al trial to support the efficacy of esomeprazole for the proposed PUB indication. Study included CYP2C19 EMs and IMs.

PK and PD data presented below supports lack of influence of CYP2C19 genotype (one of the concerns that arose at the end of Cycle 2) on the PD outcomes for either omeprazole or esomeprazole; modest increases in exposure are seen in IMs vs. EMs.

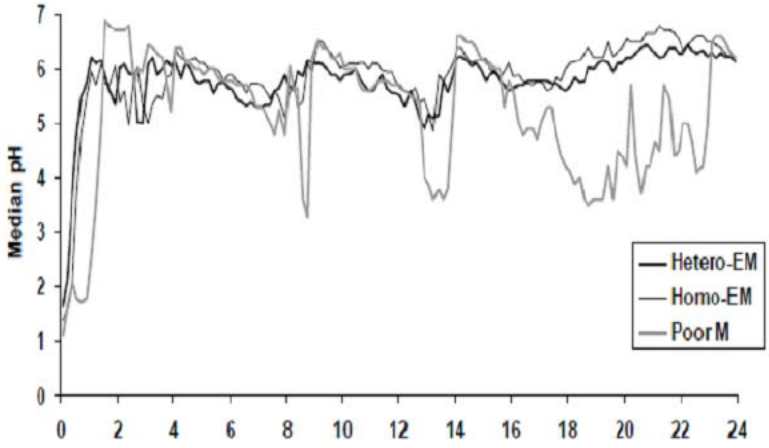
Study 004 - PK AUC (µmol.h/L)	Omeprazole	Esomeprazole
EMs (n = 20)	77 ± 21	87 ± 22
IMs (n = 18)	100 ± 34	107 ± 31

Study 004 – PD %time with pH>6 over 24 h	Omeprazole	Esomeprazole
EMs (n = 20)	45 ± 22	49 ± 21
IMs (n = 18)	40 ± 12	42 ± 16

[redacted] Median intragastric pH profile following an iv single dose of omeprazole 80 mg + 8 mg/h in heterozygote extensive metabolizers (N=18), homozygote extensive metabolizers (N=20) and poor metabolizers (N=1)



[redacted] Median intragastric pH profile following an iv single dose of esomeprazole 80 mg + 8 mg/h in heterozygote extensive metabolizers (N=18), homozygote extensive metabolizers (N=20) and poor metabolizers (N=1)



Are there any relevant clinical outcomes data from the completed trials in peptic ulcer bleed patients with respect to effects of H. pylori status or genetic polymorphism?

In response to a clinical information request, on April 22, 2013 sponsor provided data tables summarizing clinical outcomes (re-bleeding rates and time to re-bleeding etc) for available subgroups (*H. pylori* status) in active and placebo groups of both Lau et al, and study 001.

In this regard, the data tables below suggest a consistently larger clinical benefit (i.e. lower re-bleeding incidence) in *H. pylori* positive patients, in both trials.

While in the study 001, a similar trend between *H. pylori* +ve vs. –ve patients was noted even in the placebo group, no such trend was noted in the Lau trial (24, 48 and 72 h data only) where the placebo re-bleeding incidence appears comparable in *H. pylori* +ve and –ve patients.

[redacted] **D961DC00001 - Proportion of subjects who Re-Bleed within 3, 6, 12, 24, 48 and 72 hours (subgrouped by H. pylori status), ITT population**

Re-bleed within (hours)	Esomeprazole n/N(%)		Placebo n/N(%)	
	H. pylori(+)	H. pylori(-)	H. pylori(+)	H. pylori(-)
3	2/264 (0.8%)			3/119 (2.5%)
6	3/264 (1.1%)	2/92 (2.2%)	1/252 (0.4%)	4/119 (3.4%)
12	4/264 (1.5%)	4/92 (4.3%)	4/252 (1.6%)	6/119 (5%)
24	9/264 (3.4%)	7/92 (7.6%)	6/252 (2.4%)	12/119 (10.1%)
48	10/264 (3.8%)	7/92 (7.6%)	18/252 (7.1%)	13/119 (10.9%)
72	11/264 (4.2%)	9/92 (9.8%)	21/252 (8.3%)	14/119 (11.8%)

19 Ezomeprazole subjects have missing H.pylori status, 2 of them rebleed within 72 hours
18 Placebo subjects have missing H.pylori status, 5 of them rebleed within 72 hours

[redacted] **Lau et al - Proportion of subjects who Re-Bleed within 24, 48 and 72 hours (subgrouped by H. pylori status), ITT population**

Re-bleed within (hours)	Omeprazole n/N(%)		Placebo n/N(%)	
	H. pylori(+)	H. pylori(-)	H. pylori(+)	H. pylori(-)
24		2/39 (5.1%)	9/64 (14.1%)	7/54 (13%)
48		2/39 (5.1%)	11/64 (17.2%)	9/54 (16.7%)
72	1/78 (1.3%)	3/39 (7.7%)	11/64 (17.2%)	12/54 (22.2%)

3 Omeprazole subjects have missing H. pylori status and 1 of them rebleed within 72 hours
3 Placebo subjects have missing H. pylori status and 1 of them rebleed within 72 hours

Data by CYP2C19 genotype status was unavailable from clinical trials. In addition, PD (gastric pH) information was not available in these trials to evaluate correlations between gastric pH achieved and incidence of re-bleeding.

Does the modeling and simulation data provided support the proposed dosing regimen in hepatic impairment subgroups? If not, what alternate regimen(s) does the agency recommend in patients with reduced hepatic function?

Upon request from the Division, the sponsor provided modeling and simulation findings and recommendations for the constant infusion rate in patients with hepatic impairment [HI]. Agreement was previously reached regarding the loading dose [80 mg over 30 minutes] [redacted] (b) (4)

[redacted]. Dosing recommendations for the constant i.v. infusion (mg/h over 71.5 h) in patients with hepatic impairment were based on two datasets: an i.v. dataset in healthy volunteers and an oral dataset in patients with hepatic impairment. A previous population model of esomeprazole was used for estimation of model parameters. The modeling and simulation results do not support the dosing recommendations proposed by the sponsor [redacted] 4 mg/h in severe HI].

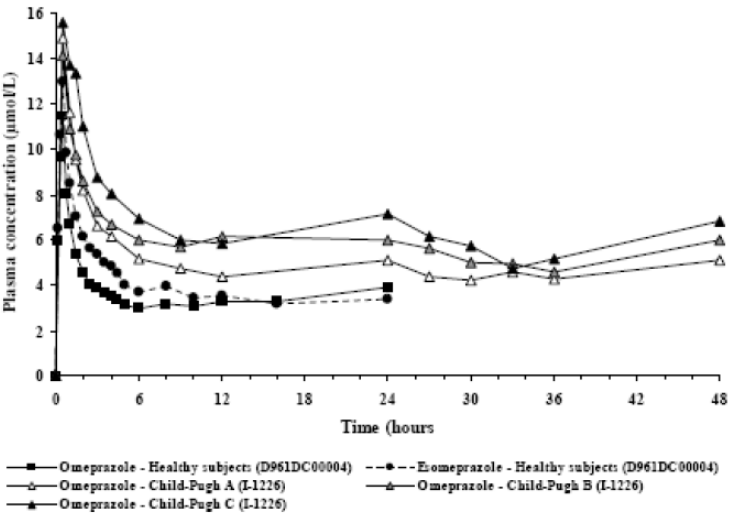
[redacted]

Instead, dosing recommendations for the constant infusion will be based on omeprazole i.v. data in hepatically impaired patients (Study I-1226) previously reviewed by Dr. Jappar (5/27/11). In this review a PK/PD link between omeprazole and esomeprazole was established (study 004). In Study I-1226, 12 hepatically impaired subjects received omeprazole 80 mg infused over 30 minutes followed by a constant infusion of 8 mg/hr up to 24 hours. Results of this study are reproduced in the table and figure below.

Comparisons of Mean (±SD) PK Parameters of Esomeprazole and Omeprazole Obtained from the Dosing Regimen of 30 Minute Infusion of 80 mg followed by a Constant Rate of 8 mg/hr up to 24 Hours

Study No.	AUC_{0-24} (µmole-h/L)	C_{max} (µmole/L)	C_{ss} (µmole/L)
I. **D9615C00015** (n=26) Esomeprazole	109.9 (± 23.1)	14.2 (± 2.6)	4.0 (± 1.0)
II. **D961DC00004** (n=39)			
Esomeprazole	98.6 (± 25.9)	13.1 (± 2.8)	3.4 (± 1.0)
Omeprazole	89.1 (± 30.5)	11.6 (± 2.8)	-----
III. **I-1226** Omeprazole			
Child-Pugh C (n=3); Severe	172.3 (± 42.9)	15.6 (± 2.9)	5.96 (± 1.69)
Child-Pugh B (n=4); Moderate	155.0 (± 32.8)	14.1 (± 2.0)	5.09 (± 1.10)
Child-Pugh A (n=5); Mild	130.8 (± 42.9)	15.0 (± 4.3)	4.33 (± 1.49)

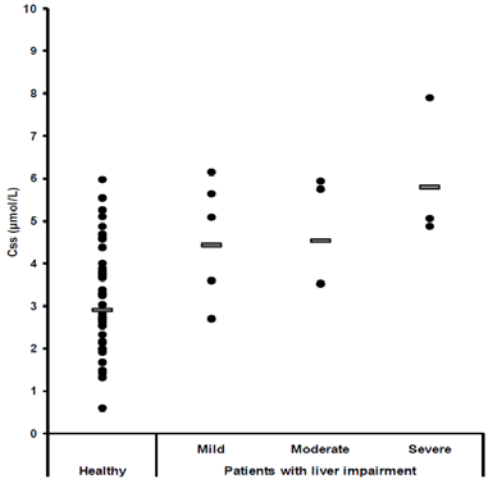
Mean Plasma Concentrations following Esomeprazole and Omeprazole (30 Minute Infusion of 80 mg followed by a Constant Rate of 8 mg/hr up to 24 Hours) in Healthy Subjects and Subjects with Hepatic Impairment



FDA asked the Applicant to provide updated dosing recommendations using i.v. omeprazole data in healthy subjects (Study 004) and patients with hepatic impairment (Study I-1226). Sponsor was advised that the dosing recommendations should provide steady state exposures in patients with different degrees of hepatic impairment that match expected steady state concentration in patients with normal hepatic function.

Sponsor responded with relevant analyses and provided new dosing recommendations based on study I-1226 and 004. A summary of the Css data in these subjects is provided in Figure below. The results support a constant infusion of 6 mg/h, 6 mg/h and 4 mg/h in patients with mild, moderate and severe hepatic impairment, respectively.

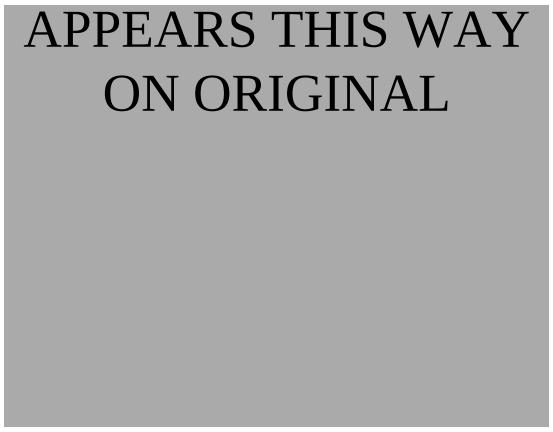
Individual and Geometric Mean Css Values in Healthy Volunteers and Patients with Hepatic Impairment Receiving 80 mg + 8 mg/h



Thus the constant infusion regimen in patients with mild, moderate and severe hepatic impairment should be 6 mg/h, 6 mg/h and 4 mg/h, respectively.

3 Labeling Recommendations

Revisions have been proposed to the Clinical Pharmacology sections of the proposed labeling corresponding to dosing and administration in special populations, pharmacokinetics and pharmacodynamics. Please refer to the final approved labeling in DARRTs.



4 Appendices

4.1 Individual Study Reviews

Chinese Volunteer PK/PD Study 007

D9615L00007: An open, randomized, multi-dosage, five-element crossover design, controlled study to observe the clinical pharmacokinetics, clinical pharmacodynamics and safety of esomeprazole sodium intravenous infusion/injection in healthy Chinese subjects

Methods:

Study population and Sample size: N = 20 healthy Chinese volunteers between 18 – 45 years of age (average age 33.3 years). 15 subjects only participated for the first two cycles (D, E) of testing, so there were no A, B, and C cycle blood drug concentration curves.

Drug product: The trial drug, esomeprazole powder for injection, was provided by the sponsor (Astra Zeneca Corporation); specifications are 40 mg/bottle. Sodium chloride solution (9 mg/mL) for intravenous use was used as the infusion solvent.

Treatments and duration: Each subject participated in a crossover evaluation of the following 5 different regimens, with at least 6 days of washout between treatments:

A. 40 mg esomeprazole 3 minute bolus
B. 40 mg esomeprazole 30 minute intravenous infusion, once every 12 hours
C. 40 mg esomeprazole 30 minute intravenous infusion, followed by 8 mg/h intravenous infusion for 23.5 h
D. 80 mg esomeprazole 30 minute intravenous infusion, followed by 4 mg/h intravenous infusion for 23.5 h
E. 80 mg esomeprazole 30 minute intravenous infusion, followed by 8 mg/h intravenous infusion for 23.5 h

(The proposed dosing regimen for the PUB indication is approximately similar to regimen E above; 80 mg esomeprazole 30 minute intravenous infusion, followed by 8 mg/h intravenous infusion for 72 h)

Pharmacokinetics: Blood samples were collected from the subjects before drug administration and 10 min, 20 min, 30 min, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after drug administration for pharmacokinetic evaluation. All blood sample esomeprazole concentrations were determined using an HPLC-MS/MS method, and the LLOQ determination was 4 ng/mL. When determining the blood samples, the standard curve sample concentrations were 4, 8, 20, 50, 200, 500, 2000, 5000, 10,000 and 20,000 ng/mL respectively, and the quality control sample concentrations were 10, 400, 8000 and 16,000 ng/mL respectively.

Blood drug concentration data was analyzed using WinNonlin pharmacokinetic software with a non-compartment model. Pharmacokinetic parameters included Cmax, Css (measured as average value at 8, 10, 12 h after the start of drug administration), AUC0-24h, and CL. Geometric mean estimate values of PK for each study dose and bilateral 95% confidence intervals are presented.

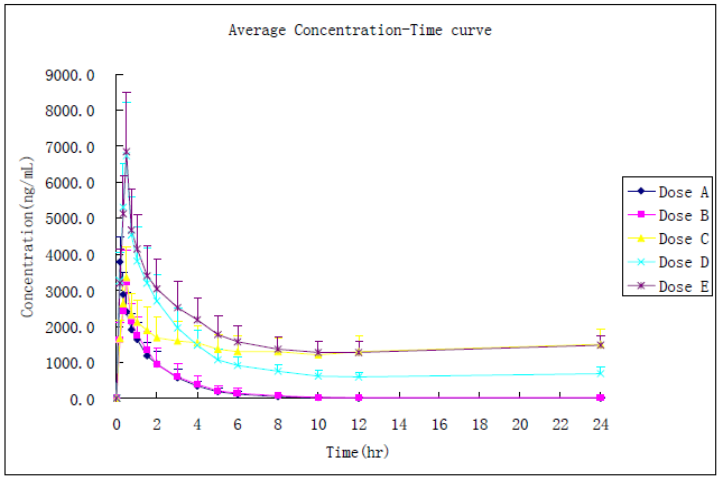
Pharmacodynamics: Intragastric pH was recorded at baseline prior to the study drug administration and following start of drug infusion on the five study days. The Medtronic pH determination system (Digitrapper MK IV, Medtronic Corporation, Denmark) was used to record pH values in the stomach. Prior to each recording, a standard buffer solution between ph 7.0 and pH 1.07 is used to calibrate the electrode at two points. During the pH value determination process, an electrode is placed 10 cm below the lower esophageal sphincter. When the first pH value is recorded, it is marked on the pH electrode. Electrode insertion was performed by the investigator or study nurse, and the subject was in a sitting position. The same electrode was used for the 5 pH recordings during the study, and it was placed in the same position. After the baseline was stable, the baseline value was recorded at 30 minutes, and then changes in the pH were recorded after medication administration was started.

The percentage of time for each subject at pH >7, pH >6, pH >5 and pH >4 in the stomach over a period of 24 hours, and the median 24-hour pH value in the stomach, start time for stomach pH 6 maintained for at least 1 hour, and the percentage of time at stomach pH 6 during the first 3 hours after starting the medication was also calculated. Descriptive statistics of the pharmacodynamic variables were determined for total population, between male/female gender, and between different 2C19 genotypes.

Safety: All adverse events, physical symptoms, blood pressure, pulse, electrocardiograms and laboratory variables were monitored during the study.

Pharmacokinetic Results:

Plasma concentration-time profiles for esomeprazole in the overall population are presented below:



Pharmacokinetic parameters (GeoMean and 95 % CI) are presented:

Dose GROUP	Cmax (ng/mL)	Css (ng/mL)	AUC_{0-12h} (hr*ng/mL)	AUC_{0-24h} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	CL (L/hr)
A	3730.1 (3526.7, 3945.3)		5045.2[a] (4725.7, 5386.2)		5041.0 (4282.7, 5799.3)	7.9[b] (7.3, 8.6)
B	3149.8 (2977.6, 3332.0)		4913.2 (4601.3, 5246.3)		5011.9 (3939.0, 6084.8)	8.0[b] (7.3, 8.7)
C	3268.9 (3090.6, 3457.5)	1206.9 (1145.1, 12□2.0)		32970.1 (30882.4, 35199.0)		6.6 (6.3, 7.0)
D	6632.5 (6270.9, 7015.1)	633.3 (600.9, 667.5)		25036.3 (23451.0, 26728.7)		6.3 (6.0, 6.7)
E	6513.0 (6157.9, 6888.7)	1253.4 (1189.3, 1321.1)		39967.3 (37436.5, 42669.1)		6.4 (6.1, 6.7)

A: Esomeprazole 40 mg 3 minute intravenous injection

B: Esomeprazole 40 mg 30 minute intravenous infusion q12h

C: Esomeprazole 40 mg 30 minutes + 8 mg/hour intravenous infusion (23.5 hours

D: Esomeprazole 80 mg 30 minutes + 4 mg/hour intravenous infusion (23.5 hours)

E: Esomeprazole 80 mg 30 minutes + 8 mg/hour intravenous infusion (23.5 hours)

PK in the overall population: The Cmax values for the 40 mg (A, B,C) and 80 mg (D, E) esomeprazole bolus regimens demonstrated dose proportional characteristics. The AUC0-24h was greater with the 8 mg/h infusions (C, and E), compared to the 4 mg/h (D) infusion. Clearance values were comparable across the regimens. Average steady-state concentrations (Css) for the 4 mg/h regimen were roughly 50 % of that seen in the 8 mg/h infusion regimens. For treatment regimen B (two 40 mg doses over 30 minutes, given 12 h apart), because the blood drug concentration at 12 hours for the first 40 mg intravenous infusion essentially reached the minimum test limit, it could therefore be inferred that the 12 hour AUC curve for the second 40 mg intravenous infusion was similar to the first 12 hours; in other words, the total AUC is twice the AUC 0-12h shown in the table.

PK in subgroups: Esomeprazole is primarily metabolized by CYP2C19. Hence PK was summarized also by CYP2C19 genotypes. The Chinese population in this study included 7 subjects with extensive metabolizer phenotype (homozygous), 10 subjects with intermediate metabolizer phenotype (heterozygous), and 2 subjects with poor metabolizer phenotype (null). PK is summarized below for the three subgroups using the 5 regimens:

Cmax (ng/mL):

Genotype	A	B	C	D	E
homoEM(n = 7)	3680.4	2937.4	2930.1	6261.5	5953.9
hetEM(n = 10)[a]	3872.4	3419.8	3683.1	6801.4	7225.1
PM(n = 2)	3774.9	3511.7	3304.8	7926.9	7846.3

For the bolus 40 mg loading dose in treatment A, Cmax values did not vary markedly with the genotype. For the loading doses administered over 30 minutes (B, C, D, E), the intermediate (heteroEMs) and poor metabolizer phenotypes had higher Cmax compared to extensive metabolizers. For the proposed dosing regimen (E), compared to EMs, the Cmax values were 21 % higher in IEMs and 32 % higher in PMs (n = 2).

AUC (ng.h/mL):

Genotype	A	B	C	D	E
homoEM(n = 7)	3935.9	3878.2	30274.1	22628.9	36573.5
hetEM(n = 10)[a]	5943.1	5708.4	37304.1	27035.4	43032.5
PM(n = 2)	6677.6	8148.5	33038.3	28480.0	46784.4

24-hour AUC values were higher in the IEM and PM groups compared to the extensive metabolizers. The only exception was in treatment regimen C (40 mg/30 min bolus + 8 mg/h over 23.5 h), where the PM subgroup had lower AUC compared to IEM. Sample size was small in the PM group (n = 2). For the proposed dosing regimen (E), compared to EMs, the overall exposure (AUC) was 18 % greater in IEMs and 28 % greater in PMs (n = 2).

Overall, PK data in genotype subgroups supports differential clearance of esomeprazole in IEMs and PMs. However, for the proposed dosing regimen (E) the differences are not substantial (Cmax and AUC increases of ~ 20 % in IEMs and ~ 30 % in PMs). Fold increases for PMs have to be interpreted with caution due to small sample.

Pharmacodynamic Results:

20 subjects enrolled and participated in this study, of which subject number 15 only participated in the first two cycles (D, E) of the trial, so there were no pH recordings for cycles A, B and C. Subject numbers (b) (6) and (b) (6) each had 1 baseline determination of stomach pH >4, so they were eliminated from this statistical analysis.

Parameter	Drug administration regimen	Number of subjects	Time percentage %	95% CI
pH >4 (0-24h)	A	18	77.8	73.4, 82.2
	B	19	91.4	87.1, 95.7
	C	18	95.4	91.0, 99.8
	D	19	95.5	91.3, 99.8
	E	19	95.7	91.4, 100.0
pH >5 (0-24h)	A	18	64.7	57.2, 72.2
	B	19	75.4	68.1, 82.8
	C	18	81.0	73.5, 88.5
	D	19	77.2	69.9, 84.5
	E	19	79.0	71.6, 86.3
pH >6 (0-3h)	A	18	49.4	36.6, 62.1
	B	19	56.6	44.1, 69.1
	C	18	62.7	50.0, 75.5
	D	19	66.3	53.9, 78.7
	E	19	64.0	51.5, 76.5
pH >6 (0-24h)	A	18	41.1	33.6, 48.6
	B	19	49.4	42.1, 56.8
	C	18	57.2	49.7, 64.7
	D	19	49.9	42.6, 57.1
	E	19	53.0	45.6, 60.3
pH >7 (0-24h)	A	18	9.3	3.6, 14.9
	B	19	16.0	10.4, 21.6
	C	18	16.7	11.0, 22.4
	D	19	15.0	9.4, 20.5
	E	19	15.1	9.5, 20.7
pH median value (0-24h)	A	18	5.4	5.1, 5.7
	B	19	5.9	5.6, 6.2
	C	18	6.2	5.9, 6.5
	D	19	6.0	5.7, 6.3
	E	19	6.1	5.8, 6.3

A: Esomeprazole 40 mg 3 minute intravenous injection

B: Esomeprazole 40 mg 30 minute intravenous infusion q12h

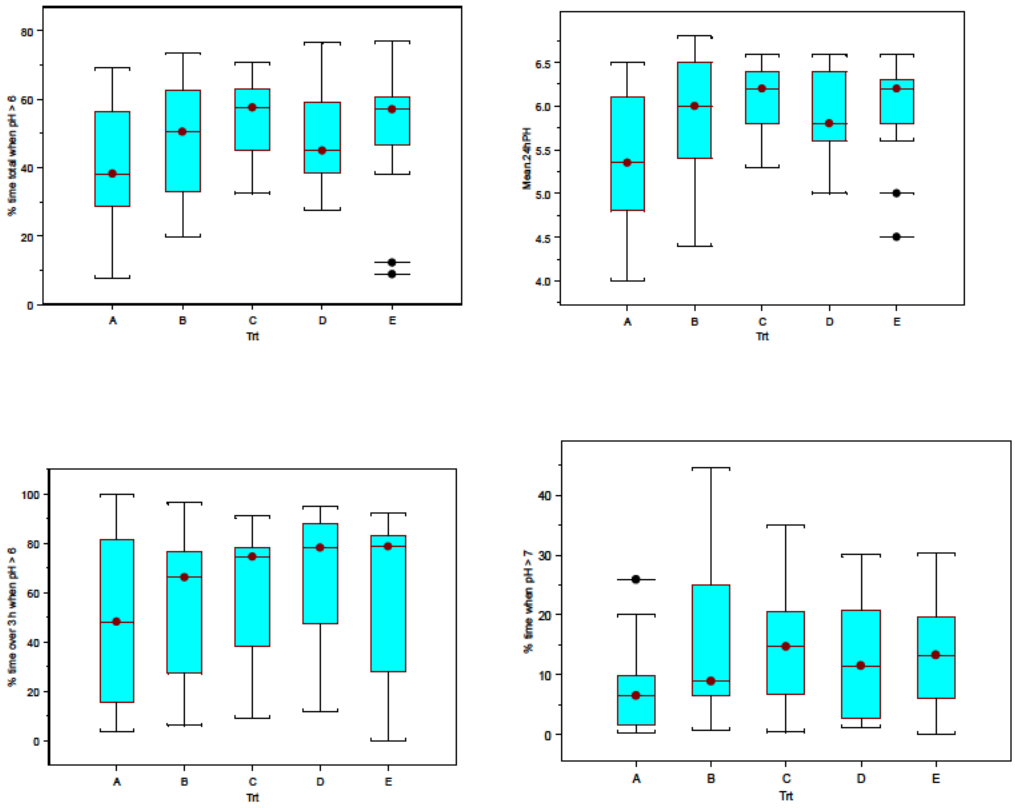
C: Esomeprazole 40 mg 30 minutes + 8 mg/hour intravenous infusion (23.5 hours

D: Esomeprazole 80 mg 30 minutes + 4 mg/hour intravenous infusion (23.5 hours)

E: Esomeprazole 80 mg 30 minutes + 8 mg/hour intravenous infusion (23.5 hours)

PD in the overall population: Based on PD information, all regimens were successful in increasing pH to above 4.0 for most of the 24 h duration. There was a trend for progressively smaller % of time over 24 hours when pH values were > 4, 5, 6 or 7. The goal of PPI therapy in peptic ulcer bleed patients is to maintain pH at or above 6.0 to stabilize the clot and prevent re-bleeding episodes. In this regard, the three regimens that included a loading dose and a longer infusion period (C, D, E) were comparable in this population with respect to % time when pH > 6.0 in the first 3 hours of treatment (~ 60 %) and the % time over 24 hours when pH was above 6.0. Regimen C that involves a lower loading dose (40 mg/30 min) and the 8 mg/h infusion appeared somewhat better than others with respect to % time when pH was greater than 6.0 over 24 h period. The

value of a higher infusion rate (8 mg/h vs. 4 mg/h) is not readily apparent from these data in the overall population. Sponsor notes that "the time percentages at 24 hours at pH >6 in groups B, C, D and E were 49.4% - 57.2%, and did not significantly increase with higher dosage". Sponsor also notes "pH >5, pH >6 and pH >7 at 24 hours for each treatment group was significantly different when comparing Group A with Group B but not between Group B and Group C, D and E. When the dosage exceeded 80 mg, the percentage of time of stomach pH above each pH cut off did not rise significantly with the increase in dosage".



PD summary in subgroups for the proposed dosing regimen [80 mg/30 min + 8 mg/h infusion]: The following tables summarize PD [mean ± s.d.] findings in subgroups (gender, CYP2C19 polymorphism and H.Pylori status) for proposed dosing regimen (E):
Gender: There were no marked differences in PD between males and females. While females for the most part exhibited a greater PD effect, the differences were modest. Of the 6 females, 3 were EMs and 3 IEMs. In the 13 males, there were 4 EM, 8 IEM, 2 PM.

	Males (n = 13)	**Females (n = 6)**
% Time pH >4 over 24 h	95.2 ± 4.7	96.6 ± 4.1
% Time pH>5 over 24 h	76.9 ± 10.3	81.1 ± 21.2
% Time pH >6 over 3 h	61.3 ± 32.9	68.5 ± 26.5
% Time pH > 6 over 24 h	49.4 ± 14.1	56.9 ± 23.6
% Time pH > 7 over 24 h	14.3 ± 9.0	12.1 ± 10.9
Median pH value over 24h	6.0 ± 0.4	6.1 ± 0.8

CYP2C19 polymorphic status: There is a trend for modestly increased PD effect in IEMs when compared to EMs, perhaps coinciding with the somewhat higher systemic exposure in IEMs. For the PD endpoints of interest in the treatment of PUB, the difference between IEMs vs. EMs was ~5 % for % time pH > 6 over 24 h and 24 % for pH > 6 for 3 h. It is difficult to comment on trends for the PMs due to their small sample.

	Extensive Metabolizers (EM) [n = 7]	**Intermediate Metabolizers (IEM) [n = 10]**	**Poor Metabolizers (PM) [n = 2]**
% Time pH >4 over 24 h	94.9 ± 4.0	95.8 ± 5.3	97.6 ± 2.0
% Time pH>5 over 24 h	76.5 ± 17.4	79.6 ± 13.8	77.6 ± 0.4
% Time pH >6 over 3 h	54.6 ± 29.4	67.9 ± 34.1	73.1 ± 10.6
% Time pH > 6 over 24h	50.6 ± 20.5	53.4 ± 17.7	47.5 ± 5.9
% Time pH > 7 over 24h	11.2 ± 7.8	16.4 ± 10.6	7.9 ± 4.7
Median pH over 24h	5.9 ± 0.7	6.1 ± 0.5	5.9 ± 0.1

H.Pylori Positive	EM (n = 2)	IM (n = 6)	PM (n =1)
%time pH>4	98.25 ± 0.63	98.27 ± 0.55	99
% time over 3h pH>6	83.85 ± 6.29	82.77 ± 5.88	80.6
%time pH>6	67 ± 13.85	57.07 ± 5.88	51.6
%time pH >7	20.6 ± 6.08	57.07 ± 7.29	11.3
mean 24h pH	6.35 ± 0.07	6.27 ± 0.28	6

H.Pylori Negative	EM (n = 5)	IM (n = 5)	PM (n = 1)
%time pH>4	93.6 ± 4.00	93.3 ± 6.79	96.1
% time over 3h pH>6	42.9 ± 26.2	52.68 ± 44.8	65.6
%time pH>6	44.02 ± 19.78	50.08 ± 25.14	43.3
%time pH >7	7.48 ± 4.68	16.12 ± 10.14	4.6
mean 24h pH	5.72 ± 0.73	5.98 ± 0.61	5.8

H.Pylori Status: Based on the PD data for the proposed dosing regimen E, there were trends for higher PD effects in the H.Pylori positive population. While the differences between H.Pylori positive and negative groups for regimens A and B (data not shown here) were found to be significant for most PD parameters, for the proposed regimen E, differences were significant for two of the PD endpoints- % time pH >4 and % time pH> 6 in first 3h. For the 24 h endpoints including the mean pH values, % time with pH >6 or > 7 over 24h were not significantly different between H.Pylori groups in treatment E (proposed). No PK differences were noted between H.Pylori groups. In this study, there was a roughly equal incidence of H.Pylori positive and negative subjects.

	H.Pylori Positive (n = 9)	H.Pylori Negative (n =11)
Baseline pH	1.6 ± 0.14	1.66 ± 0.54
Mean 24 h pH	6.25 ± 0.23	5.84 ± 0.61
% Time pH >4 over 24 h	98.37 ± 0.54	93.69 ± 5.05
% Time pH >6 over 3 h	82.77 ± 5.0	49.4 ± 33.6
% Time pH > 6 over 24 h	59.12 ± 9.56	46.7 ± 20.4
% Time pH > 7 over 24 h	18.75 ± 9.26	11.14 ± 8.56

Of all the subgroups evaluated in Chinese volunteers, H.Pylori status appears to have an impact on the PD outcomes following Nexium IV regimens. The trend is for increased PD outcomes in H.Pylori positive patients. The differences were not always statistically significant particularly at the higher infusion doses such as the proposed regimen E. PK was influenced as expected by CYP2C19 status but the differences were not marked.

Chinese Study 007	**Extensive Metabolizers (EM) [n = 7]**	**Intermediate Metabolizers (IEM) [n = 10]**	**Poor Metabolizers (PM) [n = 2]**
% Time pH >6 over 3 h	54.6 ± 29.4	67.9 ± 34.1	80.6, 65.6
% Time pH > 6 over 24h	50.6 ± 20.5	53.4 ± 17.7	51.6, 43.3
% Time pH > 7 over 24h	11.2 ± 7.8	16.4 ± 10.6	11.3, 4.6

PK- Chinese Study 007	**Extensive Metabolizers (EM) [n = 7]**	**Intermediate Metabolizers (IEM) [n = 10]**	**Poor Metabolizers (PM) [n = 2]**
Cmax (ng/mL)	5953 ± 1257	7225 ± 1815	7655, 8037
Css (ng/mL)	1199 ± 315	1354 ± 303	1463, 1176
AUC24 (ng.h/mL)	36573 ± 8058	43032 ± 8790	47411, 46157
CL (L/h)	6.98 ± 1.44	6.3 ± 2.1	5.46, 6.8

4.2 Consult Reviews

Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

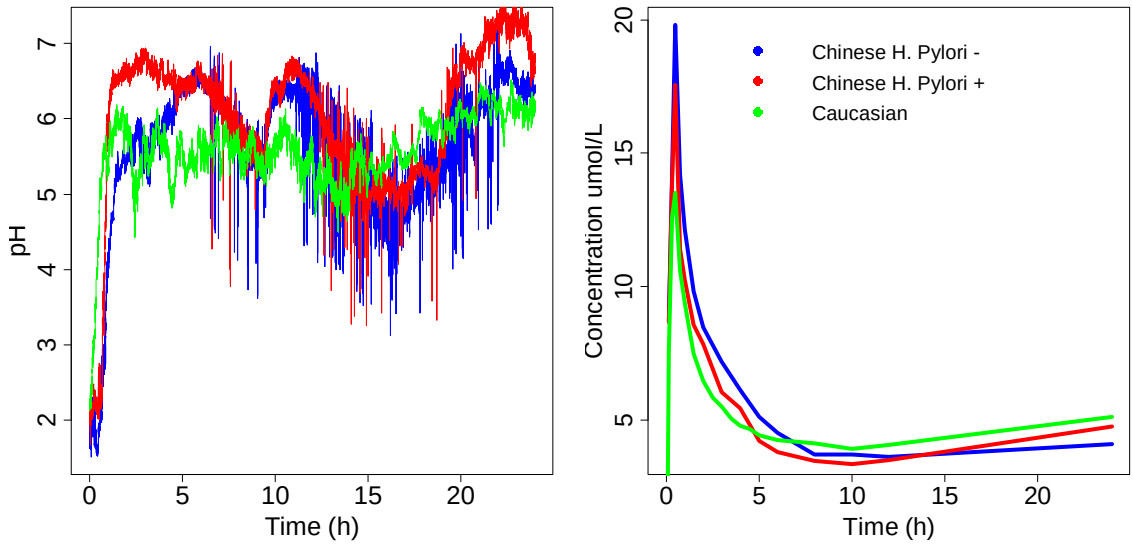
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the PK/PD of esomeprazole similar in Chinese and Caucasian subjects?

Yes, data from healthy Chinese and Caucasian subjects show that the pharmacological effect of esomeprazole on pH is consistent across the two populations. Overall, the profile of pH vs. time in Chinese and Caucasian H.pylori negative subjects receiving a dosing regimen of 80 mg over 30 min, followed by 8 mg/h infusion for 23.5 h was similar (Figure 1). A dose- or concentration response relationship, however, could not be established. H. pylori positive Chinese subjects had a faster rise in pH compared to H.pylori negative Chinese subjects. There were no H. pylori positive Caucasian subjects for comparison. It should be noted that this conclusion is based only on PD data in healthy volunteers. There is no PK/PD data in the target population of patients with peptic ulcer bleeding.

Figure 1: pH and Concentration vs. Time in Caucasian and Chinese Healthy Volunteers at 80 mg + 8 mg/h



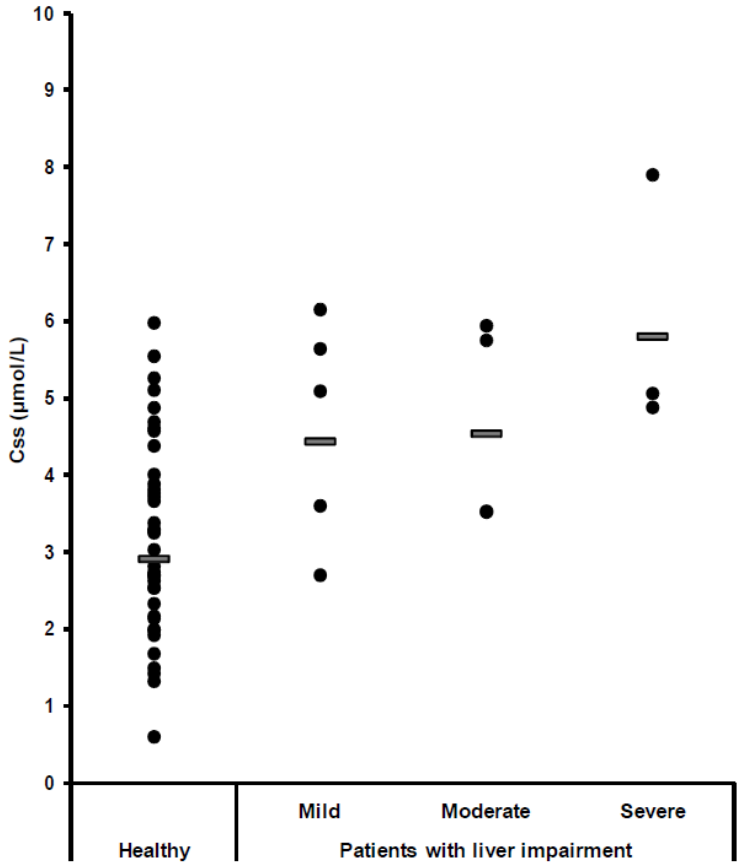
1.1.2 Does the Applicant's modeling and simulation support their proposed dosing regimen in patients with hepatic impairment?

No, the Applicant's simulations do not support their proposed dosing regimen for the following reasons:

- The model assumes [redacted] (b) (4) This assumption is not supported by the data.
- [redacted] (b) (4) It is possible that bioavailability is also increased in patients with hepatic impairment. If this is the case, the Applicant is likely to over-estimate the impact of hepatic impairment on steady-state exposure.
- The Applicant has not provided data to support [redacted] (b) (4) Exposure-response analysis in healthy subjects suggests that additional benefit in terms of pH is not achieved at higher exposures.

FDA asked the Applicant to provide updated dosing recommendations using i.v. omeprazole data in healthy subjects (Study 004) and patients with hepatic impairment (Study I-1226). A summary of the C_{ss} data in these subjects is provided in Figure 2. The results support a constant infusion of 6 mg/h, 6 mg/h and 4 mg/h in patients with mild, moderate and severe hepatic impairment, respectively.

Figure 2: Individual and Geometric Mean C_{ss} Values in Healthy Volunteers and Patients with Hepatic Impairment Receiving 80 mg + 8 mg/h



Source: Response to Information Request (July 15, 2013), Figure 2, Page 8.

1.2 Recommendations

The constant infusion regimen in patients with mild, moderate and severe hepatic impairment should be 6 mg/h, 6 mg/h and 4 mg/h.

2 PERTINENT REGULATORY BACKGROUND

The current submission is in response to a second Complete Response Letter received from FDA on June 16, 2011. In the second Complete Response Letter, the FDA notes that the clinical trial reported by Lau et al. is comparable in design to Study 01 and provides evidence of efficacy of intravenous omeprazole for the proposed indication of (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. However, the study was conducted at a single center in Hong Kong and the population enrolled was ethnically homogenous. The ability to generalize the results of the Lau trial to the U.S. population was limited because other studies have shown that Asian populations have a lower parietal cell mass, a higher prevalence of H. Pylori infection and a higher prevalence of CYP2C19 polymorphism, all of which could have contributed to the larger

treatment effect size in the Lau trial. In a meeting on March 21, 2012, the Applicant stated that they plan to submit additional PK, PD and clinical data to address the relevance of the Lau trial to the U.S. population. In a subsequent meeting held on June 12, 2012, the FDA advised the Applicant to provide any available PK/PD data from patients treated in the Lau trial. If these data were not available, the Applicant was told to generate a comparison of available PK/PD data from Chinese and Caucasian patients treated with esomeprazole/omeprazole who have H. Pylori, bleeding ulcers and/or ulcers due to H. Pylori. The Applicant stated that no PK/PD data were available from the Lau trial and that no PK/PD data was available to compare H. Pylori positive Chinese and Caucasian patients. FDA stated that all data should be submitted for review.

Another issue from previous Complete Response Letters was the lack of agreement on the proper maintenance i.v. dose in patients with hepatic impairment. The FDA sent the following information request to the Applicant on April 29, 2011: "The proposed loading dose of 80 mg over 30 min for all degrees of hepatic impairment appears acceptable. (b) (4) However, based on the data you have provided, we have concerns regarding the proposed constant intravenous infusion rate of Nexium for both patients with moderate (b) (4) and severe (4 mg/hr) hepatic impairment. Please conduct a modeling and simulation to estimate the proper constant infusion rate in moderate and severe hepatic impairment patients and provide the results including simulated concentration-time profiles." In the current submission the Applicant provides the results of the modeling and simulation exercise supporting the dose of i.v. esomeprazole.

3 RESULTS OF SPONSOR'S ANALYSIS

Because the efficacy data have been reviewed in previous cycles, only a summary table of the primary endpoint will be provided here for context (Table 1).

Table 1: Rebleeding Within 72 Hours of Therapeutic Endoscopy

Study	Study Drug*	Placebo	Treatment Difference
01	5.9% (22/376)	10.3% (40/389)	**-4.4%**
Lau	4.2% (5/120)	20.0% (24/120)	**-15.8%**

Source: Regulatory Briefing Background Materials.

3.1 PK/PD Relationship

The Applicant submitted the results of two PK/PD studies to support their bridge for efficacy between Asian and Caucasian populations: Study 007 in Chinese healthy volunteers and Study 015, a previously reviewed dose ranging trial in healthy Caucasian volunteers. Both studies included the proposed dosing regimen of 80 mg over 30 min,

followed by 8 mg/h infusion for 23.5 h. The PD marker of interest is the time with intragastric pH greater than 6.

Study 007: This was a single-dose, randomized, crossover study in 20 healthy Chinese subjects. Nine subjects were H.pylori positive and 11 were H.pylori negative. The CYP2C19 genotype was assessed and included 7 extensive metabolizers (EM), 11 intermediate metabolizers (IM) and 2 poor metabolizers (PM).

The esomeprazole intravenous dose regimens assessed in this study were as follows:

1. 40 mg bolus administered over 3 minutes
2. 40 mg administered over 30 min; two doses separated by 12 h
3. 40 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
4. 80 mg over 30 min, followed by 4 mg/h infusion for 23.5 h
5. 80 mg over 30 min, followed by 8 mg/h infusion for 23.5 h

Study 015: This was a randomized, crossover PK and PD study of esomeprazole given as five different intravenous regimens in healthy Caucasian subjects. Twenty-six subjects were enrolled in this study, all of whom were documented H. pylori negative. Subjects included 17 EMs, 8 IMs and 1 PM.

The esomeprazole intravenous dose regimens assessed in this study were as follows:

1. 40 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
2. 80 mg over 30 min, followed by 4 mg/h infusion for 23.5 h
3. 80 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
4. 120 mg over 30 min, followed by 8 mg/h infusion for 23.5 h
5. 120 mg over 2 h, followed by 8 mg/h infusion for 23.5 h

The Applicant summarizes the results of only the 80 mg over 30 min, followed by 8 mg/h infusion for 23.5 h dose arm in both studies. The results are presented in Table 2. The Applicant concludes that irrespective of genotype and parietal cell mass, 80 mg + 8 mg/h has similar effects on intragastric pH in Chinese and Caucasian healthy H. pylori negative volunteers. Also, administration of 80 mg + 8 mg/h is expected to result in a larger effect in H.pylori positive individuals compared to H. pylori negative individuals in both Caucasian and Chinese populations.

Table 2: Mean (range) Percentage of Time with Intragastric pH>6 During IV Administration of Esomeprazole as a 30 minute Bolus of 80 mg followed by a Continuous Infusion of 8 mg/h over 23.5 Hours.

CYP2C19 genotype	Caucasian	Chinese	
	H. pylori negative (n=24)	*H. pylori* negative (n=11)	*H. pylori* Positive (n=8)
All	46.6 (4.0-92.5)	46.7 (8.8-75.7)	58.7 (46.7-76.8)
Homo-EM	45.2 (4.0-92.5)	44.0 (12.2-60.6)	67.0 (57.2-76.8)
Hetero-EM	56.9 (30.9-68.3)	50.1 (8.8-75.7)	56.8 (46.7-63.8)
PM	7.4	43.3	51.6

homo-EM: homozygous extensive CYP2C19 metabolizer; hetero-EM: heterozygous extensive CYP2C19 metabolizer; PM: poor CYP2C19 metabolizer
Data derived from study D9615C00015 (Caucasian; 17 homo-EM, 6 hetero-EM, 1 PM) and D9615L00007 (*H. pylori* negative; 5 homo-EM, 5 hetero-EM, 1 PM, *H. pylori* positive; 2 homo-EM, 5 hetero-EM and 1 PM).

Source: Complete Response, Table 3, Page 4.

Reviewer's Comments: Study 015 was conducted in only H.Pylori negative individuals. Therefore these data can not be used to show that the effect of H.pylori status is the same in Chinese and Caucasian subjects. The Applicant's analysis only considers the data at the proposed dose and does not explore the PK/PD relationship. It is also important to re-state that these studies were performed in healthy volunteers and not patients with peptic ulcer bleeding.

3.2 Dosing in Patients with Hepatic Impairment

Dosing recommendations were based on two datasets: an i.v. dataset in healthy volunteers and an oral dataset in patients with hepatic impairment. The pharmacokinetic parameter of interest is steady-state concentration (C_{ss}) because the dose in question is the constant infusion following the initial bolus. A previous population model of esomeprazole was used for estimation of model parameters. Briefly, it is a two compartment model with oral absorption described by a transit compartment model.

3.3 I.V. Dataset

Data from two studies of esomeprazole i.v. infusion (n=65) were used to derive parameter estimates of the i.v. model: Study 015 described above and Study 04, a 2-way crossover comparative study of esomeprazole and omeprazole given as 80 mg followed by a continuous infusion of 8 mg/h. Parameter estimates are displayed in Table 3.

Table 3: Parameter Estimates of Model Using I.V. Dataset

	Typical estimate (RSE %)	IIV % CV (RSE %)	IOV % CV (RSE %)
iv model (Run36)			
CL for study D961DC00004 (L/h)	7.31 (4.8)	28 (32)	
CL for study D9615C00015 (L/h)	6.21 (6.3)	SAME	22 (37)
V (L)	9.86 (4.0)	30 (23)	
Q (L/h)	15.81 (5.9)	39 (49)	
VP (L)	13.82 (10.4)	85 (39)	
Proportional residual error (%) - for study D961DC00004 - for study D9615C00015	 9.85 (4.8) 17.5 (9.3)		

Source: Appendix C of Complete Response, Table 1, Page 9.

Reviewer's Comments: The Applicant's model of i.v. data is reasonable.

3.4 Oral Dataset

The oral dataset was comprised of 12 individuals with varying degrees of hepatic impairment. None of the twelve patients had normal hepatic function. Subjects received 40 mg of oral omeprazole once daily for 5 days. Blood samples were collected up to 24 hours on Day 5. These data were reviewed in the previous cycle by Dr. Jappar. A summary of the results of this study is reproduced in Table 4 below. The normal hepatic function data in this table is from a separate study and was not included in the PK model.

Table 4: PK Parameters following Oral Administration of Esomeprazole 40 mg Once Daily to Cirrhotic Patients with Varying Degrees of Hepatic Impairment and Gastro-Esophageal Reflux Disease Patients with Normal Hepatic Function

	Pharmacokinetic parameter (mean [95% CI])			
	C_{max} (μmol/l)[a]	t_{max} (h)[b]	AUC_τ (μmol·h/l)[a]	$t_{1/2}$ (h)[a]
Normal hepatic function ($n = 36$)	4.7 (4.1–5.5)	1.6 (1.3–1.8)	12.8 (10.9–15.0)	1.5 (1.4–1.7)
Hepatic impairment				
Mild ($n = 4$)	6.5 (3.8–11.4)	1.7 (1.1–2.3)	18.2 (11.3–29.3)	1.3 (1.0–1.5)
Moderate ($n = 4$)	5.4 (2.5–11.5)	2.3 (0.6–4.1)	22.6 (13.8–36.9)	2.4 (1.3–4.3)
Severe ($n = 4$)	6.4 (5.2–8.0)	1.8 (1.0–2.5)	30.0 (22.1–40.6)	3.1 (1.6–6.1)

AUC_τ, area under the plasma concentration–time curve during the dosage interval; C_{max}, maximum plasma concentration; $t_{1/2}$, plasma elimination half-life; t_{max}, time to C_{max}.
[a]Geometric mean (95% CI); [b]estimated mean (95% CI).

The impact of hepatic impairment on clearance (CL) in the model was described by the following equation: $TVCL = TVCL_{no\ impairment} \times (1 - frct \times CPG)$ where TVCL is the typical CL/F value in the population, frct is the fractional change in CL with decreasing hepatic function groups according to the Child-Pugh Score (CPG). Because the fractional change in CL is assumed to be constant over the categories of CPG, the CL in subjects with normal hepatic function can be inferred from the data. (b) (4)

(b) (4)

(b) (4) The parameter estimates of this model are displayed in Table 5.

Table 5: Parameter Estimates of Model Using Oral Dataset

Mean transit time (h)	0.98 (8.1)	31 (56)
Number of transit compartments	9.11 (25.8)	63 (49)
Bioavailability	1 FIX	29 (29)
CL/F (no hepatic impairment) (L/h)	9.32 (7.8)	Not significant
V/F (L)	18.0 (8.6)	35 (35)
Frct	0.226 (7.2)	Not significant
Proportional residual error (%)	24 (13)	

Source: Appendix C of Complete Response, Table 1, Page 9.

Reviewer's Comments: (b)(4) (b) (4) *it is apparent that this assumption is not supported. Furthermore, data in patients with normal hepatic function were not included in the model. Therefore, modeling the data in these 12 hepatically impaired subjects does not add additional insight compared to a simple summary of the noncompartmental PK parameters.*

3.5 Simulations

The Applicant used the results of the two models to simulate dosing regimens in patients with varying degrees of hepatic impairment. The parameter values for the simulation model are displayed in Table 6.

Table 6: Parameter Values Used for Simulation of Dosing Regimens in Patients with Hepatic Impairment

simulation model		
TVCL	7.3	28
Frct	0.23	
V	9.9	30
Q	15.8	39
VP	13.8	85

Source: Appendix C of Complete Response, Table 1, Page 9.

The results of the simulations are summarized in Table 7. The results show that reducing the infusion rate to 4 mg/h and 2 mg/h in patients with moderate and severe hepatic function, respectively, is predicted to result in similar steady-state concentrations as that for patients with normal hepatic function.

Table 7: Steady-State Plasma Concentrations of Esomeprazole in Patients with Hepatic Impairment

Liver function	Dose (esomeprazole XX mg bolus infusion during 30 min followed by esomeprazole X mg per h for 47.5 hrs)	Median (µmol/L)	Lower 95% prediction interval (µmol/L)	Upper 95% prediction interval (µmol/L)
No impairment	80/8	3.2	1.8	5.5
Mild	80/8	4.2	2.3	7.1
Moderate	80/4	3.2	1.8	5.6
Moderate	80/6	4.5	2.6	7.9
Moderate	80/8	5.9	3.3	9.9
Severe	80/2	3.4	1.7	6.0
Severe	80/3	4.4	2.4	7.5
Severe	80/4	5.4	3.0	9.2

Liver function according to Child-Pugh Score: 0-4 no impairment, 5-6 mild, 7-9 moderate, and >10 severe impairment

a based on 2000 simulated patients per group

Source: Appendix C of Complete Response, Table 2, Page 10.

The Applicant's proposal, [redacted] Steady-state concentrations in these patients are therefore predicted to be 25%, 75% and 63% higher, respectively, than patients with normal hepatic function. The Applicant [redacted]

Reviewer's Comments: The reviewer does not agree with the Applicant's rationale for dosing in patients in hepatic impairment for the following reasons:

- *As described above, the reviewer does not agree with* [redacted]
- *The reviewer does not agree with the application* [redacted] *If this is the case, the Applicant is likely to over-estimate the impact of hepatic impairment on steady-state exposure*
- *The Applicant has not provided data to support* [redacted] *Exposure-response analysis in healthy subjects suggests that additional benefit in terms of pH is not achieved at higher exposures.*

These comments were conveyed to the Applicant in an information request on 7/9/2013. FDA asked the Applicant to provide updated dosing recommendations using i.v. omeprazole data in healthy subjects (Study 004) and patients with hepatic impairment

(Study I-1226). Both of these studies have been reviewed by the Clinical Pharmacology reviewer in previous cycles. In Study 004, healthy volunteers (n=39) received i.v. omeprazole and i.v. esomeprazole at a dose of 80 mg + 8 mg/h. There was an unexpected trend for increased concentrations at 24 hours post-dose so C_{ss} was calculated using plasma concentrations taken at 8, 10, 12 and 16 hours post-dose. PK parameters were similar for esomeprazole and omeprazole. This finding supports the use of omeprazole data for dosing recommendations of esomeprazole in patients with hepatic impairment. Descriptive statistics of key omeprazole PK parameters are displayed in Table 8.

Table 8: Clearance (CL) and Steady State Plasma Concentration (Css) for Omeprazole 80 mg + 8 mg/h in Study 004

	CL (L/h)	Css (µmol/L)
Geometric mean	7.93	2.92
Min	3.87	0.61
Median	7.62	3.04
Max	37.89	5.99

Source: Response to Information Request (July 15, 2013), Table 2, Page 5.

In Study I-1226 patients with mild, moderate and severe hepatic impairment received the 80 mg + 8 mg/h regimen over 48 hours. The PK results are summarized in Table 9.

Table 9: Pharmacokinetic Parameters for Omeprazole 80 mg + 8 mg/h in Patients with Hepatic Impairment in Study I-1226

	AUC_{0-24} * (µmol*h/L)	Cmax (µmol/h)	CL (L/h)	Css (µmol/L)	t1/2 (h)
Child-Pugh class A (n=5)					
Geometric mean	135.32	14.15	5.20	4.45	3.29
Min	81.94	10.25	3.75	2.71	2.23
Median	161.38	13.5	4.53	5.10	3.39
Max	192.82	21.68	8.54	6.16	4.56
Child-Pugh class B (n=4)					
Geometric mean	137.38	14.54	5.08	4.55	3.55
Min	107.26	12.01	3.88	3.53	2.23
Median	138.87	14.92	5.27	4.65	4.02
Max	181.14	16.76	6.55	5.95	4.43
Child-Pugh class C (n=3)					
Gmean	169.05	15.38	3.98	5.81	5.69
Min	146.08	12.61	2.92	4.89	4.94
Median	149.10	15.74	4.55	5.07	5.74
Max	221.82	18.34	4.73	7.91	6.51

*AUC_{0-24} was calculated post hoc for comparative reasons

Source: Response to Information Request (July 15, 2013), Table 3, Page 6.

A graphical summary of the parameters of interest, CL and C_{ss}, is provided in Figure 2.

The Applicant calculated the constant infusion rate in hepatically impaired patients that is needed to match C_{ss} in healthy volunteers by multiplying 8 mg/h by the ratio of patient CL to healthy CL. Using this approach, the exact dose in patients with mild, moderate and severe hepatic impairment would be 5.24 mg/h, 5.12 mg/h and 4.01 mg/h. The Applicant is asking for doses of 6 mg/h in patients with mild and moderate impairment and 4 mg/h in patients with severe hepatic impairment. The Applicant points out that the impact of hepatic impairment may be greater for omeprazole compared to esomeprazole because the contribution of CYP2C19 and CYP3A4 to the metabolism of omeprazole

(98% and 2%, respectively) is different than esomeprazole (73% and 27%, respectively). It has been shown that the activity of CYP2C19 is reduced to a greater extent by hepatic impairment than CYP3A4.

Reviewer's Comments: Based on the available data, the Applicant's current proposal appears reasonable.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The reviewer performed additional exploratory graphical analysis to investigate the relationship between esomeprazole concentrations and time with intragastric pH>6 in Caucasian and Chinese subjects.

4.2 Methods

4.2.1 Data Sets

PK/PD data were obtained from Study 007 and Study 015. Data sets used are summarized in Table 10.

Table 10. Analysis Data Sets

Study Number	Name	Link to EDR
015	phmonnm.xpt	\\CDSESUB1\evsprod\NDA021689\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gastro-esophageal-reflux-disease-gerd-01\5351-stud-rep-contr\d9615c00015\crt\datasets
015	kinetic.xpt	\\CDSESUB1\evsprod\NDA021689\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gastro-esophageal-reflux-disease-gerd-01\5351-stud-rep-contr\d9615c00015\crt\datasets
015	convit.xpt	\\CDSESUB1\evsprod\NDA021689\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gastro-esophageal-reflux-disease-gerd-01\5351-stud-rep-contr\d9615c00015\crt\datasets
007	conc.xpt	\\CDSESUB1\evsprod\NDA021689\0112\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\d9615l00007\crt\tabulations\legacy
007	giph.xpt	\\CDSESUB1\evsprod\NDA021689\0112\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\d9615l00007\crt\tabulations\legacy
007	hptest.xpt	\\CDSESUB1\evsprod\NDA021689\0112\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\d9615l00007\crt\tabulations\legacy

007	pk.xpt	\\CDSESUB1\evsprod\NDA021689\0112\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\d9615l00007\crt\tabulations\legacy
007	rd-giph.xpt	\\CDSESUB1\evsprod\NDA021689\0115\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\d9615l00007\crt\datasets\legacy

4.2.2 Software

R was used for the analysis.

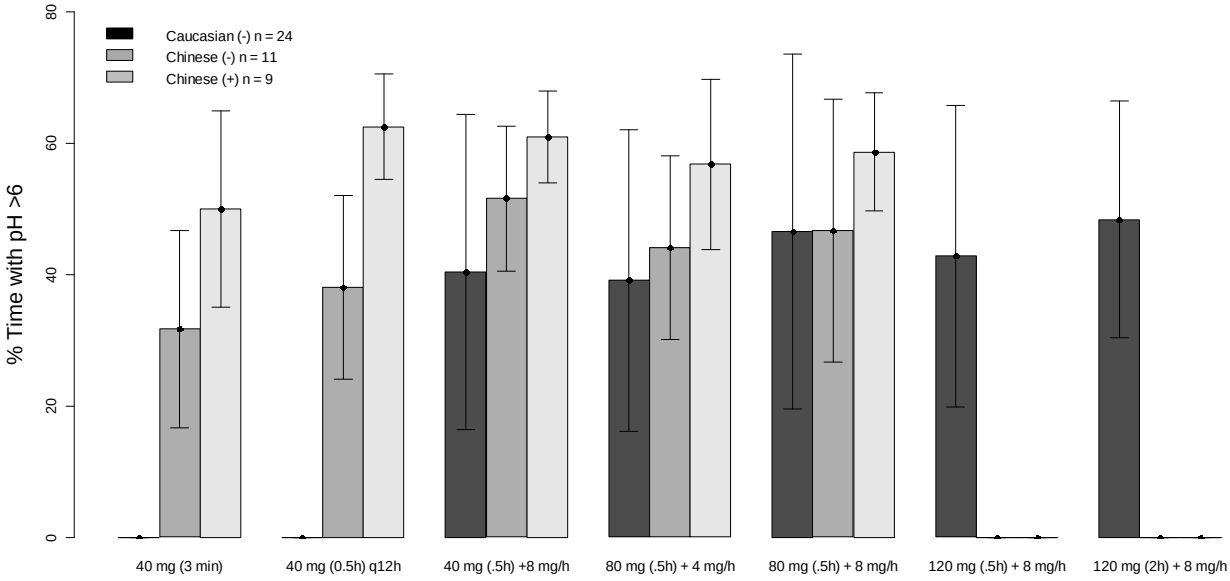
4.3 Results

To compare the dose-response relationship in the two studies, a summary of the data was plotted (Figure 3). It can be noted in Figure 3 that three dose regimens were common in the two studies. A few observations from the data include:

- The time with intragastric pH>6 is greater in H. pylori positive Chinese subjects compared to H.pylori negative Chinese subjects across doses
- There does not appear to be a dose-response relationship across the doses studied in either Chinese or Caucasian subjects
- The time with intragastric pH>6 is similar in H. pylori negative Chinese and Caucasian subjects

The reviewer attempted to establish relationships between pharmacokinetic parameters and time with pH>6, but no trends were apparent. This is consistent with the fact that a dose-response relationship was not observed.

Figure 3: Percentage of Time with pH>6 Across Doses in Caucasian and Chinese Healthy Volunteers



To further compare the PK/PD relationships in Chinese and Caucasian subjects, mean profiles were plotted for concentration and pH versus time. The results are illustrated in Figure 1 and show:

- Chinese subjects have a higher C_{max} probably due to their lower body size
- The H. pylori positive Chinese subjects had a faster rise in pH compared to H.pylori negative Chinese subjects
- Overall, the profile of pH vs. time in Chinese and Caucasian H.pylori negative subjects was similar

Taken together, these results suggest that the effect of 80 mg + 8 mg/h esomeprazole is similar in Chinese and Caucasian healthy volunteers.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
make.ph007.R	Used to create Figure 1 in review	Reviews\Ongoing PM Reviews\Nexium_NDA21689_KMK\ER Analysis
make.comparedose.R	Used to create Figure 2 in review	Reviews\Ongoing PM Reviews\Nexium_NDA21689_KMK\ER Analysis

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SANDHYA K APPARAJU
07/19/2013

KEVIN M KRUDYS
07/19/2013

NITIN MEHROTRA
07/19/2013

SUE CHIH H LEE
07/20/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-689/S-014	Submission Date(s): 09/15/2010
Submission Type; Code	Resubmission to Complete Response Efficacy supplement (SE1)
Priority:	Priority (6 months)
Brand Name	Nexium IV
Generic Name	Esomeprazole
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products
Sponsor	AstraZeneca
Formulation; Strength(s)	Intravenous Injection/ Lyophilized powder for Injection and 20 mg or 40 mg per single-use vial
Proposed Indication	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Proposed Dosing Regiment	Nexium IV 80 mg given by a 30-min infusion and then 8 mg/hr given by constant-rate infusion for 71.5 hr, (b) (4)
PDUFA Goal Date:	06/16/2011

Table of Contents

1 Executive Summary

1.1 Recommendation

The resubmission for Complete Response (CR) for NDA 21-689, S-014 for Nexium IV has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III), and it has be found to be acceptable from a clinical pharmacology standpoint except for the label language, including the issue of dosage adjustment in hepatic impairment patients.

Note that an information request was sent to the sponsor on 04/29/2011 requesting the sponsor to conduct a modeling and simulation to estimate the proper constant infusion rate in moderate and severe hepatic impairment patients and provide the results including simulated concentration-time profiles. The response for this information request was received on 05/19/2011. This new information will be reviewed during the next review cycle as there are other unresolved clinical issues and the PDUFA date is approaching soon. .

1.2 Regulatory Background

On May 2008, AstraZeneca had submitted supplemental NDA 21-689, S-14 for approval of Nexium IV (esomeprazole sodium) Injection for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. In that submission, sponsor had submitted the results of a single pivotal phase III study, Study D961DC00001, "A randomized, double-blind, parallel-group, placebo controlled study of esomeprazole iv (bolus infusion of 80 mg followed by a continuous infusion of 8 mg per hour) administered for 72 hours to assess prevention of rebleeding in patients that have undergone successful primary endoscopic haemostasis of a bleeding peptic ulcer – the PUB study" along with two new pharmacokinetics studies D961DC00004 and D9615C00015.

On November 26th of 2008, the sponsor was issued a Complete Response (CR) letter indicating that the primary efficacy results for this non-U.S. single phase III study did not provide substantial evidence of efficacy. The CR letter also stated that for a single study to stand alone as substantial evidence of efficacy, it should demonstrate highly statistically significant and clinically meaningful results. The CR letter listed the specific deficiencies and recommendations for the sponsor. However, from the clinical pharmacology standpoint, the NDA had deficiencies that were not approval issues but needed to be addressed by the sponsor.

On June 11th, 2009, the sponsor had a Type C-meeting with the Agency. At the meeting, the Agency stated that: "We appreciate that there are considerable practical and ethical challenges to conduct an additional placebo controlled trial. We propose that one path forward is to review/analyze the data from previously conducted, well-controlled trials using esomeprazole. Omeprazole studies would be considered supportive." At the meeting, the sponsor has also agreed to prepare a proposal for FDA review as a preliminary response to the CR letter, addressing the issues identified during this meeting that can support the new indication for Nexium IV using additional literature support, claims databases, and studies that may provide a clinical bridge for omeprazole to esomeprazole.

1.3 Submission Content

On September 15th, 2010, the sponsor has resubmitted their response to complete response letter. The resubmission included: 1) sponsor's response to deficiencies and recommendations in the Complete Response letter and 2) supporting documentation from related compounds (omeprazole) and epidemiologic data. In the second document, sponsor has submitted supporting omeprazole IV data, which included data from 3 separate randomized controlled clinical trials with omerpazole IV (Lau et all 2000, I-840 and I-841) (see table-2 for dosing), observational studies with omeprazole iv, and supporting esomeprazole IV data to support their application. In order to use the results of omeprazole iv data to support this application, sponsor has also provided data and literature references for PK/PD bridging between omeprazole and esomeprazole.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In this sponsor's response to CR letter, there are 3 items that are related to clinical pharmacology. The sponsor addressed 2 clinical pharmacology issues stated in CR letter and also submitted some data for PK/PD bridging between esomeprazole and omeprazole.

Dose Adjustment in Hepatic Impairment Patients:

In the *CR letter*, it was stated that there weren't adequate PK information to permit proper dose adjustment in patients with various degrees of hepatic impairment and also recommended the sponsor to conduct a pharmacokinetic study in sufficient number of patient with hepatic impairment and to include matching healthy subject as control. In this response to the CR letter, the sponsor acknowledged that they have not performed any study with esomeprazole iv in hepatically impaired patients. However, they indicated that there is a study with esomeprazole oral in hepatically impaired patients (study SH-QBE-0026, Sjövall et al 2002), and another study with omeprazole iv in hepatically impaired patients (CSR I-1226, Piqué et al 2002). Both of these studies were inter-study comparison with control group.

When esomeprazole 40 mg was given orally for 5 days to hepatically impaired patients, the AUC increased with severity of the liver impairment in overall trend. However, C_{max} was not influenced significantly by the severity of liver impairment. AUCs of patients with severe hepatic insufficiency were about 2-3 fold higher than that of patient with normal hepatic function.

When omeprazole IV 80 mg was infused over 30 minutes followed by a constant infusion of 8 mg/hr up to 24 hr in hepatically impaired patients, subjects with various degrees of hepatic impairments had higher omeprazole AUC than those from healthy subjects with normal liver function, and the omeprazole AUC increased with the severity of the liver impairment. Patient with mild to moderate hepatic impairment function had approximately 1.46 fold (46%) and 1.74 fold (74%) higher mean AUC compared to the subjects with normal liver function where as the patients with severe hepatic impairment function had almost 2 fold higher mean AUC compared to the subjects with normal hepatic function. Mean omeprazole C_{max} values, however, were less influenced by the severity of hepatic impairment.

In a dose finding study conducted by the sponsor during the last review cycle, it was found that the recommended dose for subjects with normal liver function (80 mg infusion over 30 minutes followed by a 8 mg/hr constant infusion) showed 50% higher AUC (111 vs. 74 μmol*h/L) and comparable C_{max} compared to the recommended dose for subjects with severe hepatic impairment (80 mg infused over 30 min followed by 4 mg/hr constant infusion).

The sponsor proposed [redacted] (b) (4) ic [redacted] (b) (4) a dose adjustment for severely hepatic impairment patient by reducing the dose to 80 mg infused over 30 min followed by a maximum continuous infusion dose of 4 mg/hr [redacted] (b) (4)

Reviewer's Conclusion:

[redacted] (b) (4)

Additionally, the proposed loading dose of 80 mg over 30 minutes for all degrees of hepatic impairments appears to be acceptable. However, agency has some concern regarding the proposed constant intravenous infusion rate of Nexium for both patients with moderate [redacted] (b) (4) and severe (4 mg/hr) hepatic impairment. We recommend the sponsor to conduct a modeling and simulation in order to estimate the proper constant infusion rate in moderate and severe hepatic impairment patients.

Conducting an Additional Dose Finding Study in the Target Population

In the recommendation to address deficiencies section of the *CR letter,* it was stated that the desired pharmacodynamic (PD) effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. Therefore, the sponsor was recommended to conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting the treatment. In this response to the CR letter, the sponsor stated that the submitted PK/PD studies were conducted in *Helicobacter pylori* negative healthy subjects, subjects in whom it would be more difficult to suppress intragastric acidity, and the acid suppressive effect of the proposed esomeprazole iv dosage regimen, 80 mg as a bolus infusion followed by a continuous infusion of 8 mg/h, can be expected to be more pronounced when given to PUB patients. Therefore, sponsor suggests that the submitted 2 PK/PD studies are appropriate and well justified to provide data for dose selection, and that conducting an additional dose finding study including PK and PD measurements in patients with PUB would place an unnecessary burden to the patients.

During the last submission, the sponsor has submitted a dose finding study (study D9615C00015) where 5 different infusion regiments (shown in below table-1) were explores in *H. Pylori* negative healthy subjects:

Table 1. Study Doses Per Treatment

Treatment	Dose of the short term infusion	Rate and length of constant infusion	Total dose (mg)
A	40 mg (0,5 h)	8 mg/h (23.5 h)	228
B	80 mg (0,5 h)	4 mg/h (23.5 h)	174
C	80 mg (0,5 h)	8 mg/h (23.5 h)	268
D	120 mg (0,5 h)	8 mg/h (23.5 h)	308
E	120 mg (2 h)	8 mg/h (22 h)	296

When mean percentage of time with intragastric pH>6 and the proportion of subjects reaching intragastric pH>6 during 24-hr periods were used as the PD markers, treatments C-E had a mean of ~ 50% (or greater) of time for the intragastric pH >6.0, which was higher than that of Treatments A and B (around 45%). In addition, all 5 different infusion rates of esomeprazole

(treatment A through E) resulted in similar proportion of subjects (80-90%) reaching intragastric pH>6 for at least one hour during 24-hr period of time. Treatments D and E did not appear to result in further improvement of any of the PD variables when compared to Treatment C. Based on the results of this study, sponsor has proposed the dosing regimen of 80 mg given by short-term infusion (0.5 hr) + 8 mg/hr continuous infusion (for 71.5 hrs) for the pivotal Phase 3 clinical trial.

The results of this dose finding study in *H. Pylori* negative healthy subject demonstrates that the PD effect appears to plateau off after dose of 80 mg bolus infusion over 30 minutes followed by 8 mg/hr constant infusion for 23.5 hr (treatment C) among evaluated dosing regiments. Higher initial bolus dose (120 mg vs. 80 mg) does not appear increase the PD effect. However, in this dose finding study, the sponsor did not explore infusion rate that is higher than 8 mg/hr.

Additionally, the sponsor has provided a literature (Gillen et al 1999) to support that it is more difficult to suppress intragastric acidity in *Helicobacter pylori* negative healthy subjects compared to *H. Pylori* positive subjects. In this study, 20 *H. Pylori* positive and 12 *H. Pylori* negative healthy volunteers were treated with 40 mg/day omeprazole for 6-8 weeks, and gastric acid output were measured before and after the treatment. Although both *H. Pylori* positive and negative volunteers had similar level of acid output prior to the omprazole treatment, the basal, submaximal and maximal acid outputs were lower in *H. Pylori* positive subjects compared to *H. Pylori* negative subjects after omeprazole treatment suggesting that presence of *H. Pylori* lead to more profound suppression of acid secretion with omprazole treatment.

Reviewer's Conclusion: Based on all the information provided by the sponsor, FDA concurs with sponsor's explanation and agrees that no further dose finding study in target population is necessary.

PK and PD Bridging between Esomeprazole and Omeprazole:

In this cycle of submission, sponsor has submitted data from 3 supporting studies with omeprazole iv (Lau et all 2000, I-840 and I-841) to support their application for esomeprazole. In order to use the results of omeprazole iv data, PK and PD profiles of omeprazole and esomeprazole following same dosing regiments needs to be evaluated. The proposed dosing regiment for esomeprazole in this application is Nexium IV 80 mg administered by a 30-min intravenous infusion and followed by a constant infusion of 8 mg/hr for 71.5 hr, (b) (4) (b) (4) The safety and efficacy of the clinical studies (Table 2) are being evaluated by Dr. Wynn, the Medical Officer of DGIEP. This review focuses only on the PK and PD studies submitted by the sponsor to bridge between esomeprazole and omeprazole.

Table-2. Dosing comparison between reference study and supporting studies

Dosing	**D961DC00001**	**Lau et al 2000**	**I-840**	**I-841**
Drug	Esomeprazole vs. placebo	Omeprazole vs. placebo	Omeprazole vs. placebo	Omeprazole vs. placebo

IV	a bolus infusion of 80 mg over 30 min followed by a continuous infusion of 8 mg/h for 71.5 hours	a bolus iv injection of 80 mg followed by a continuous infusion of 8 mg/h for 72 hours	a bolus infusion of 80 mg over 30 min followed by a continuous infusion of 8 mg/h for 72 hours	a bolus infusion of 80 mg over 30 min followed by a continuous infusion of 8 mg/h for 72 hours
Oral follow-up treatment after iv treatment	40 mg once daily for 27 days	20 mg once daily for 8 weeks	20 mg once daily for 21day	20 mg once daily for 21 days

Continuous Intravenous Administration:

The PK and effect on intragastric pH of esomeprazole iv 80 mg as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hr was compared to that of corresponding dosage regimen of omeprazole iv in Study D961DC00004. The geometric mean of AUC_t and C_{max} values for esomeprazole were 14% higher than those for omeprazole, 95.47 vs. 83.97 µmol*h/L for AUC and 12.82 vs. 11.28 µmol/L for C_{max}. Esomeprazole and omeprazole has similar intragastric pH vs. times profiles and median intragastric pH (5.9 vs. 5.8). Therefore, there is lack of a major difference between two treatments with respect to both PK and PD parameters when they are given as 80 mg bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/hr for 23.5hr. Nonetheless, there was a less interindividual variability for esomeprazole compared to omeprazole regarding AUC and percentage of time with intragastric pH>4.

Once Daily Short Term Intravenous Administration

The sponsor has referred to two studies to compare the PK and PD of esomeprazole and omerpazole following short term infusion over 30 minutes.

In the first study, following a single dose of 30 minutes iv infusion, esomeprazole 40 mg had 36% higher AUC (6.88 vs. 5.07 µmol·h/L) and 18% higher C_{max} (5.4 vs. 4.57 µmol/L) compared to 30-min infusion of omeprazole 40 mg. Geometric mean half-life of esomeprazole was approximately 12% (1.01 vs. 0.90 hr) longer compared to that of omeprazole. Regarding the PD parameters, esomeprazole 40 mg and omeprazole 40 mg iv administration resulted in a pronounced reduction of peak acid output (PAO) from a mean baseline value (33.9 mmol/h) when measured at 4-5.5 hours after the dose, with more profound effect from esomeprazole compared to omerpazole (5.4 mmol/h for esomeprazole vs. 9.5 mmol/h for omeprazole). However, the effect on PAO was somewhat less pronounced when measured at 24-25.5 hours after the dose (15.7 mmol/h for esomeprazole and 20.0 mmol/h for omeprazole). Additionally, both treatments had similar reduction in basal acid output (BAO) when measured after 3-4 hours (0.7 mmol/h for esomeprazole, 1.1 mmol/h for omeprazole, and 4.4 mmol/h at baseline) and after 23-24 hours (1.0 mmol/h for esomeprazole and 1.5 mmol/h for omeprazole). The observed more pronounced PD effect of esomeprazole likely is a reflection of its higher AUC compared to omeprazole.

In the second study, following both single and multiple dose of short term intravenous infusion over 30 minutes, administration of 40 mg esomeprazole resulted in 43 % higher AUC (7.78 vs. 5.45 µmol.h/L on day 1 and 14.25 vs. 9.94 µmol.h/L on day 5) and 12% - 15% higher C_{max} (5.73 vs. 4.99 µmol/L on day 1 and 6.67 vs. 5.95 µmol/L on day 5) compared to 40 mg of omeprazole in extensive metabolisers (EM). Additionally, on both day 1 and day 5, esomeprazole has 30 % lower clearance and 25% longer half-life

compared to omeprazole in extensive metabolisers. Contrary to extensive metabolisers, in poor metabolizers (PM), esomeprazole has lower AUC compared to omeprazole (23% lower on both day 1 and 34% lower on day 5), while the C_{max} were comparable for those two treatments. Furthermore, the difference in AUC between PMs and EMs for esomeprazole was less compared to omeprazole on both day 1 and day 5, suggesting a less influence of polymorphism on the metabolism of esomeprazole (H 199/18) compared omeprazole.

Oral Administration:

The greatest difference in PK parameters between esomeprazole and omeprazole were observed when they were administered orally compared to when they were administered intravenously. Following the oral administration, AUC and C_{max} of esomeprazole were significantly higher than those of omeprazole in extensive metabolizers. Following a single dose oral administration, AUCs of esomeprazole were approximately 35% and 60% higher than that of omeprazole at 20 mg and 40 mg dose, respectively. At steady state following multiple dosing, AUCs of esomeprazole were approximately 70% higher than that of omeprazole at both 20 mg and 40 mg. C_{max} of esomeprazole was only approximately 25-30% higher than that of omeprazole following both single and multiple doses at 20 mg and 40 mg. Following multiple dosing, AUC and C_{max} of both esomeprazole and omeprazole increased compared to single dose administration. In contrast to EM, in poor metabolizers, AUC of esomeprazole is approximately 20-30% lower than that of omeprazole following single and multiple doses, while the C_{max} remained comparable between esomeprazole and omeprazole.

The difference in PK profiles of esomeprazole and omeprazole was reflected in PD marker as well, although the difference wasn't as significant as the PK parameters. Following multiple dosing, the mean percentage time with intragastric pH > 4 was 53% for esomeprazole vs. 43.7% for omeprazole at 20 mg dose, and 68.4% for esomeprazole vs. 62.0% for omeprazole at 40 mg dose.

It is important to note that the dose for oral follow-up treatment after the iv treatment in supporting studies (20 mg omeprazole) is different than the oral dose for the reference study (40 mg esomeprazole). Since significantly lower exposure is observed with omeprazole compared to esomeprazole following oral dosing even at the same dose (40 mg), 20 mg of omeprazole is expected to yield even lower AUC compared to 40 mg of esomeprazole.

Overall Conclusion:

The extent of differences between the esomeprazole and omeprazole PK/PD parameters is dependent on the route of administration. When they were given as continuous intravenous infusion (80 mg as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hr), esomeprazole and omeprazole did not have a major difference in PK and PD parameters (AUC_t and C_{max} of esomeprazole were only 14% higher than those for omeprazole). However, following short term intravenous infusion over 30 minutes, AUC and C_{max} of 40 mg esomeprazole were 36-43% and 12-18% higher than those of 40 mg omeprazole, respectively. Higher AUC of esomeprazole was also reflected in its higher PD effect. The greatest difference between esomeprazole and omeprazole PK/PD was observed they are given orally. Following multiple oral dosing, AUC and C_{max} of esomeprazole were approximately 70% and 25-30% higher than those of omeprazole, respectively, at both 20 mg and 40 mg. Higher AUC of

esomeprazole was also reflected in its PD parameter, although the difference in PD marker was not as significant as the difference in AUC.

For the various administration routes and dosing regimens studied, the acid suppression effect of esomeprazole was similar to or greater than that of omeprazole when given at the same dose. Overall, a reasonable PD bridging is established between omeprazole and esomeprazole for the proposed IV dosing regimen.

2 Question Based Review

2.1 General Attributes

2.1.1 What is the regulatory background?

On May 2008, AstraZeneca submitted supplemental NDA 21-689, S-14 for approval of Nexium IV (esomeprazole sodium) Injection for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. In this submission, sponsor has submitted the results of a single pivotal phase III study, Study D961DC00001, along with two pharmacokinetics studies D961DC00004 and D9615C00015.

On November 26th of 2008, the sponsor was issued a Complete Response (CR) letter indicating that the primary efficacy results for this non-U.S. single phase III study did not provide substantial evidence of efficacy. However, from the clinical pharmacology standpoint, the NDA had deficiencies that were not approval issues but needed to be addressed by the sponsor.

On June 11th, 2009, the sponsor had a Type C-meeting with the Agency. At the meeting, the Agency stated that: "We appreciate that there are considerable practical and ethical challenges to conduct an additional placebo controlled trial. We propose that one path forward is to review/analyze the data from previously conducted, well-controlled trials using esomeprazole. Omeprazole studies would be considered supportive." At the meeting, the sponsor has also agreed to prepare a proposal for FDA review as a preliminary response to the CR letter, addressing the issues identified during this meeting that can support the new indication for Nexium IV using additional literature support, claims databases, and studies that may provide a clinical bridge for omeprazole to esomeprazole.

Nexium IV dosage form for injection and infusion has been approved in US since March of 2005 for the short-term treatment (up to 10 days) of GERD patients with a history of erosive esophagitis. The recommended adult dose is either 20 or 40 mg esomeprazole given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 to 30 minutes).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug products being proposed?

The active ingredient of Nexium IV is esomeprazole sodium. Esomeprazole is the S-enantimoer of approved PPI, omeprazole.

2.1.3 What is the proposed indication?

The proposed indication for Nexium IV in this application is (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute gastric or duodenal ulcers.

2.1.4 What are the proposed mechanisms of actions?

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion via specific inhibition of the H^+, K^+-ATPase enzyme (proton pump) located in the secretory membrane of the gastric parietal cell. In the acidic compartment of the parietal cell, esomeprazole is protonated and converted into a pharmacologically active inhibitor that react with luminally accessible cysteines of H^+, K^+-ATPase to form a disulfide bond, thus irreversibly inhibiting H^+, K^+-ATPase activity. Since PPIs block the final common pathway of acid production in the stomach, they inhibit both basal and stimulated gastric acid secretion.

2.1.5 What are the proposed dosage and route of administration?

The proposed dose for adults is Nexium IV 80 mg administered by a 30-min intravenous infusion and followed by a constant infusion of 8 mg/hr for 71.5 hr, (b) (4) (b) (4)

2.2 General Clinical Pharmacology

2.2.1 Is the sponsor's proposed dose adjustment for liver impairment acceptable, (b) (4)

In the *CR letter*, it was stated that "There is inadequate information to permit proper dosing in patients with hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the randomized, placebo controlled clinical trial and there is no adequate pharmacokinetic (PK) study conducted to evaluate esomeprazole in subjects with various degrees of hepatic impairment. Based on the data provided in the current submission, we are unable to determine the appropriate dose adjustment of esomeprazole for patients with hepatic impairment". The CR letter also recommended to the sponsor to conduct a pharmacokinetic study in sufficient number of patient with hepatic impairment and to include matching healthy subject as control.

AstraZeneca's Response:

"AstraZeneca has not performed any study with esomeprazole iv in hepatically impaired patients. There is, however, a study with esomeprazole oral in hepatically impaired patients, study SH-QBE-0026, that was submitted in the original NDA file for Nexium Delayed- Release Capsules (NDA 21-153, SE/H/211/01-02, Sjövall et al 2002). In addition, there is a study with omeprazole iv in hepatically impaired patients, and the data obtained in that study demonstrate a 70% higher AUC and a 30% higher C_{max} than in healthy subjects (CSR I-1226, Piqué et al 2002). (b) (4) Based on this and the discussion in the present application, Section

3.1.4.3 in Module 2.7.2, AstraZeneca therefore would like to pursue the recommendation suggested. With regard to plasma protein binding, (b) (4) [redacted] Furthermore, there is no difference in plasma protein binding between oral and iv administration of esomeprazole.
In conclusion, in AstraZeneca's opinion the proposed dose recommendation for esomeprazole iv should ensure clinical efficacy and safety also in hepatically impaired patients."

FDA Review:

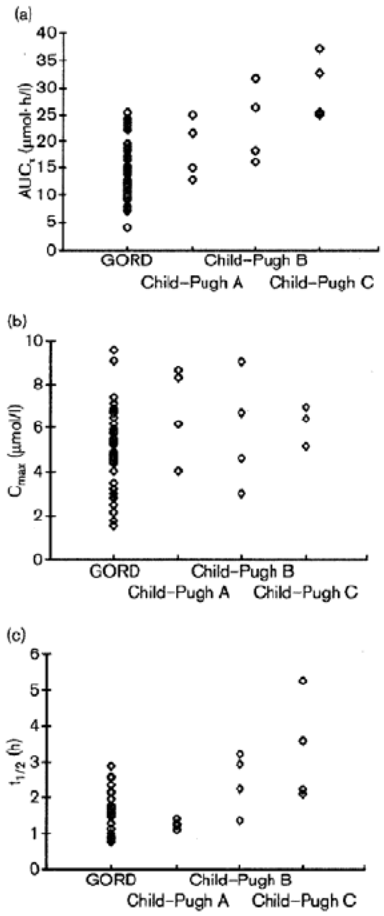
As sponsor indicated, there is one study with esomeprazole administered orally in hepatically impaired patients where 12 patients with mild to severe hepatic impairment received once-daily oral esomeprazole dose of 40 mg for 5 days. Blood samples were collected up to 24 hr on Day 5. The obtained steady state pharmacokinetic parameters were compared with a historical control group of 36 GERD patients with normal hepatic function (Sjövall et al 2002).

Table 3. Pharmacokinetic parameters following oral administration of esomeprazole 40 mg once daily for 5 days to cirrhotic patients with varying degrees of hepatic impairment (n = 12) and gastro-esophageal reflux disease (GERD) patients with normal hepatic function (n = 36)

	Pharmacokinetic parameter (mean [95% CI])			
	C_{max} (μmol/l)[a]	t_{max} (h)[b]	AUC_τ (μmol·h/l)[a]	$t_{1/2}$ (h)[a]
Normal hepatic function ($n = 36$)	4.7 (4.1–5.5)	1.6 (1.3–1.8)	12.8 (10.9–15.0)	1.5 (1.4–1.7)
Hepatic impairment				
Mild ($n = 4$)	6.5 (3.8–11.4)	1.7 (1.1–2.3)	18.2 (11.3–29.3)	1.3 (1.0–1.5)
Moderate ($n = 4$)	5.4 (2.5–11.5)	2.3 (0.6–4.1)	22.6 (13.8–36.9)	2.4 (1.3–4.3)
Severe ($n = 4$)	6.4 (5.2–8.0)	1.8 (1.0–2.5)	30.0 (22.1–40.6)	3.1 (1.6–6.1)

AUC_τ, area under the plasma concentration–time curve during the dosage interval; C_{max}, maximum plasma concentration; $t_{1/2}$, plasma elimination half-life; t_{max}, time to C_{max}.
[a]Geometric mean (95% CI); [b]estimated mean (95% CI).

Figure 1.



Individual values of (a) the area under the plasma concentration–time curve during the dosage interval (AUC_t), (b) the maximum plasma concentration (C_{max}), and (c) the plasma elimination half-life ($t_{1/2}$) in gastro-oesophageal reflux disease (GORD) patients with normal hepatic function and in cirrhotic patients with mild (Child–Pugh A), moderate (Child–Pugh B) and severe (Child–Pugh C) hepatic impairment.

The above inter-study comparison of esomeprazole PK in hepatically impaired and normal liver function patients showed that AUC increased with severity of the liver impairment in overall trend. However, C_{max} was not influenced significantly by the severity of liver impairment. Despite the general increase in average AUC with severity of liver impairment, AUCs of patients with mild to moderate hepatic insufficiency were mostly within the range that was observed in patients with normal liver function. AUCs of patients with severe hepatic insufficiency, however, were about 2-3 fold higher than that of the patient with normal hepatic function.

(b) (4)

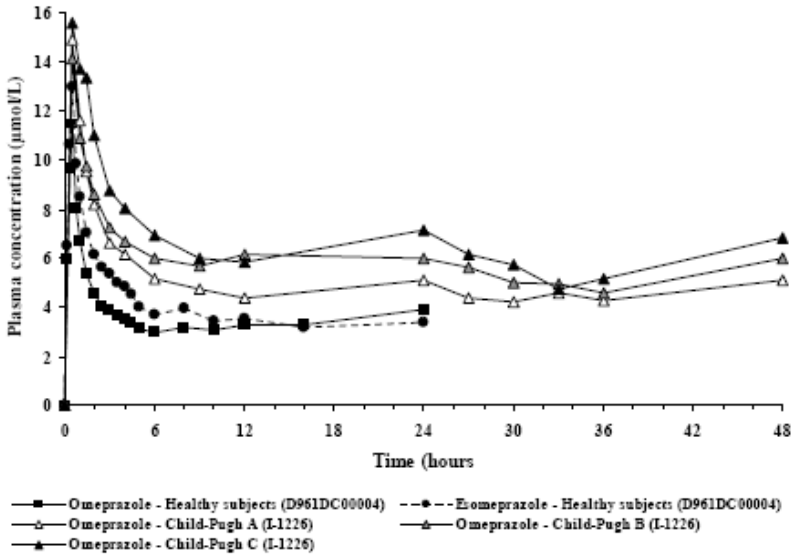
Reviewer's comments: The sponsor proposes (b) (4)

Additionally, there is also another study with omeprazole IV in 12 hepatically impaired patients (Study I-226, Piqué et al 2002) where 80 mg was infused over 30 minutes followed by a constant infusion of 8 mg/hr up to 24 hr. The obtained pharmacokinetic parameters were compared with omeprazole and esomeprazole (with same dosing regiment) PK profiles from healthy subjects from separate studies D9615C00015 (n=26) and D961DC00004 (n=39).

Table 4. Comparisons of Mean (±SD) PK Parameters of Esomeprazole and Omeprazole Obtained From the Dosing Regimen of A 30-min Infusion of 80 mg followed by a Constant Rate (8 mg/hr) Infusion up to 24 hrs

Study No.	**AUC_{0-24} (µmole-h/L)**	**C_{max} (µmole/L)**	**C_{ss} (µmole/L)**
I. **D9615C00015** (n=26) Esomeprazole	109.9 (± 23.1)	14.2 (± 2.6)	4.0 (± 1.0)
II. **D961DC00004** (n=39) Esomeprazole	98.6 (± 25.9)	13.1 (± 2.8)	3.4 (± 1.0)
Omeprazole	89.1 (± 30.5)	11.6 (± 2.8)	-----
III. **I-1226** Omeprazole			
Child-Pugh C (n=3); Severe	172.3 (± 42.9)	15.6 (± 2.9)	5.96 (± 1.69)
Child-Pugh B (n=4); Moderate	155.0 (± 32.8)	14.1 (± 2.0)	5.09 (± 1.10)
Child-Pugh A (n=5); Mild	130.8 (± 42.9)	15.0 (± 4.3)	4.33 (± 1.49)

Figure 2. Mean Plasma Concentrations following Esomeprazole IV 80 mg + 8 mg/h and Omeprazole IV 80 mg + 8 mg/h in Healthy Subjects (D961DC00004), and following Omeprazole iv 80 mg + 8 mg/h in Subjects with Mild to Severe Impairment of Liver Function (Child- Pugh classification A, B and C, respectively; I-1226).



The above inter-study comparison of omeprazole PK showed that when omeprazole IV 80 mg was infused over 30 minutes followed by a constant infusion of 8 mg/hr up to 24 hr in hepatically impaired patients, subjects with various degrees of hepatic impairment had higher mean omeprazole AUC (Study I-1226) compared to healthy subjects with normal liver function (Study D961DC00004), and the omeprazole AUC increased with the severity of the liver impairment. Patient with mild to moderate hepatic impairment had approximately 1.46 fold (46%) and 1.74

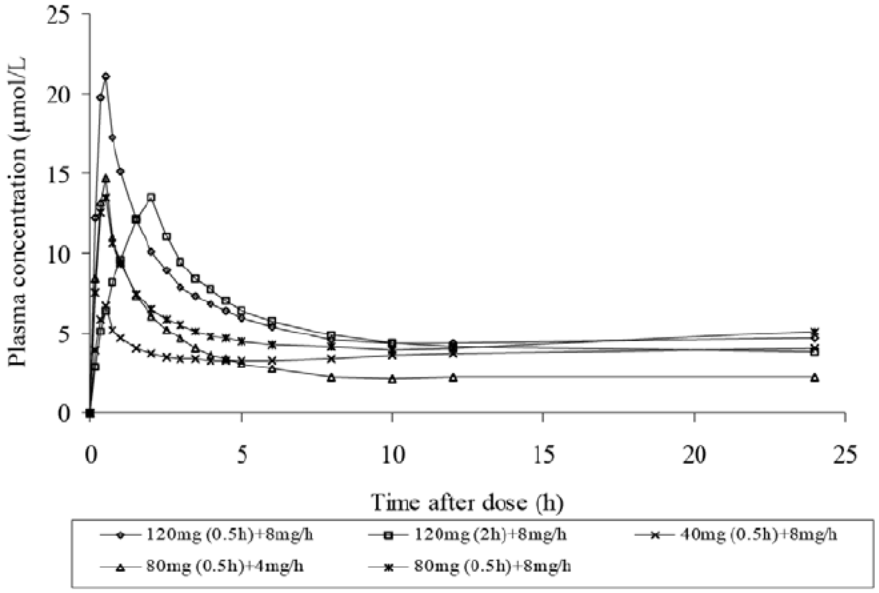
fold (74%) higher mean AUC compared to subjects with normal liver function, respectively, where as the patients with severe hepatic impairment had almost 2 fold higher mean AUC compared to the subjects with normal hepatic function. Mean omeprazole C_{max} values, however, were less influenced by the severity of hepatic impairment (Study I-1226). Regarding to the steady state concentration level, omeprazole Css level was not reported in the study with normal hepatic subjects (D961DC00004). Nonetheless, based on Figure-2, omeprazole and esomeprazole appears to have very similar concentration level at 10, 12, 16, and 24 hr in healthy subjects. Based on this information, Css of omeprazole also appears to increase with severity of hepatic impairment. Patient with mild, moderate, and severe hepatic impairment had approximately 27%, 50%, and 75% higher Css compared to healthy subjects, respectively.

In the previous cycle of submission, the sponsor had submitted a dose finding study D9615C00015 where 5 different dosing regiments were compared.

Table 5. Geometric means and 95% CI of the pharmacokinetic parameters of esomeprazole following intravenous infusion of esomeprazole at 5 different infusion rates in healthy male and female subjects (D9615C00015)

Parameter	Unit	Treatment	N	Estimate	95% CI	
					Lower	Upper
AUC_{0-24}	µmol*h/L	40mg (0.5h)+8mg/h	22	89.69	81.31	98.93
		80mg (0.5h)+4mg/h	24	73.68	66.75	81.33
		80mg (0.5h)+8mg/h	23	111.05	100.51	122.69
		120mg (0.5h)+8mg/h	22	134.66	121.54	149.20
		120mg (2h)+8mg/h	20	126.23	113.80	140.01
CL	L/h	40mg (0.5h)+8mg/h	23	6.70	5.93	7.58
		80mg (0.5h)+4mg/h	24	5.51	4.86	6.24
		80mg (0.5h)+8mg/h	24	5.89	5.20	6.67
		120mg (0.5h)+8mg/h	22	5.40	4.74	6.14
		120mg (2h)+8mg/h	21	5.45	4.78	6.20
C_{max}	µmol/L	40mg (0.5h)+8mg/h	23	7.11	6.44	7.84
		80mg (0.5h)+4mg/h	24	16.01	14.48	17.71
		80mg (0.5h)+8mg/h	24	14.97	13.53	16.56
		120mg (0.5h)+8mg/h	22	23.12	20.81	25.68
		120mg (2h)+8mg/h	21	14.33	12.90	15.93
C_{ss}	µmol/L	40mg (0.5h)+8mg/h	23	3.46	3.06	3.92
		80mg (0.5h)+4mg/h	24	2.10	1.86	2.38
		80mg (0.5h)+8mg/h	24	3.94	3.48	4.46
		120mg (0.5h)+8mg/h	22	4.30	3.78	4.90
		120mg (2h)+8mg/h	21	4.26	3.74	4.85

Figure 3. Mean plasma concentrations of esomeprazole following intravenous infusion of esomeprazole at 5 different infusion rates in healthy male and female subjects (D9615C00015)



The sponsor proposed [redacted] (b) (4) a dose adjustment for severely hepatic impairment patient by reducing the dose to 80 mg infused over 30 min followed by a maximum continuous infusion dose of 4 mg/hr [redacted] (b) (4)

In the dose finding study, the recommended dose for subjects with normal liver function (80 mg infusion over 30 minutes followed by a 8 mg/hr constant infusion) showed 50% higher AUC (111 vs. 74 µmol*h/L), 88% higher Css (3.94 vs. 2.1 µmol/L) level, and comparable C_{max} compared to the recommended dose for subjects with severe hepatic impairment (80 mg infused over 30 min followed by 4 mg/hr constant infusion).

Reviewer's comment:
Both studies with hepatic impairment patients (esomeprazole oral and omeprazole iv) 1) do not a have control group with healthy subjects with normal liver function and 2) have small number of subjects in the 3 classifications of hepatic impairment groups (n = 3-5).

[redacted] (b) (4)

Additionally, the proposed loading dose of 80 mg over 30 minutes for all degrees of hepatic impairments appears to be acceptable. However, based on the data that the sponsor have provided, agency has some concern regarding the proposed constant intravenous infusion rate of Nexium for both patients with moderate [redacted] (b) (4) and severe (4 mg/hr) hepatic impairment. We recommend the sponsor to conduct a modeling and simulation to estimate the proper constant infusion rate in moderate and severe hepatic impairment patients and provide the results including simulated concentration-time profiles.

Reference:

Piqué JM, Faust F, de Prada G, Röhss K, Hasselgren G. Pharmacokinetics of omeprazole given by continuous intravenous infusion to patients with varying degrees of hepatic dysfunction. Clin Pharmacokinet 2002;41:999-1004.

Sjövall H, Björnsson E, Holmberg J, Hasselgren G, Röhss K, Hassan-Alin M. Pharmacokinetic study of esomeprazole in patients with hepatic impairment. Eur J Gastroenterol Hepatol 2002;14:491-496.

2.2.2 Is there need for conducting an additional dose finding study in the target population?

In the recommendation to address deficiencies section of the *CR letter,* it was stated that:

"You should consider whether the dose evaluated in the study submitted for review in this NDA supplement was adequate to achieve the desired efficacy, in light of the pharmacodynamic effects observed in the two pharmacokinetic/pharmacodynamic (PK/PD) studies that you conducted and submitted for review. The desired pharmacodynamic effect, i.e. target intragastric pH, was not achieved by a substantial proportion of patients in the first 24 hours of treatment in the PK/PD studies and was not sustained for a prolonged duration of time within that period. This insufficient PD response may have contributed to the lack of robustness of the treatment effect observed in your major randomized, placebo controlled study. The proportion of patients who experienced rebleeding in the first 24 hours of treatment in the phase 3 study was, in fact, similar between treatment arms, and the majority of rebleeding events on the esomeprazole arm occurred within the first 24 hours of treatment.

For the reasons stated above, conduct an additional dose finding study in the target population to evaluate dose optimization, at least for the initial 24 hours after starting treatment. The study would require evaluation of PK and PD, and should incorporate clinical outcome measures. A higher hourly infusion dose may be required to optimize the PD effects, but the appropriateness of the higher doses from a safety standpoint should be supported by appropriate nonclinical and/or clinical safety data."

AstraZeneca's response:

"AstraZeneca notes the reviewer's comments that the level of intragastric pH observed in the pharmacokinetic/pharmacodynamic (PK/PD) studies, 1 dose-finding study (D9615C00015) and 1 comparative study (D961DC00004), submitted for review in the sNDA, may have contributed to the lack of robustness of treatment effect. However, it is important to observe that the PK/PD studies were performed in *Helicobacter pylori* negative healthy subjects, ie, subjects in whom it would be more difficult to suppress intragastric acidity (Gillen et al 1999). However, the acid suppressive effect of the proposed esomeprazole iv dosage regimen, 80 mg as a bolus infusion followed by a continuous infusion of 8 mg/h, can be expected to be more pronounced when given to PUB patients. Thus, it has been shown that omeprazole iv 80 mg + 8 mg/h (i.e., the comparator in study D961DC00004) given to patients with bleeding gastric and duodenal ulcers resulted in a rapid increase to intragastric pH>6 (median time 36

minutes), which was maintained at this high level throughout the remainder of the 24-hour period. The median intragastric pH was 6.6-6.8 during the period 2-24 hours after start of treatment (Labenz et al 1997). Since the submitted comparative PK/PD study showed that esomeprazole iv 80 mg bolus followed by 8 mg/h resulted in at least as pronounced effect on intragastric pH as the corresponding dosage regimen of omeprazole iv, there are no reasons not to expect that also esomeprazole iv 80 mg + 8 mg/h will result in a level of acid suppression (sustained intragastric pH>6) sufficient to achieve the desired efficacy in PUB patients. The dosage regimen is also supported by recommendations in clinical guidelines (Palmer 2002, Barkun et al 2010), and by results from the randomized omeprazole iv studies in PUB patients described in section 3.1 in Supporting Documentation from Related Compounds and Epidemiologic Data (Module 5.3.5.3).
In light of this, it is AstraZeneca's opinion that the 2 submitted PK/PD studies are appropriate and well justified to provide data for dose selection, and that conducting an additional dose finding study including PK and PD measurements in patients with PUB would place an unnecessary burden to the patients."

FDA Review:

The sponsor had submitted one dose finding study D9615C00015 where 5 different infusion regiments were explores in *H. Pylori* negative healthy subjects as shown below:

Table 6. Study Dose Per Treatment (D9615C00015; N=26)

Treatment	Dose of the short term infusion	Rate and length of constant infusion	Total dose (mg)
A	40 mg (0,5 h)	8 mg/h (23.5 h)	228
B	80 mg (0,5 h)	4 mg/h (23.5 h)	174
C	80 mg (0,5 h)	8 mg/h (23.5 h)	268
D	120 mg (0,5 h)	8 mg/h (23.5 h)	308
E	120 mg (2 h)	8 mg/h (22 h)	296

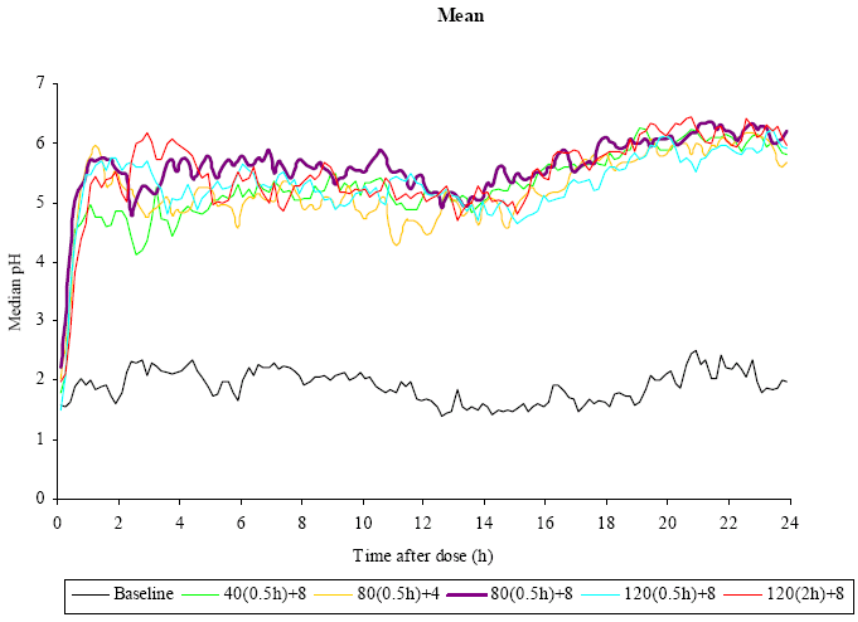
Intragastric pH was recorded over 24- hour period, at baseline and following start of infusion, and the % of time for the intragastric pH >4, 6, or 7 and % of patients with intragastric pH >4, 6, or 7 in 24-hr period were assessed.

For intragastric pH >6.0 (primary variable) in 24-hr period, the mean % of time is shown below:

Table 7. Estimates (and 95% Confidence Intervals) of Mean Percentage of Time with Intragastric pH>6 at Baseline and during IV infusion of Esomeprazole at 5 Different Infusion Rates in Healthy Subjects (D9615C00015)

Variable	Treatment	N	Estimate	95% CI	
				Lower	Upper
pH>6 (0-24h)	Baseline	25	1.7	0.5	2.8
	40mg (0.5h)+8mg/h	23	46.0	34.1	57.8
	80mg (0.5h)+4mg/h	24	44.4	32.4	56.5
	80mg (0.5h)+8mg/h	24	52.3	40.3	64.4
	120mg (0.5h)+8mg/h	22	49.0	36.5	61.6
	120mg (2h)+8mg/h	20	56.3	43.5	69.0
pH>6 (0-3h)	Baseline	25	2.0	0.1	3.8
	40mg (0.5h)+8mg/h	23	24.6	12.4	36.9
	80mg (0.5h)+4mg/h	24	35.2	22.8	47.7
	80mg (0.5h)+8mg/h	24	45.8	33.3	58.3
	120mg (0.5h)+8mg/h	22	45.7	32.6	58.7
	120mg (2h)+8mg/h	20	44.6	31.3	57.9

Figure 4. Median Intragastric pH Profiles at Baseline and during administration of Esomeprazole to Healthy Subjects, Treatments A-E (D9615C00015)



Based on this PD result, the previous reviewer has concluded that:

- Treatments C-E had a mean of around 50% (or greater) of time for the intragastric pH >6.0 which is higher than that of Treatments A and B (around 45%) and baseline (1.7%).

- During the initial 0-3 hrs studied, Treatments C-E also had a higher mean % of time for the intragastric pH >6 (around 45% of time) which is better than that of Treatments A and B (≤ 35% of time) and baseline (2.0%).
- Treatments D and E, however, did not result in further improvement of any of the PD variables when compared to Treatment C.

The proportion of subjects reaching intragastric pH>6 (and maintained for at least 1 hr duration) during 0-3 hr and 0-24 hr periods following the 5 different IV infusion rates are shown below.

Table 8. Proportion of Subjects Reaching Intragastric pH>6 (at least 1 hour duration) following the Intravenous Infusion of Esomeprazole at 5 Different Infusion Rates in Healthy Subjects (D9615C00015)

Treatment	**No. of Subjects** (n=25)	**Proportion (%) of Subjects**	
		During 0 - 3 hr (Baseline: 4.0%)	**During 0 - 24 hr** (Baseline: 8.0%)
A: 40 mg (0.5 hr)+8 mg/hr (23.5 hrs)	23	17.4%	82.6%
B: 80 mg (0.5 hr)+4 mg/hr (23.5 hrs)	24	45.8%	83.3%
C: 80 mg (0.5 hr)+8 mg/hr (23.5 hrs)	24	54.2%	83.3%
D: 120 mg (0.5 hr)+8 mg/hr (23.5 hrs)	22	54.5%	90.9%
E: 120 mg (2.0 hr)+8 mg/hr (22.0 hrs)	21	38.1%	85.7%

Based on this PD result, the previous reviewer has concluded that:

- During the first 3-hr period there are no major differences between Treatments C-D which are better than that of Treatments A, B, and E.
- For the 24-hr period, they are, however, comparable among 5 treatments.
- Mean (± SD) times reaching this endpoint variable (intragastric pH>6 at least 1 hour duration) are calculated to be 9.78 (± 7.07), 6.02 (± 7.25), 5.67 (± 6.97), 5.20 (± 7.30), and 5.52 (± 6.33) hrs, respectively (not shown in Table 6).

Based on the study results on 24-hr intragastric pH data obtained from the Phase-1 program, the dosing regimen of 80 mg given by short-term infusion (0.5 hr)+8 mg/hr continuous infusion (for 71.5 hrs) was, therefore, proposed by the sponsor for the pivotal Phase 3 clinical trial.

Additionally, the sponsor has provided a literature (Gillen et al 1999) to support that it is more difficult to suppress intragastric acidity in *Helicobacter pylori* negative healthy subjects compared to *H. Pylori* positive subjects. In this study, 20 *H. Pylori* positive and 12 *H. Pylori* negative healthy volunteers were treated with 40 mg/day omeprazole for 6-8 weeks, and gastric acid output were measured before and after the treatment. Although both *H. Pylori* positive and negative volunteers had similar level of acid output prior to omprazole treatment, the basal, submaximal and maximal acid outputs were lower in *H. Pylori* positive subjects compared to *H. Pylori* negative subjects after omeprazole treatment suggesting that presence of *H. Pylori* lead to more profound suppression of acid secretion with omprazole treatment.

Reviewer's comment:
PD effect appears to plateau after dose of 80 mg bolus infusion over 30 minutes followed by 8 mg/hr constant infusion for 23.5 hr among tested dosing regiments. Higher initial bolus dose (120 mg vs. 80 mg) does not appear increase the PD effect. However, in this dose finding study, the sponsor did not explore infusion rate that is higher than 8 mg/hr. Additionally, this dose

finding study was conducted in *Helicobacter pylori* negative healthy subjects. Based on the provided literature, agency agrees that the acid suppressive effect of the proposed esomeprazole is expected to be more pronounced when given to PUB patients than given to *Helicobacter pylori* negative healthy subjects as in this dose finding study. After further internal discussion, FDA concurs with sponsor's explanation and agrees that no further dose finding study in target population is necessary.

Reference:

Gillen D, Wirz AA, Neithercut WD, Ardill JES, McColl KEL. Helicobacter pylori infection potentiates the inhibition of gastric acid secretion by omeprazole. Gut 1999;44:468-475

2.2.3 How do esomeprazole and omeprazole pharmacokinetic and pharmacodynamic profile compare following a dosing regimen of a 30-min Infusion of 80 mg followed by a constant rate (8 mg/hr) infusion?

The PK and effect on intragastric pH of esomeprazole iv 80 mg as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg/h was compared to that of corresponding dosage regimen of omeprazole iv in Study D961DC00004, and study was reviewed and found to be acceptable during the last review cycle.

Study D961DC00004 was a double-blind, randomized, 2-way crossover, single-center (Switzerland) comparative study of esomeprazole and omeprazole given as short-term intravenous infusion of 80 mg over 30 minutes followed by continuous infusion of 8 mg/h for 23.5 hr regarding the effect on 24- hour intragastric pH and pharmacokinetics in 39 healthy male and female volunteers with washout period of 13 days between the treatments. In this study, the subjects did not remain fasting but instead were given a total of 800 mL of nutrition drink during daytime on study days in order to ensure adequate fluid and energy supply. Plasma samples were collected over 24 hrs after the start of drug infusion. Intragastric pH was recorded over 24-hour period at baseline and following the start of drug infusion on the study days.

The mean PK profiles and parameters obtained from this study are summarized below for comparison:

Figure 5. Mean plasma concentrations following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects (N=39)

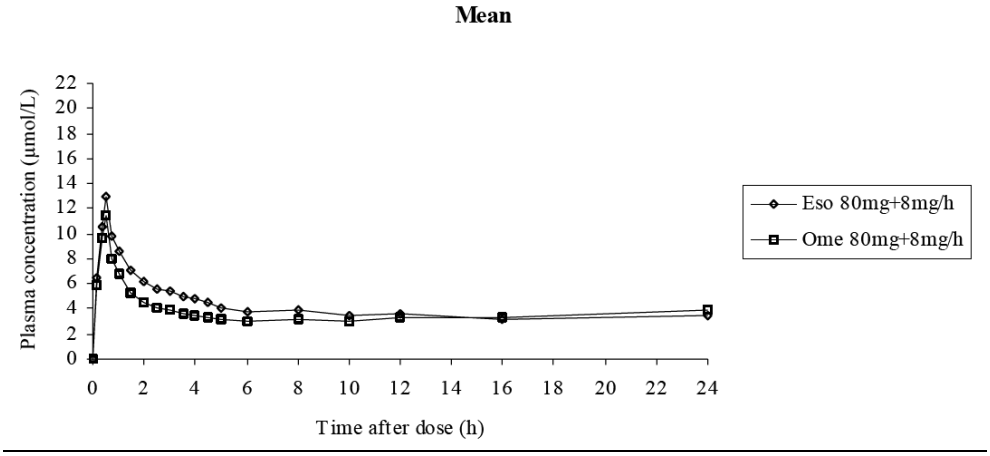


*Table 9. Estimated geometric means and 95% CIs for C_{max} (µmol/L), $AUC_{)}$ (µmol*h/L), C_{ss} (µmol/L) and CL (L/h) following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects*

Variable	Treatment	N	Estimate	95% CI	
				Lower	Upper
C_{max}	Esomeprazole	39	12.82	11.92	13.78
	Omeprazole	39	11.28	10.49	12.13
AUC_t	Esomeprazole	38	95.47	86.03	105.94
	Omeprazole	38	83.97	75.67	93.19
C_{ss}*	Esomeprazole	39	3.23	2.93	3.57
CL*	Esomeprazole	39	7.17	6.49	7.91

* C_{ss} and CL could not be calculated for omeprazole

*Table 10. Ratios (esomeprazole/omeprazole) of geometric means and 95% CIs for Cmax (µmol/L) and AUCt (µmol*h/L) following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects*

Variable	Ratio	N	Estimate	95% CI	
				Lower	Upper
C_{max}	Esomeprazole/Omeprazole	39	1.14	1.06	1.21
AUC_t	Esomeprazole/Omeprazole	38	1.14	1.07	1.21

The above result showed that the AUC_t and C_{max} values for esomeprazole were slightly (14%) higher than those for omeprazole.

*Table 11. Test of equal variance, where the estimated variances are correlated, for Cmax (µmol/L) and AUCt (µmol*h/L) following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects*

Variable	N	Esomeprazole		Omeprazole		
		Mean	SD	Mean	SD	p-value
C_{max}	39	2.55	0.22	2.42	0.23	0.7718
AUC_t	38	4.56	0.26	4.43	0.35	0.0011

When test of equal variance was evaluated, the interindividual variability in AUC_t was lower for esomeprazole compared to that of omeprazole, while the variability was similar for C_{max} for both treatments. The observed less variability for esomeprazole PK could be due to its less dependency on CYP2C19 for its metaboslim compared to omeprazole.

The mean PD profile and parameters for omeprazole and esomeprazole obtained in this study are presented below for comparison:

Figure 6. Median intragastric pH profile following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects (N=39)

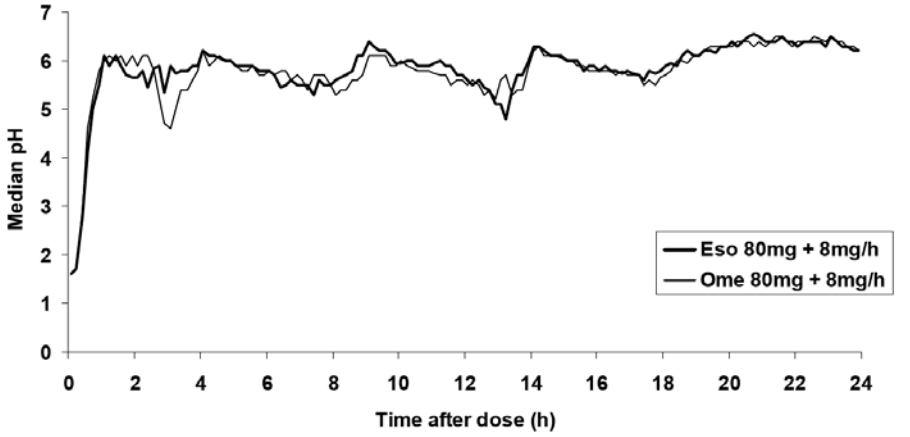


Table 12. Estimated means and 95% CIs for median intragastric pH following iv single doses of esomeprazole 80mg + 8mg/h and omeprazole 80mg + 8mg/h in healthy male and female subjects, during the 24-hour period at baseline and by treatment

Treatment	N	Estimate	95% CI	
			Lower	Upper
Baseline	39	1.6	1.5	1.8
Eso 80 mg + 8 mg/h	39	5.9	5.7	6.0
Ome 80 mg + 8 mg/h	39	5.8	5.6	5.9

As shown above in Figure 6 and table 12, both omeprazole and esomeprazole has rapid onset effect on intragastric pH, and their intragastric pH vs. times profiles and 24-hour median intragastric pH are similar.

Table 13. Estimated means and 95% CI for percentage of time with intragastric pH>4, pH>5 and pH>6 following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects, during the 24-hour period at baseline and by treatment

Variable	Treatment	N	Estimate	95% CI	
				Lower	Upper
pH>4 (0-24h)	Baseline	39	10.0	7.4	12.6
	Esomeprazole	39	89.3	85.8	92.8
	Omeprazole	39	88.1	84.6	91.6
pH>5 (0-24h)	Baseline	39	5.3	3.5	7.0
	Esomeprazole	39	77.8	72.9	82.7
	Omeprazole	39	76.0	71.1	81.0
pH>6 (0-24h)	Baseline	39	2.3	1.3	3.4
	Esomeprazole	39	44.6	38.6	50.7
	Omeprazole	39	41.4	35.4	47.5

Table 14. Estimated mean differences between treatments and 95% CIs for percentage of time with intragastric pH>4, pH>5 and pH>6 following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects

	Variable	N	Estimate	95% CI		p-value
				Lower	Upper	
Esomeprazole-Omeprazole	pH>4 (0-24h)	39	1.2	-1.6	4.1	0.39
	pH>5 (0-24h)	39	1.8	-1.5	5.0	0.29
	pH>6 (0-24h)	39	3.2	-1.1	7.5	0.14

The above tables demonstrate that the percentage of times with intragastric pH>4, pH>5 and pH>6 were slightly higher for esomeprazole, and the difference increased with higher pH cut-off levels. However, the differences between the two treatments were not statistically significant. The slightly higher percentage of times with intragastric pH>4, pH>5 and pH>6 for esomeprazole corresponds to its slightly higher (14%) exposure at this dose compared to omerpazole.

Table 15. Test of equal variance, where the estimated variances are correlated, for percentage of time with pH>4, pH>5 and pH>6 following iv single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy male and female subjects

Variable	N	Esomeprazole		Omeprazole		
		Mean	SD	Mean	SD	p-value
pH>4	39	89.36	8.81	88.11	12.22	0.0071
pH>5	39	77.87	13.62	76.07	16.61	0.0556
pH>6	39	44.68	18.95	41.46	18.11	0.6789

When inter-individual variabilities for pharmacodynamic variable were compared between the two treatments, less variability was shown for esomeprazole compared to omeprazole with respect to percentage of time with intragastric pH>4. This lower variability for esomeprazole for PD marker is consistent with observed reduced variability in AUC for esomeprazole compared to omeprazole. The observed lower variability for esomeprazole compared to omeprazole with respect to both PK and PD parameter could be due to its less dependency on CYP2C19 for its metabolism.

<u>*Reviewer's Comments:*</u>
The geometric mean C_{max} and AUC_t of esomeprazole were 14% higher compared to omeprazole. However, there is lack of major difference between two treatments with respect to both PK and

PD parameters when esomeprazole iv and omeprazole iv were given as an 80 mg bolus infusion over 30 minutes followed by continuous infusion of 8 mg/h for 23.5 hr. Nonetheless, there was a less interindividual variability for esomeprazole compared to omeprazole regarding AUC and percentage of time with intragastric pH>4.

2.2.4 How do esomeprazole and omeprazole pharmacokinetic and pharmacodynamic profile compare after the bolus intravenous injection?

The sponsor has referenced two studies D9615C00018 and SH-QBE-0061 to compare the PK and PD parameters of esomeprazole and omeprazole after IV bolus injection.

D9615C00018

D9615C00018 was a single-centre (Sweden), open-label, randomized, two-way cross-over study comparing the effect of single 30-minutes intravenous infusion of esomeprazole 40 mg and omeprazole 40 mg under fasting conditions on basal and pentagastrin stimulated acid output in 24 male and female healthy subjects. The two treatment periods were separated by at least 6 days. Of 24 enrolled subjects, 23 subjects have completed the study. Plasma samples were collected up to 12-hours for pharmacokinetic evaluation.

Pharmacokinetic profiles and parameters for these two treatments are summarized below:

Figure 7. Mean plasma concentrations after 30-minute iv infusion of esomeprazole 40 mg and omeprazole 40 mg in healthy male and female subjects. Values below LOQ are set to half the LOQ value. n = 23

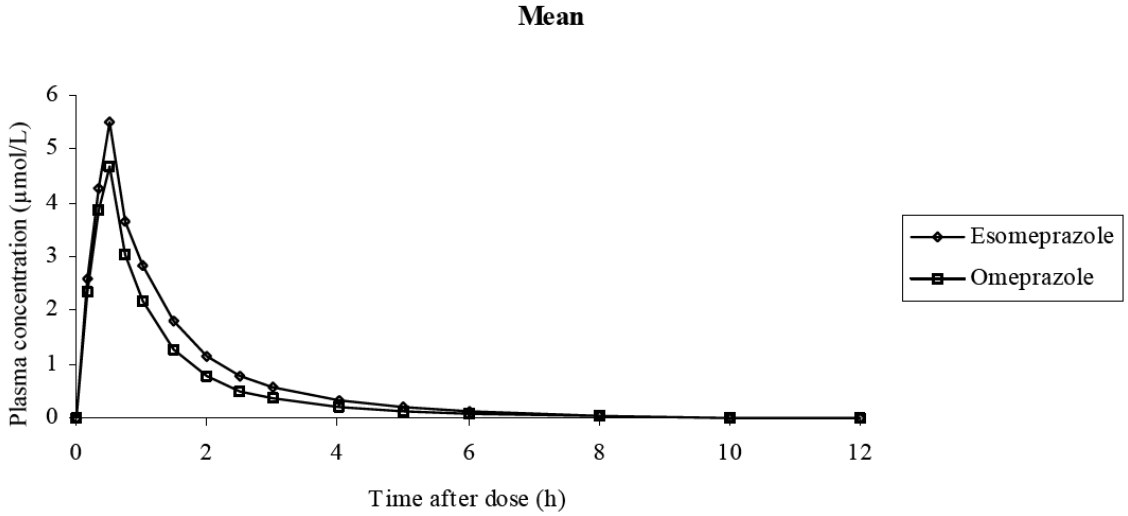


Table 16. Geometric means of AUC (µmol·h/L), AUC_t (µmol·h/L), C_{max} (µmol/L), $t_{1/2}$ (h), CL (L/h) and V_{ss} (L) after 30-minute iv infusion of esomeprazole 40 mg and omeprazole 40 mg in healthy male and female subjects

Parameter	n	Treatment	Estimate	95% CI	
				Lower	Upper
AUC	21	Esomeprazole	6.88	5.70	8.29
	21	Omeprazole	5.07	4.20	6.11
AUC_t	23	Esomeprazole	6.76	5.65	8.09
	23	Omeprazole	4.95	4.14	5.93
C_{max}	23	Esomeprazole	5.40	4.91	5.93
	23	Omeprazole	4.57	4.16	5.03
$t_{1/2}$	21	Esomeprazole	1.01	0.91	1.13
	21	Omeprazole	0.90	0.81	1.00
CL	21	Esomeprazole	16.84	13.97	20.30
	21	Omeprazole	22.85	18.95	27.54
V_{ss}	21	Esomeprazole	19.42	17.86	21.12
	21	Omeprazole	20.93	19.25	22.77

As shown in above table and figure, the AUC and C_{max} of esomeprazole 40 mg following iv infusion is 36% and 18% higher compared to those of 30-infusion of omeprazole 40 mg, respectively. Geometric mean half-life of esomeprazole is approximately 12% longer compared to omeprazole.

The PD parameters evaluated in this study were the peak acid output (PAO) (at 4-5.5 hours and 24-25.5 hours) and the basal acid output (BAO) (at 3-4 hours and 23-24 hours) after administration of the investigational products.

Table 17. Means and the mean differences between treatments of PAO (mmol/h) at baseline, 4-5.5 h and 24-25.5 h after 30-minute iv infusion of esomeprazole 40 mg and omeprazole 40 mg in healthy male and female subjects (n=23)

			95% CI	
	Treatment	Estimate	Lower	Upper
PAO baseline		33.9	30.8	37.1
PAO 4-5.5 hours	Esomeprazole	5.4	3.2	7.6
	Omeprazole	9.5	7.3	11.7
	Esomeprazole-Omeprazole	-4.1	-6.2*	-1.9*
PAO 24-25.5 hours	Esomeprazole	15.7	13	18.3
	Omeprazole	20.0	17.3	22.6
	Esomeprazole-Omeprazole	-4.3	-7.1	-1.5

Table 18. Means and the mean differences between treatments of BAO (mmol/h) at baseline, 3-4 h and 23-24 h after 30-minute iv infusion of esomeprazole 40 mg and

omeprazole 40 mg in healthy male and female subjects (n=23)

			95% CI	
	Treatment	**Estimate**	**Lower**	**Upper**
BAO baseline		4.4	3.0	5.8
BAO 3-4 hours	Esomeprazole	0.7	0.3	1.0
	Omeprazole	1.1	0.7	1.4
	Esomeprazole-Omeprazole	-0.4	-0.8	0.0
BAO 23-24 hours	Esomeprazole	1.0	0.5	1.4
	Omeprazole	1.5	1.1	2.0
	Esomeprazole-Omeprazole	-0.5	-0.8	-0.2

As demonstrated in above table, both esomeprazole 40 mg and omeprazole 40 mg iv administration resulted in a pronounced reduction of PAO from a mean baseline value when measured 4-5.5 hours after the dose, with more profound effect from esomeprazole compared to omerpazole. However, the effect on PAO was somewhat less pronounced when measured 24-25.5 hours after the dose. Additionally, both treatments had significant reduction in basal acid output (BAO), when measured after 3-4 hours and after 23-24 hours.

Reviewer's Comments:
Following single dose of 30 minutes iv infusion, esomeprazole 40 mg had higher exposure (36% for AUC and 18% for C_{max}) and longer half-life (12%) compared to omeprazole with respect to PK parameters. Regarding PD parameters, both esomeprazole and omeprazole resulted in a significant reduction in PAO and BAO from the baseline, with more significant effect from esomeprazole compared to omeprazole. The more pronounced PD effect of esomeprazole likely is a reflection of its higher AUC compared to omeprazole.

SH-QBE-0061

SH-QBE-0061 was a two-centers, open-label, randomized, two-way cross-over study to compare PK of single and multiple dose of 40 mg esomeprazole and 40 mg omeprazole administered as a short term intravenous infusion for 30 minutes once daily for five days in healthy male subjects. Two treatment periods, each consisting of 5 days, were separated with a wash-out period of at least 13 days. Drugs were administered following over-night fasting on Day 1. PK plasma samples were collected over 24-hr following drug administration on day 1 and day 5 in each period. Of 16 enrolled subjects, 15 of them completed the study. Subjects were classified as extensive metabolisers (EM) or poor metabolizer (PM) according to the omeprazole/hydroxyomprazole ration or S/R mephenytio methods. Of 15 subjects who completed the study, 13 of them were extensive metabolisers (EM) and only 2 of the subjects were poor metabolisers (PM).

In this study, esomeprazole was referred as H199/18 as this study was conducted before Nexium (esomeprazole) was approved.

Pharmacokinetic profiles and parameters for extensive metabolisers for those two treatments are presented below:

Figure 8. Mean plasma concentration of H 199/18 and omeprazole after single (day 1) i.v. administration of 40 mg omeprazole or 40 mg H 199/18 in healthy male extensive metabolisers. (n=13)

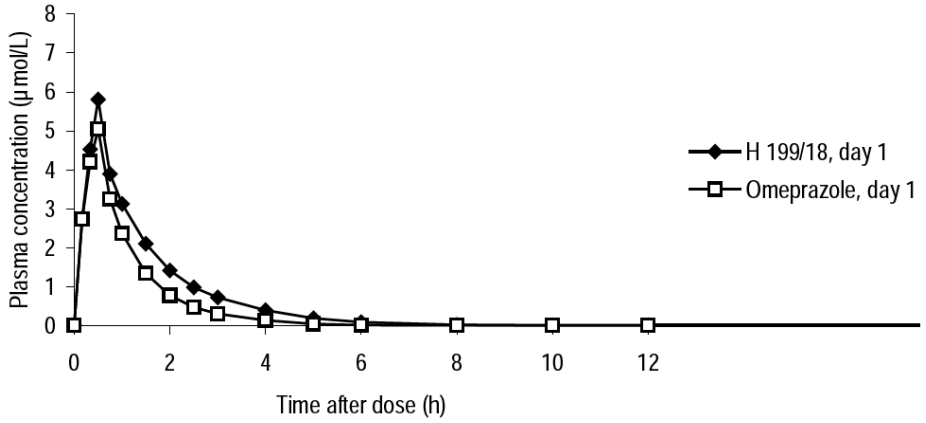


Figure 9. Mean plasma concentration of H 199/18 and omeprazole on day 5 after once daily i.v. administration of 40 mg omeprazole or 40 mg H 199/18 for 5 days in healthy male extensive metabolisers. (n=13)

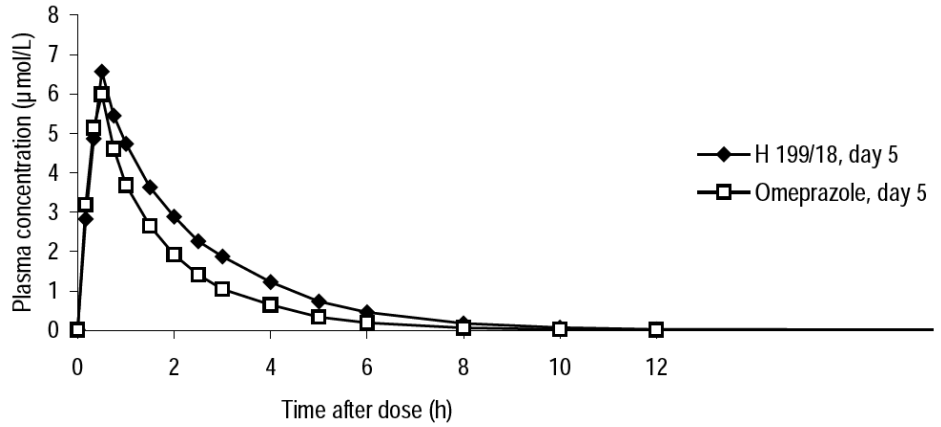


Table 19. Geometric means of AUC (µmol.h/L), C_{max} (µmol/L), t1/2(h) and CL (L/h) and the ratio of the geometric means on day 1 and day 5 following once daily i.v. administration of 40 mg omeprazole or 40 mg H199/18 for five days in extensive metabolisers. Estimates, limits for 95% Cl and p-values for test of equal geometric means are presented (n=13)

	Day 1				Day 5			
	Geometric mean	95% confidence interval		p-value	Geometric mean	95% confidence interval		p-value
		lower	upper			lower	upper	
AUC								
Omeprazole	5.45	4.63	6.41		9.94	8.48	11.67	
H 199/18	7.78	6.61	9.16		14.25	12.15	16.72	
H 199/18 / Omeprazole	1.43	1.28	1.60	<0.001	1.43	1.29	1.59	<0.001
C_{max}								
Omeprazole	4.99	4.51	5.51		5.95	5.47	6.48	
H 199/18	5.73	5.18	6.33		6.67	6.13	7.26	
H 199/18 / Omeprazole	1.15	1.06	1.25	0.003	1.12	1.05	1.20	0.003
$t_{1/2}$								
Omeprazole	0.76	0.67	0.86		1.09	0.98	1.22	
H 199/18	0.96	0.85	1.09		1.36	1.22	1.52	
H 199/18 / Omeprazole	1.26	1.19	1.34	<0.001	1.24	1.15	1.34	<0.001
CL								
Omeprazole	21.26	18.06	25.03		11.65	9.93	13.66	
H 199/18	14.88	12.64	17.52		8.13	6.93	9.53	
H 199/18 / Omeprazole	0.70	0.63	0.78	<0.001	0.70	0.63	0.77	<0.001

As shown in above figure and table, both single and multiple dose of i.v. administration of 40 mg esomeprazole (H 199/18) resulted in higher AUC (43% on both day 1 and day 5) and C_{max} (15% on day 1 and 12% on day 5) compared to same dose regiment of omeprazole in extensive metabolisers. Additionally, on both day 1 and day 5, esomeprazole has 30 % lower clearance and 25% longer half-life compared to omeprazole.

Pharmacokinetic profile and parameters for poor metabolisers for those two treatments are presented below:

Figure 10. Mean plasma concentration of H 199/18 and omeprazole after single (day 1) i.v. administration of 40 mg omeprazole or 40 mg H 199/18 in healthy male poor metabolisers. (n=2)

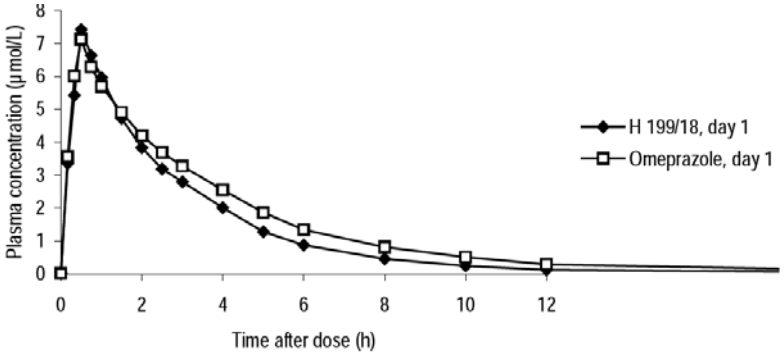


Figure 11. Mean plasma concentration of H 199/18 and omeprazole on day 5 after once daily i.v. administration of 40 mg omeprazole or 40 mg H 199/18 for 5 days in healthy male poor metabolisers. (n=2)

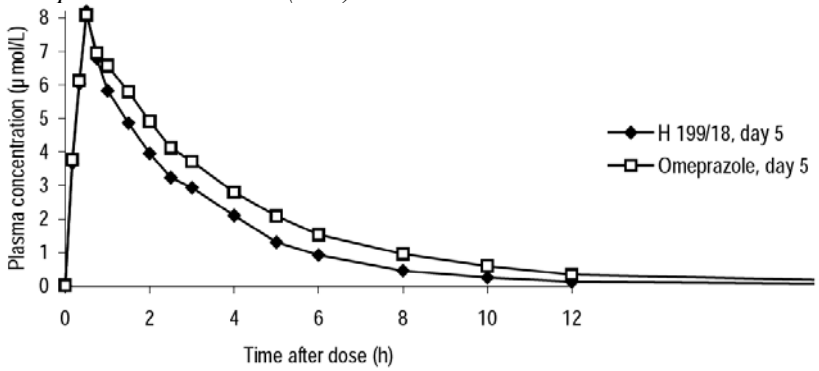


Table 20. Individual and geometric means of AUC (µmol.h/L), C_{max} (µmol/L), t1/2(h) and CL (L/h) on day 1 and day 5 following once daily i.v. administration of 40 mg omeprazole or 40 mg H199/18 for five days in poor metabolisers (n=2)

	Day 1		Day 5	
	Omeprazole	H 199/18	Omeprazole	H 199/18
AUC				
Subject 3	26.92	22.65	31.84	23.24
Subject 16	24.97	19.72	27.32	20.78
Geometric mean	25.93	21.13	29.49	21.97
C_{max}				
Subject 3	7.24	8.40	8.90	8.94
Subject 16	7.02	6.46	7.29	7.44
Geometric mean	7.13	7.36	8.05	8.15
$t_{1/2}$				
Subject 3	2.57	1.92	2.54	1.87
Subject 16	2.66	2.09	2.83	2.21
Geometric mean	2.61	2.00	2.68	2.03
CL				
Subject 3	4.30	5.11	3.64	4.98
Subject 16	4.64	5.87	4.24	5.57
Geometric mean	4.47	5.48	3.93	5.27

Contrary to extensive metabolisers, AUC for esomeprazole was lower compare omeprazole in these two poor metabolisers on both day 1 and day 5, while the C_{max} were comparable for those two treatments. Furthermore, the difference in AUC between PMs and EMs for esomeprazole (H 199/18) was a less pronounced compared to omeprazole on both day 1 and day 5, suggesting a less influence of polymorphism on the metabolism of esomeprazole (H 199/18) compared omeprazole.

Reviewer's comment

Following once daily intravenous administration of 40 mg esomeprazole (H 199/18) or 40 mg omeprazole over 30- minutes for five days, AUC was higher for esomeprazole than for omeprazole on both day 1 and day 5 in extensive meraboliser. However, in poor metaboliser, the effect on AUC was opposite, where the AUC was lower for esomeprazole compared to omeprazole on both day 1 and day 5 following the same dosing regiment. Moreover, the observed difference in AUC between poor and extensive metabolisers for esomeprazole was less than for omeprazole. However, there were only 2 subjects in poor metaboliser group to make a definitive conclusion.

2.2.5 How do esomeprazole and omeprazole pharmacokinetic and pharmacodynamic profile compare after the oral administration at 20 mg and 40 mg?

The sponsor referred to one AstraZeneca study D9612C00023 and following published literatures to address the PK and PD difference between esomeprazole and omeprazole when they were administered orally.

Andersson T, Hassan-Alin M, Hasselgren G, Röhss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001; 40:411-426.

Andersson T, Rohss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther 2001;15:1563-1569.

Lind Y, Rydberg L, Kylebäck A, Jonsson A, Andersson T, Hasselgren G, et al. Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastrooesophageal reflux disease. Aliment Pharmacol Ther 2000; 14: 861-867.

Röhss K, Hasselgren G, Hedenström H. Effect of esomeprazole 40 mg vs. omeprazole 40 mg on 24-hour intragastric pH in patients with symptoms of gastroesophageal reflux disease. Digestive Diseases Sciences 2002; 47: 954-958.

Miner P, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003; 98: 2616-2620.

Additionally, the following literature was also reviewed:

M. Hassan-Alin . T. Andersson' M. Niazi . K. Rôhss, A pharmacokinetic study comparing single and repeated oral doses of 20 mg and 40 mg omeprazole and its two optical isomers, S-omeprazole (esomeprazole) and Ilomeprazole, in healthy subjects. Eur J Clin Pharmacol 2005; 60: 779-784

Based on those literatures, AUC and C_{max} of esomeprazole were significantly higher than those of omeprazole following oral dosing in extensive metabolizers (EM). Following single dose, AUC of esomeprazole were approximately 35% and 60% higher than that of omeprazole at 20 mg and 40 mg, respectively. At steady state following multiple dosing, AUCs of esomeprazole were approximately 70% higher than that of omeprazole at both 20 mg and 40 mg. C_{max} of esomeprazole was only approximately 25-30% higher than that of omeprazole following both single and multiple doses at 20 mg and 40 mg. Following multiple dosing, AUC and C_{max} of both esomeprazole and omeprazole increased compared to single dose.

In contrast to EM, in poor metabolizers (PM), AUC of esomeprazole is approximately 20-30% lower than that of omeprazole following single and multiple doses, while the C_{max} remained comparable between esomeprazole and omeprazole.

The difference in PK profiles of esomeprazole and omeprazole was reflected in PD marker as well, although the difference wasn't as significant as the PK parameters. Following multiple dosing, the mean percentage time with intragastric pH > 4 was 53% for esomeprazole vs. 43.7% for omeprazole at 20 mg dose and 68.4% for esomeprazole vs. 62.0% for omeprazole at 40 mg dose.

3 Detailed Labeling Recommendations

All recommended changes are noted by color font. Specifically, any additions are noted by underlined text in blue and any deletions are identified by ~~strikethrough text in red~~. Additional reviewer's comments are noted by *italic font*.

7 DRUG INTERACTIONS

Concomitant use of atazanavir and [redacted] proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Reviewer's comment to the sponsor:
This recommendation was based on the current Nexium IV label.

8.6 Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). For patients with severe hepatic insufficiency (Child Pugh Class C) a [redacted] dose of 20 mg once daily should not be exceeded [redacted] [*see Dosage and Administration (2) and Clinical Pharmacology, Pharmacokinetics (12.3)*].

Reviewer's comment to the sponsor:
Sponsor needs to provide dosing recommendations in hepatic impairment for the proposed new indication.

12.3 Pharmacokinetics

Absorption

During administration of esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/hr for 23.5 hours (for a total of 24 hours) in healthy volunteers, the geometric mean value for AUC_t was [redacted] to 111.1 µmol*h/L, for Cmax was [redacted] to 15.0 µmol/L, and for steady state plasma concentration (Css) was [redacted] to 3.9 µmol/L.

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

/s/

DILARA JAPPAR
05/27/2011

SUE CHIH H LEE
05/28/2011

Clinical Pharmacology Review

NDA:	21-689
Brand Name:	Nexium IV
Generic Name:	Esomeprazole
Dosage form and Strength:	Lyophilized powder for Injection and 20 mg or 40 mg per single-use vial
Route of administration:	Intravenous (IV) Infusion
Indication:	(b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.
Sponsor:	AstraZeneca
Type of submission:	Efficacy supplement (SE1)
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Priority (6 months)
Submission date:	05/29/08, 08/07/08, and 10/09/08
PDUFA Goal Date:	11/29/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Table of Contents

1. Executive Summary

1.1 Recommendations

The efficacy supplement (SE1) submitted on 05/29/08 to NDA 21-689 for Nexium IV has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From the OCP standpoint, the NDA has deficiencies that are not approval issues but need to be addressed by the sponsor (See Comment #1 below.). The following comments should be conveyed to the reviewing medical office (MO) and the sponsor.

1.2 Comments (Comment Nos. 1 and 2 need to be sent to the sponsor)

1. The dose ranging study (**D9615C00015**) was conducted in healthy subjects and the results showed that gastric pH did not reach the anticipated desirable range. Even so, a dosing regimen was chosen for the Phase 3 studies. As such, this dose ranging study had its limitations.

   Furthermore, as stated in the meeting minutes dated 01/15/04, the Agency suggested measurement of PD (i.e., gastric pH) following the IV to oral switch in a subgroup of patients on days 1, 4, and 8, but gastric pH was not determined in the phase 3 trial.

   We recommend that the sponsor conduct a new dose ranging study in the target patient population for better dose selection. In this study, the sponsor should consider higher IV infusion maintenance doses following the loading dose. Evaluation of PK, PD (gastric pH), and clinical outcome in both IV and oral treatment phases should be performed. It should be noted that the higher doses to be studied should have supporting nonclinical and/or preliminary clinical safety data as appropriate.

2. Patients with moderately or severely hepatic impairment were excluded from the pivotal clinical trial (No. D961DC00001) and there is no pharmacokinetic (PK) study conducted for esomeprazole in subjects with various degrees of hepatic impairment. You assessed the dose adjustment for esomeprazole in subjects with severely hepatic impairment based on the PK comparisons between omeprazole and esomeprazole in healthy subjects (n=39) and the results of a previous omeprazole PK study (Study I-1226) in subjects with hepatic impairment. Study I-1226 enrolled subjects with various degrees of hepatic impairment (5 mildly, 4

moderately, and 3 severely impaired) without matching healthy controls, 24-hr pH profile, and genotype information, making it difficult to evaluate the results for dosage adjustment in hepatic impairment patients.

You have the option of 1) conducting a PK study in subjects with various degrees of hepatic impairment along with matching healthy subjects as controls or 2) revising the labeling with restrictions for use of esomeprazole IV in patients with hepatic impairment. For study design details, the sponsor should refer to the guidance document on hepatic impairment studies. In addition, genotyping for CYP2C19 is recommended.

3. No specific drug-drug interaction (DDI) studies were conducted for the proposed IV dosing regimen of esomeprazole. Due to the higher dose and continuous infusion (total dose of 652 mg over 3 days), a higher potential for interaction with coadministered drugs that are metabolized by CYP2C19 cannot be ruled out. Also, interaction with a different spectrum of drugs with pH-sensitive absorption may be expected as a result of the more profound effect (on elevation of intragastric pH) for the proposed indication compared to other approved indications of this product. Therefore, the labeling will be revised to reflect the lack of DDI study for this new dosing regimen.

1.3 Phase IV Commitments: N/A

10/29/08, 11/05/08
Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. _____

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Esomeprazole is the S-enantiomer of omeprazole, a proton pump inhibitor (PPI), and acts through inhibition of the proton pumping enzyme H^+/K^+-ATPase located in the parietal cells of the gastric oxyntic mucosa, thus preventing hydrochloric acid secretion to the gastric lumen. Nexium (esomeprazole) IV dosage form for injection and infusion has been approved since March 31, 2005 (NDA 21-689).

On 05/29/08, AstraZeneca submitted an efficacy supplement (SE1) to the above NDA seeking approval for use of Nexium IV for (b) (4) (b) (4) rebleeding in patients following therapeutic endoscopy for bleeding gastric or duodenal ulcers. The proposed dosing regimen is Nexium IV 80 mg given by a 30-min infusion and then 8 mg/hr given by constant-rate infusion for 71.5 hr, (b) (4) (b) (4)

Three phase-1 clinical pharmacology studies plus a pivotal phase 3 trial were submitted for review and they are summarized below.

Table 1. Studies included in the Clinical Pharmacology and Clinical Programs

Study No.	Study Design[1]	Drug, Dose, and Dosing Regimen	Subjects	2C19 Genotyping
D9615C00015 (Phase-1, PK & PD)	R, OL, 5 x 5 (washout period: > 13 days)	Esomeprazole: A: 40 mg (0.5 hr)+8 mg/hr (23.5 hr) B: 80 mg (0.5 hr)+4 mg/hr (23.5 hr) C: 80 mg (0.5 hr)+8 mg/hr (23.5 hr) D: 120 mg (0.5 hr)+8 mg/hr (23.5 hr) E: 120 mg (2.0 hr)+8 mg/hr (22.0 hr)	N=25 healthy subjects (19M+6F) *H. pylori*: all negative	Homo-EM: 17 Hetero-EM: 7 PM: 1
D961DC00004 (Phase-1, PK & PD)	R, DB, 2 x 2 (washout period: > 13 days)	Esomeprzole or Omeprazole; 80 mg (0.5 hr)+8 mg/hr (23.5 hr)	N=39 healthy subjects (23M+16F) *H. pylori*: all negative	Homo-EM: 20 Hetero-EM: 18 PM: 1
I-1226[2] (Phase-1, PK)	OL	Omeprazole: 80 mg (0.5 hr)+8 mg/hr (47.5 hr)	N=12 subjects with liver Impairment: mild (n=5), moderate (n=4) severe (n=3)	------
D961DC00001 (Pivotal Phase-3, Efficacy & Safety trial)	R, DB, PG, PC	Esomeprazole or Placebo 80 mg (0.5 hr)+ 8 mg/hr (71.5 hr) followed by oral Nexium 40 mg qd x 28 days	Active: N=375 Placebo: N=389 *H. pylori*: negative: ≈ 30% positive: ≈ 60% trace: ≈ 5.0% unknown: ≈ 5.0%	------

[1] R: randomized; OL: open label; 5 x 5: 5-way crossover; M: male; F: female; Homo-EM: homozygous extensive metabolizer; Hetro-EM: heterozygous extensive metabolizer; PM: poor metaboliser; DB: double blind; PG: parrallel group; PC: placebo controlled; PK: pharmacokinetics; PD: pharmacodynmics.

[2] Study of omeprazole IV infusion in subjects with various degrees of liver impairment submitted later upon request.

Study D9615C00015 and D961DC00004 were of similar design, single center, randomized, crossover studies with a washout period of at least 13 days. All male and female healthy subjects were free from *Helicobacter pylori* (*H. pylori*) infection. According to genotype status of cytochrome P450 (CYP) isoenzyme CYP2C19, they were classified to poor or extensive metabolizers (PM or EM) and EM was further stratified to homozygous-EM (Homo-EM) and heterozygous-EM (Hetero-EM).

In study D9615C00015 (an open label study), the subjects however, remained fasting throughout each study day, i.e., for approximately 36 hrs (throughout the 24-hr pH recordings). To ensure adequate fluid and energy supply, they received 2000 mL 5% glucose as an IV drip starting after the end of the bolus infusions until bedtime. In the subsequent study, D961DC00004 (a double blind study), the subjects did not remain fasting but were given a total of 800 mL of a nutrition drink (4 x 200 mL) during daytime on study days to ensure adequate fluid and energy supply.

Blood samples for PK calculations were collected for up to 24 hrs during each study day. In the above two studies, only the parent compound (esomeprazole or omeprazole) was determined. A 24-hour intragastric pH recording was performed at pre-entry (baseline recording) and on each study day. The % of time for the intragastric pH >4, 6, or 7 and % of subjects with intragastric pH >4, 6, or 7 in 24-hr period were assessed.

In Study I-1226 which was conducted previously for omeprazole, two metabolites of omeprazole were also determined. For this study, the number of subjects with various degrees of liver impairment enrolled was small (n≤5 per Child-Pugh classification) and no control arm was employed (healthy subjects with normal liver function). No 24-hour intragastric pH recording was performed for this study.

For Phase-3 pivotal trial, a placebo controlled study, the proposed dosing of 80 mg was given by a 30-min infusion followed by 8 mg/hr continuous infusion for 71.5 hrs (total 3 days) and then followed by an open-label treatment of esomeprazole 40 mg qd for 4 weeks for both active and placebo groups. No PK or PD (24-hr intragastric pH), however, was determined in these patients.

Selection of Dosing Regimen for the Phase 3 Trial:
In study D9615C00015, 5 different infusion regimens (Treatments A-E) were explored as shown below.

Table 2. Study Dose Per Treatment (D9615C00015; N=26)

Treatment	Dose of the short term infusion	Rate and length of constant infusion	Total dose (mg)
A	40 mg (0,5 h)	8 mg/h (23.5 h)	228
B	80 mg (0,5 h)	4 mg/h (23.5 h)	174
C	80 mg (0,5 h)	8 mg/h (23.5 h)	268
D	120 mg (0,5 h)	8 mg/h (23.5 h)	308
E	120 mg (2 h)	8 mg/h (22 h)	296

For the above Treatments A to E, the esomeprazole PK appeared to follow linear kinetics. Mean (geometric) clearance (CL) of esomeprazole was approximately 5 – 7 L/h across the IV doses studied.

For 24-hr intragastric pH monitored, all investigated doses (Treatment A-E) of esomeprazole had

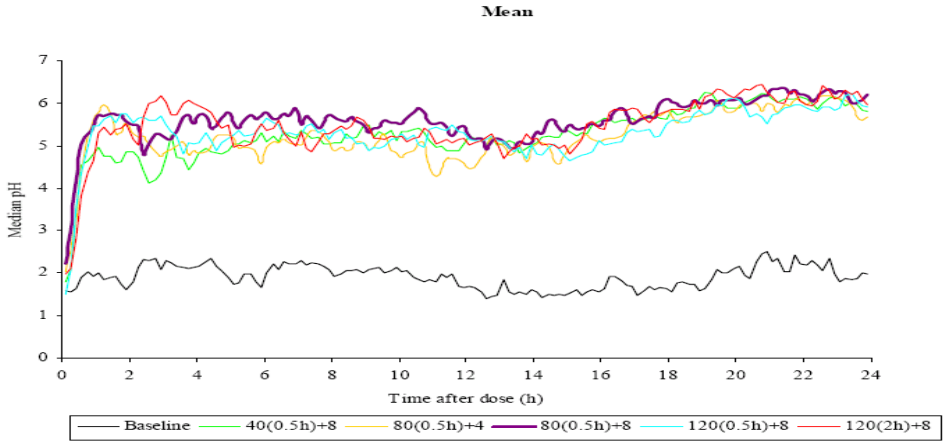
a. A mean of >80% of time for intragastric pH >4.0 during the 24-hr period which was much higher than the pre-treatment baseline value (6.0%),
b. A mean of <5% of time for intragastric pH >7.0 during the 24-hr period compared to baseline (0.1%) at baseline.

For intragastric pH >6.0 (primary variable) in 24-hr period,

a. Treatments C-E had a mean of around 50% (or greater) of time for the intragastric pH >6.0 which is higher than that of Treatments A and B (around 45%) and baseline (1.7%).
b. During the initial 0-3 hrs studied, Treatments C-E also had a higher mean % of time for the intragastric pH >6 (around 45% of time) which is better than that of Treatments A and B (≤ 35% of time) and baseline (2.0%).
c. Treatments D and E, however, did not result in further improvement of any of the PD variables when compared to Treatment C.

The 24-hr median intragastric profiles for Treatments A-E are shown below.

Figure 1. Median Intragastric pH Profiles at Baseline and during administration of Esomeprazole to Healthy Subjects, Treatments A-E (D9615C00015)



Based on the 24-hr PD data (intragastric pH), the dosing regimen of 80 mg given by short-term infusion (0.5 hr)+8 mg/hr continuous infusion (71.5 hrs) was therefore, proposed by the sponsor for the pivotal Phase 3 clinical trial.

Pharmacokinetics:

Mean PK parameters for the IV regimen of 80 mg (0.5hr) + 8 mg/hr (23.5hrs) obtained from Studies D9615C00015 (esomeprazole) and D961DC00004 (esomeprazole vs. omeprazole) are summarized here for comparisons.

Table 3. Mean (± SD) PK Parameters of Esomeprazole and Omeprazole After Given the Same Dosing Regimen (80 mg by 0.5-hr Infusion followed by 8 mg/hr Continuous Infusion for 23.5 hrs)

Study No.	AUC_{0-24} (µmole-h/L)	C_{max} (µmole/L)	C_{ss}[1] (µmole/L)
I. **D9615C00015** (n=26) Esomeprazole	109.9 (± 23.1)	14.2 (± 2.6)	4.0 (± 1.0)
II. **D961DC00004** (n=39) Esomeprazole	98.6 (± 25.9)	13.1 (± 2.8)	3.4 (± 1.0)
Omeprazole	89.1 (± 30.5)	11.6 (± 2.8)	-----[2]

[1] C_{ss}: Mean steady-state plasma level.

[2] The C_{ss} was reportedly not determined for omeprazole due to continuous increase of plasma level towards the end of 24 hr infusion.

Inter-study comparison showed comparable esomeprazole PK between Studies D9615C00015 and D961DC00004, Within Study D961DC00004 (when compared with the same dose of omeprazole), esomeprazole had slightly higher mean C_{max} and AUC_{0-24} (11-13% higher) than omeprazole which is consistent with previous findings that R-isomer of omeprazole (a racemate of R- and S- isomers) is eliminated faster than the S-isomer (esomeprazole). Omeprazole showed continued increase of plasma levels even towards the end of the 24-hr infusion and did not reach a steady state. This characteristics was not apparent with esomeprazole in this study.

Additionally, the results of IV dosing of esomeprazole or omeprazole further showed that

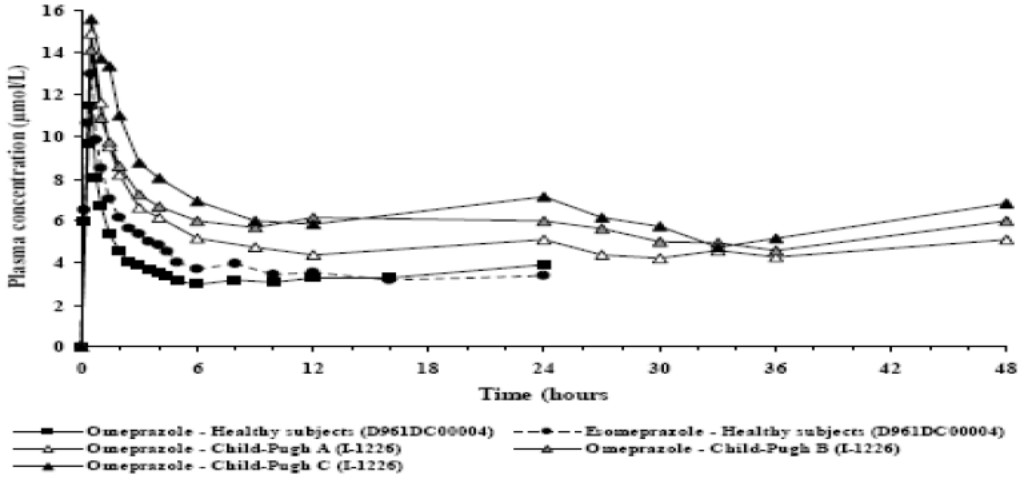
a. Males and females had comparable mean PK parameters for esomeprazole or for omeprazole.
b. Homozygous-EM had slightly lower (4-16%) mean esomeprazole PK parameters than heterozygous-EM in terms of C_{max} and AUC_{0-24}.
c. Only one PM was included in each of the above two studies and their PK parameters were not higher as would have been expected for a PM and the values were within the range for EMs. The exact reason for these 2 PMs having similar exposure as those of EMs, however, is not known.

Dosage adjustment in hepatic impairment patients:

No specific PK study was conducted for esomeprazole in subjects with various degrees of hepatic impairment. Patients with moderately or severely hepatic impairment were excluded in the pivotal Phase 3 trial (D961DC00001). The sponsor determined the dose adjustment for esomeprazole in severely hepatic impairment based on the comparisons of omeprazole PK obtained from Study D961DC00004 and a previous PK study of omeprazole in subjects with mildly (n=5), moderately (n=4), and severely (n=3) hepatic impairment (Study I-1226) using the same dosing regimen.

The mean PK profiles combined from Study D961DC00004 and I-1226 are shown below.

Figure 2. **Mean Plasma Concentrations following Esomeprazole iv 80 mg + 8 mg/h and Omeprazole iv 80 mg + 8 mg/h in Healthy Subjects (D961DC00004), and following Omeprazole iv 80 mg + 8 mg/h in Subjects with Mild to Severe Impairment of Liver Function (Child-Pugh classification A, B and C, respectively; I-1226).**



Based on the results of overall inter-study comparisons, the sponsor estimated tha (b) (4) (b) (4) (b) (4) adjusting the dosing regimen for severely hepatic impairment, 80 mg (0.5 hr)+ 4mg/hr ntinuous infusion (71.5 hrs), may be sufficient to maintain adequate acid control in patients with severely hepatic impairment for esomeprazole.

Reviewer's Comments:
The sponsor's proposed dose adjustment of esomeprazole for patients with various degrees of liver impairment relies on a hepatic impairment study without healthy controls. (b) (4)

Ideally, a PK study on esomeprazole in subjects with mildly (n≥6), moderately (n≥6), and severely (n≥6) hepatic impairment plus healthy subjects as controls should have been conducted.

Formulation
The currently marketed Nexium (esomeprazole) IV dosage form for injection and infusion was employed in the clinical pharmacology and clinical studies. This formulation will also be used for the proposed indication.

2. Question Based Review

2.1 General Attributes

Drug Substance:
Esomeprazole is the S-enantiomer of the approved PPI, omeprazole (a racemate).

Formulations:
Nexium (esomeprazole) IV dosage form for injection and infusion has been approved since March 31, 2005.

Mechanism of Action:
A peptic ulcer bleeding (PUB) is the result of erosion by acid and peptic enzymes of a blood vessel in the submucosa or the muscularis mucosae. Severe blood loss may lead to shock and circulatory collapse. It was reported that after a successful primary endoscopic haemostatic treatment for PUB, rebleeding occurs in about 10-20% of the cases during the first month after the initial bleeding episode. Rebleeding has been reported to increase the risk for a fatal outcome.

Hemostatic mechanisms are pH-dependent, and rebleeding is associated with the aggressive effect of gastric acid and pepsin enzymatic activity on the clots and through platelet disaggregation. It has been reported in the literature that the time with intragastric pH>6 has been considered a relevant PD variable for the initial treatment in PUB. Thus, the effects of potent acid suppressive therapy are overall beneficial in patients with PUB with high-risk endoscopic stigmata.

Proposed Indication:
Nexium IV dosing is indicated for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute gastric or duodenal ulcers.

Dosing Regimen:
Adult dose is 80 mg administered as an IV infusion over 30 minutes followed by a continuous infusion of 8 mg/hr given over 3 days (b) (4) (b) (4)

2.2 General Clinical Pharmacology

Pharmacokinetics and Pharmacodynamic Evaluations

Q1. How Was The Proposed Dosing Regimen Selected?

A1. The doses tested in study D9615C00015 were selected based on available PK and PD data from literature reports and previous studies on omeprazole, i.e., 80 mg omeprazole given as a 30-minute IV infusion followed by a continuous infusion of 4 and 8 mg/h for 21.5 hours in patients with a history of duodenal ulcer.

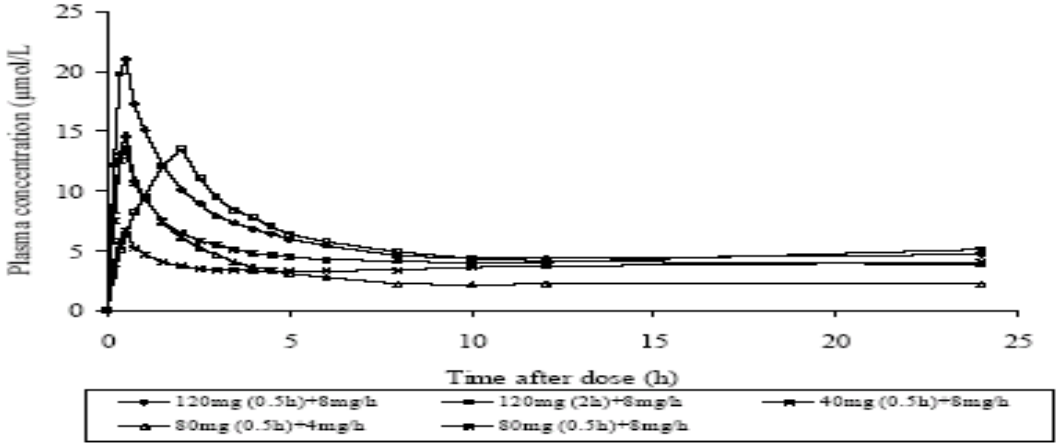
In the current study, higher loading dose (120 mg) of esomeprazole and different infusion time/rate were also explored. The infusion regimens (Treatments A-E) and the total doses tested for esomeprazole in study D9615C00015 are shown below.

Table 4. Study Doses Per Treatment (D9615C00015; N=26)

Treatment	Dose of the short term infusion	Rate and length of constant infusion	Total dose (mg)
A	40 mg (0,5 h)	8 mg/h (23.5 h)	228
B	80 mg (0,5 h)	4 mg/h (23.5 h)	174
C	80 mg (0,5 h)	8 mg/h (23.5 h)	268
D	120 mg (0,5 h)	8 mg/h (23.5 h)	308
E	120 mg (2 h)	8 mg/h (22 h)	296

The mean plasma profiles of esomeprazole with 5 infusion rates are shown below.

Figure 3. Mean Plasma Concentrations of Esomeprazole following IV infusion of Esomeprazole at 5 Different Infusion Rates in Healthy Subjects (D9615C00015; N=26)



For the above Treatments A to E, the esomeprazole PK appeared to follow linear kinetics. Mean (geometric) clearance (CL) of esomeprazole was approximately 5 – 7 L/h across the IV doses studied.

Intragastric pH was recorded over a 24-hour period at baseline and following start of 5 infusion regimens. In both Phase 1 PK studies a 24-hour gastric pH-recording, a naso-gastric microelectrode (Ingold bipolar glass) attached to an MMS Orion pH-data logger (Medical Measurement System, Netherlands) was used for the pH-recordings in both studies. During the ongoing pH recording, the electrode was placed about 10 cm below the lower esophageal sphincter. The position was marked on the pH electrode during the first pH-recording. The same electrode was used and placed in the same position during all pH recordings and each subject had his/her own electrode.

The % of time for the intragastric pH >4, 6, or 7 and % of patients with intragastric pH >4, 6, or 7 in 24-hr period were assessed. All investigated doses (Treatments A-E) of esomeprazole had

a. A mean of >80% of time for intragastric pH >4.0 during the 24-hr period compared to baseline (6.0%),
b. A mean of ≤5% of time for intragastric pH >7.0 during the 24-hr period compared to baseline (0.1%).

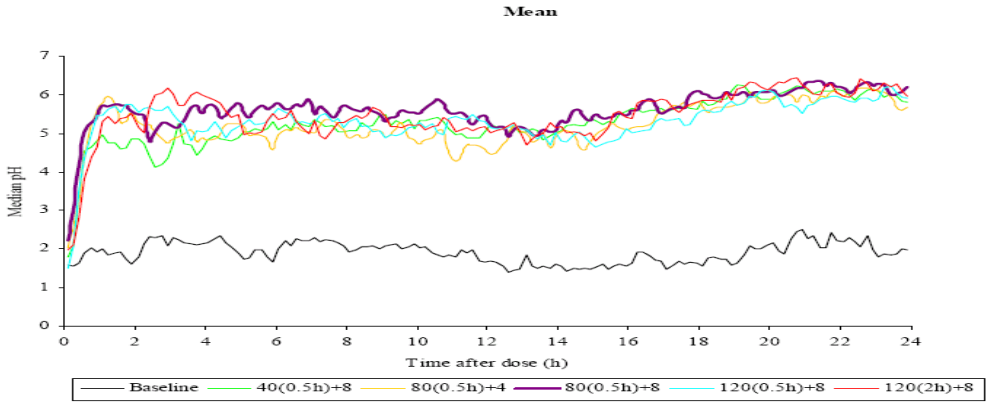
For the intragastric pH >6.0 (primary variable) in 24-hr period, the mean % of time is shown below.

Table 5. Estimates (and 95% Confidence Intervals) of Mean Percentage of Time with Intragastric pH>6 at Baseline and during IV infusion of Esomeprazole at 5 Different Infusion Rates in Healthy Subjects (D9615C00015)

Variable	Treatment	N	Estimate	95% CI	
				Lower	Upper
pH>6 (0-24h)	Baseline	25	1.7	0.5	2.8
	40mg (0.5h)+8mg/h	23	46.0	34.1	57.8
	80mg (0.5h)+4mg/h	24	44.4	32.4	56.5
	80mg (0.5h)+8mg/h	24	52.3	40.3	64.4
	120mg (0.5h)+8mg/h	22	49.0	36.5	61.6
	120mg (2h)+8mg/h	20	56.3	43.5	69.0
pH>6 (0-3h)	Baseline	25	2.0	0.1	3.8
	40mg (0.5h)+8mg/h	23	24.6	12.4	36.9
	80mg (0.5h)+4mg/h	24	35.2	22.8	47.7
	80mg (0.5h)+8mg/h	24	45.8	33.3	58.3
	120mg (0.5h)+8mg/h	22	45.7	32.6	58.7
	120mg (2h)+8mg/h	20	44.6	31.3	57.9

The 24-hr median intragastric pH profiles for Treatments A-E are shown below for comparisons.

Figure 4. Median Intragastric pH Profiles at Baseline and during administration of Esomeprazole to Healthy Subjects, Treatments A-E (D9615C00015)



The % of time for intragastric pH>6 (Table 5), showed that

a. Treatments C-E had a mean of around 50% (or greater) of time for the intragastric pH >6.0 in 24-hr period which is higher than that of Treatments A and B (around 45%) and baseline (1.7%).
b. During the initial 0-3 hrs studied, Treatments C-E also had a higher mean % of time for the intragastric pH >6 (around 45% of time) which is better than that of Treatments A and B (≤ 35% of time) and baseline (2.0%).
c. Treatments D and E, however, did not result in further improvement of any of the PD variables when compared to Treatment C.

Other PD parameters obtained were also presented here. The proportion of subjects reaching intragastric pH>6 (and maintained for at least 1 hr duration) during 0-3 hr and 0-24 hr periods following the 5 different IV infusion rates are shown below.

Table 6. Proportion of Subjects Reaching Intragastric pH>6 (at least 1 hour duration) following the Intravenous Infusion of Esomeprazole at 5 Different Infusion Rates in Healthy Subjects (D9615C00015)

Treatment	**No. of Subjects** (n=25)	**Proportion (%) of Subjects**	
		During 0 - 3 hr (Baseline: 4.0%)	**During 0 - 24 hr** (Baseline: 8.0%)
A: 40 mg (0.5 hr)+8 mg/hr (23.5 hrs)	23	17.4%	82.6%
B: 80 mg (0.5 hr)+4 mg/hr (23.5 hrs)	24	45.8%	83.3%
C: 80 mg (0.5 hr)+8 mg/hr (23.5 hrs)	24	54.2%	83.3%
D: 120 mg (0.5 hr)+8 mg/hr (23.5 hrs)	22	54.5%	90.9%
E: 120 mg (2.0 hr)+8 mg/hr (22.0 hrs)	21	38.1%	85.7%

The results showed that 1) during the first 3-hr period there are no major differences between Treatments C-D which are better than that of Treatments A, B, and E and 2) for the 24-hr period, they are, however, comparable among 5 treatments. Mean (± SD) times reaching this endpoint variable (intragastric pH>6 at least 1 hour duration) are calculated to be 9.78 (± 7.07), 6.02 (± 7.25), 5.67 (± 6.97), 5.20 (± 7.30), and 5.52 (± 6.33) hrs, respectively (not shown in Table 6).

Based on the study results on 24-hr intragastric pH data obtained from the Phase-1 program, the dosing regimen of 80 mg given by short-term infusion (0.5 hr)+8 mg/hr continuous infusion (for 71.5 hrs) was therefore, proposed by the sponsor for the pivotal Phase 3 clinical trial.

Q2. What Are the PK and PD Characteristics of Esomeprazole and Omeprazole Obtained from the Dosing Regimen of 0.5-hr Infusion of 80 mg followed by a Constant Rate (8 mg/hr) Infusion for 23.5 hrs?

A2. Mean PK parameters obtained from Study D961500015 and D961D00004 are summarized here for comparisons.

Table 7. Mean (± SD) PK Parameters of Esomeprazole and Omeprazole after Given the Same Dosing Regimen (80 mg by 0.5-hr infusion followed by 8 mg/hr continuous infusion for 23.5 hrs)

Study No.	AUC_{0-24} (µmole-h/L)	C_{max} (µmole/L)	C_{ss}[1] (µmole/L)
I. **D9615C00015** (n=26) Esomeprazole	**109.9 (± 23.1)** Male: 107.8 (± 26.0) Female: 115.7 (± 11.1) Homo-EM: 105.1 (± 18.8) Hetero-EM: 123.2 (± 31.5) PM: 105.4 (Suject # 20; M)	**14.2 (± 2.6)** Male: 13.4 (± 2.4) Female: 16.7 (± 1.5) Homo-EM: 13.9 (± 3.0) Hetero-EM: 14.5 (± 1.2) PM: 17.0	**4.0 (± 1.0)** Male: 4.1 (± 1.1) Female: 4.0 (± 0.5) Homo-EM: 3.9 (± 0.9) Hetero-EM: 4.4 (± 1.5) PM: 3.7
II. **D961DC00004** (n=39) Esomeprazole	**98.6 (± 25.9)** Male: 100.0 (± 24.7) Female: 96.5 (± 28.4) Homo-EM: 90.4 (± 18.1) Hetero-EM: 107.9 (± 30.6) PM: 86.9	**13.1 (± 2.8)** Male: 12.9 (± 3.2) Female: 13.4 (± 2.3) Homo-EM: 12.3 (± 2.2) Hetero-EM: 14.0 (± 3.3) PM: 14.0	**3.4 (± 1.0)** Male: 3.5 (± 0.9) Female: 3.2 (± 1.1) Homo-EM: 3.1 (± 0.8) Hetero-EM: 3.7 (± 1.1) PM: 2.7
Omeprazole	**89.1 (± 30.5)** Male: 91.2 (± 29.2) Female: 85.9 (± 33.1) Homo-EM: 76.8 (± 21.2) Hetero-EM: 100.3 (± 34.2) PM: 122.7 (Suject # 7; M)	**11.6 (± 2.8)** Male: 11.7 (± 3.0) Female: 11.3 (± 2.7) Homo-EM: 10.3 (± 1.8) Hetero-EM: 12.6 (± 2.8) PM: 14.0	-----[2]

[1] C_{ss}: Mean steady-state plasma level.

[2] The C_{ss} was reportedly not determined for omeprazole due to continuous increase of plasma level towards the end of 24 hr infusion.

The above results showed that

1. For inter-study comparison of esomeprazole PK data, Study D9615C00015 had around 8-18 % higher in PK parameters than those obtained from Study D961DC00004.
2. Compared to the same dose of omeprazole (within Study D961DC00004), esomeprazole had slightly larger (11-13%) mean PK parameters which is consistent with previous findings that R-isomer of omeprazole (a racemate) is eliminated faster than the S-isomer (esomeprazole).
3. Between males and females, their mean PK parameters are comparable.
4. Homo-EM had slightly lower mean PK parameters than those of Hetero-EM.
5. Only one PM was included in each of the above two studies and their PK parameters are not as high as expected for a PM and the values are within the range for Homo-EMs and Hetero-EMs.

The reason for the PM having similar PK data as those of Homo-EM or Hetero-EM is not known, however, it could be due to 1) only one PM being included in each study, 2). esomeprazole and omeprazole also inhibiting CYP 2C19 after multiple dose (or continuous infusion), and PM being less influenced by this inhibition mechanism on 2C19, and 3) crossover study design of IV infusion

(washout period being 13 days) complicating the inhibition mechanism on 2C19 for EMs.

It was reported that no C_{ss} (based on at least 3 consecutive time points during continuous infusion) for omeprazole could be determined nor was CL calculated since omeprazole plasma levels tended to increase during the continuous infusion.

Mean plasma profiles of esomeprazole and omeprazole and their median 24-hr intragastric pH profiles obtained from D961DC00004 are shown below.

Figure 5. Mean plasma concentrations following IV single doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy subjects (N=39) (D961DC00004)

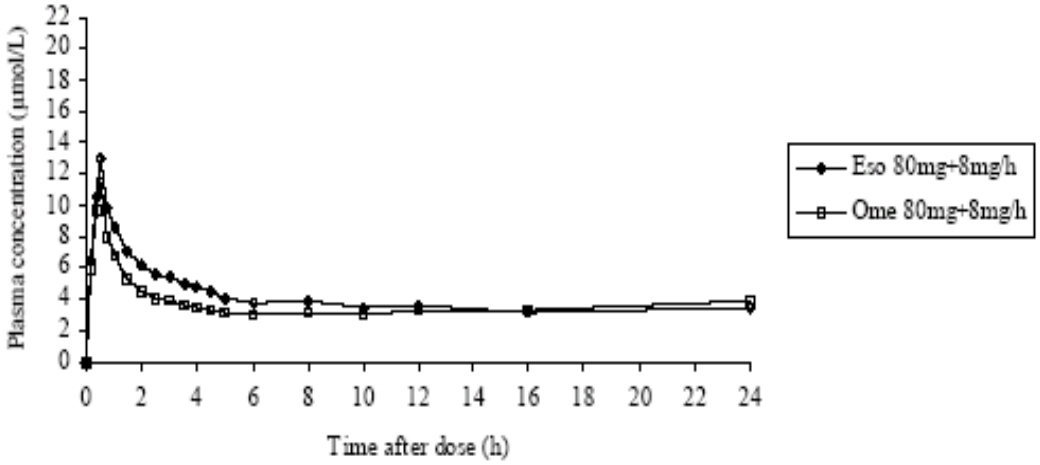
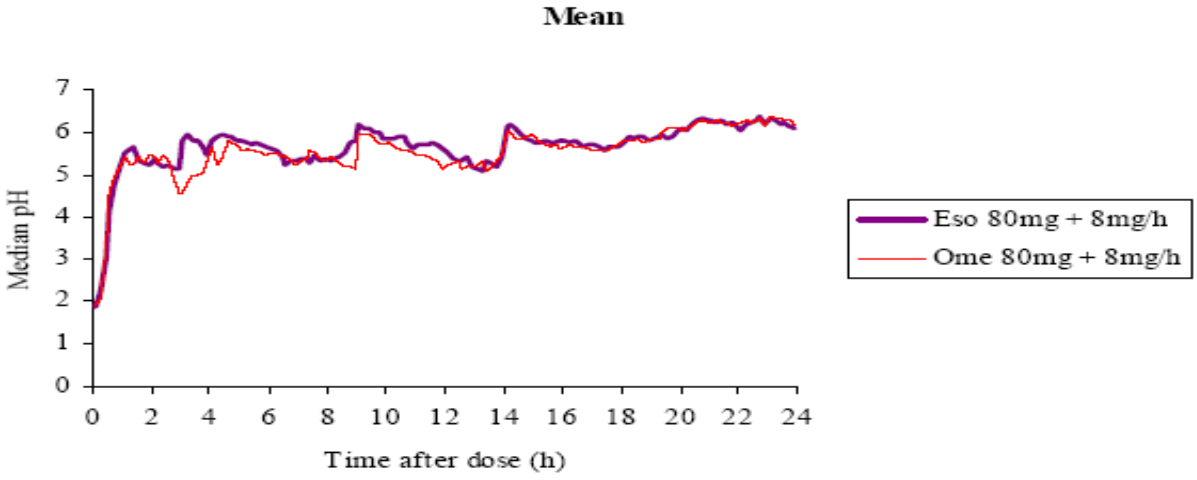


Figure 6. Median intragastric pH profile following iv doses of esomeprazole 80 mg + 8 mg/h and omeprazole 80 mg + 8 mg/h in healthy subjects (N=39) (D961DC00004)



Comparisons of mean % of time for intragastric pH>6.0 during the 24-hr period between esomeprazole and omeprazole in Study D961DC00004 are shown below.

Table 8. Comparison of % Time for 24-hr Intragastric pH > 6.0 between Esomeprazole vs. Omeprazole (D961DC00004)

Variable	Treatment	N	Estimate	95% CI	
pH>6 (0-24h)	Baseline	39	2.3	1.3	3.4
	Esomeprazole	39	44.6	38.6	50.7
	Omeprazole	39	41.4	35.4	47.5

The above PD results obtained from Study D961DC00004 showed that

a. For esomeprazole and omeprazole, mean % of time for pH>6.0 in 24-hr period were 44.6 and 41.4%, respectively and there were no major differences in PD (p. value of 0.6789) observed.
b. The above mean % of time obtained from this study were lower than that from D9615C00015 (around 50%)
c. Mean time to reach pH>6 for esomeprazole and omeprazole are calculated to be 7.26 (± 6.85) hrs and 8.54 (± 7.78) hrs which were longer than that from Study D9615C00015 [5.67 (± 6.97) hr for esomeprazole].

The differences between inter-study comparisons for mean % of time for pH>6.0 (point b.) are complicated due to different fasting status in these two studies. The sponsor indicates that there is no other obvious explanation for these differences.

Q3. Is the Sponsor's Proposed Dose Adjustment for Liver Impairment Acceptable (b) (4)

A3. No. No specific PK study was conducted for esomeprazole in subjects with various degrees of hepatic impairment. It should be noted that patients with moderately or severely hepatic impairment were excluded from the pivotal trial (D961DC00001).

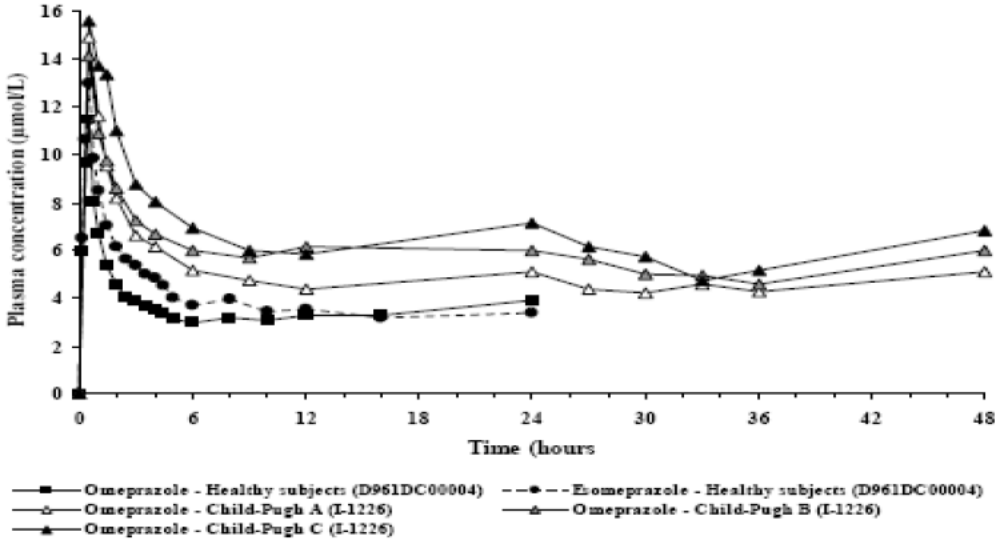
The sponsor predicted dose adjustment of esomeprazole for patients with various degrees of hepatic impairment based on the comparisons of omeprazole PK obtained from Study D961DC00004 and a previous PK study of omeprazole in subjects with mildly (n=5), moderately (n=4), and severely (n=3) hepatic impairment (Study I-1226) using the same dosing regimen. No 24-hr intragastirc pH profiles were obtained from Study I-1226. The mean PK parameters obtained from all these three studies are summarized here for easy comparisons.

Table 9. Comparisons of Mean (±SD) PK Parameters of Esomeprazole and Omeprazole Obtained From the Dosing Regimen of A 30-min Infusion of 80 mg followed by a Constant Rate (8 mg/hr) Infusion up to 24 hrs

Study No.	AUC_{0-24} (µmole-h/L)	C_{max} (µmole/L)	C_{ss} (µmole/L)
I. **D9615C00015** (n=26) Esomeprazole	109.9 (± 23.1)	14.2 (± 2.6)	4.0 (± 1.0)
II. **D961DC00004** (n=39)			
Esomeprazole	98.6 (± 25.9)	13.1 (± 2.8)	3.4 (± 1.0)
Omeprazole	89.1 (± 30.5)	11.6 (± 2.8)	-----
III. **I-1226** Omeprazole			
Child-Pugh C (n=3); Severe	172.3 (± 42.9)	15.6 (± 2.9)	5.96 (± 1.69)
Child-Pugh B (n=4); Moderate	155.0 (± 32.8)	14.1 (± 2.0)	5.09 (± 1.10)
Child-Pugh A (n=5); Mild	130.8 (± 42.9)	15.0 (± 4.3)	4.33 (± 1.49)

The mean PK profiles obtained from Study D961DC00004 and I-1226 are combined and shown below.

Figure 7. Mean Plasma Concentrations following Esomeprazole IV 80 mg + 8 mg/h and Omeprazole IV 80 mg + 8 mg/h in Healthy Subjects (D961DC00004), and following Omeprazole iv 80 mg + 8 mg/h in Subjects with Mild to Severe Impairment of Liver Function (Child-Pugh classification A, B and C, respectively; I-1226).



The above inter-study comparison of omeprazole PK between Studies D961DC00004 and I-1226 showed that subjects with various degrees of hepatic impairment had higher mean omeprazole exposure (Study I-1226) than those obtained from healthy subjects with normal liver function (Study D961DC00004). Mean omeprazole C_{max} values (around 15 ng/mL for all three Child-Pugh classifications), however, were less influenced by the severity of hepatic impairment, whereas mean AUC_{0-24} values did reflect those (Study I-1226).

The sponsor proposed that [redacted] (b) (4) adjusting the dosing regimen [redacted] (b) (4)

severely hepatic impairment [i.e., to 80 mg (0.5 hr)+ 4 mg/hr continuous infusion] may be sufficient to maintain adequate acid control in patients with severely hepatic impairment for esomeprazole.

Reviewer's Comments:
The sponsor's proposed dose adjustment of esomeprazole for patients with various degrees of liver impairments, however, relies on a hepatic impairment study with omeprazole without matching healthy controls and genotyping. (b) (4)

[redacted]

It should be noted that 1) in Study I-1226, no healthy subjects with normal liver function were included as a control arm and 2) the number of subjects enrolled in the 3 classifications of hepatic impairment is small (n=3-5 only). Therefore, it rendered difficult to assess dose adjustments of esomeprazole for patients with various degrees of hepatic impairment. Ideally, a thorough PK study on esomeprazole in subjects with mildly (n≥6), moderately (n≥6), and severely (n≥6) hepatic impairment plus healthy controls should have been conducted.

The following Efficacy and Safety data are under review by the medical office (Dr. Anil Nayyar) of GI division.

Q4. What are the Efficacy Outcome Measures?

A4. For the pivotal Phase-3 study D961DC00001, esomeprazole IV reduced clinically significant rate of rebleedings within 72 hours compared to placebo. For the primary endpoint, the number of patients with a rebleeding within 72 hours treated with esomeprazole was 22 (22/375; 5.9%) compared to 40 (40/389; 10.3%) with placebo. The reported mean absolute reduction (4.4%) obtained from the overall study centers was statistically significant (p=0.0256) for the ITT population.

Table 10. Primary Endpoint: 72 Hour Rebleeding

Time	Eso (n=375)	Placebo (n=389)	p-value
72 hours	22 **(5.9%)**	40 **(10.3%)**	0.0256

Most of the secondary endpoints were also in favor of esomeprazole treatment group as shown below.

Table 11. Second Endpoint: Endoscopic Retreatment

Time	Eso (n=375)	Placebo (n=389)	p-value
72 hours	**16 (4.3%)**	**32 (8.2%)**	0.0244
4-7 days	**6**	**10**	
7-30 days	**2**	**3**	

Table 12. Second Endpoint: Rebleeding 4-7 and 7-30 Days

Time	Eso (n=375)	Placebo (n=389)
4-7 days	**5**	**10**
7-30 days	**2**	**3**

Results from study D961DC00001, therefore, showed that esomeprazole IV is more effective than placebo in preventing rebleeding in patients with PUB who have undergone successful endoscopic hemostasis and are at high risk for rebleeding. The most of second endpoints also support the treatment with Nexium IV. However, detailed review of the study reveals some issues which are under evaluation by the reviewing statistician and Medical Officer.

Q5. What are the Safety Outcome Measures?

A5. For study D961DC00001, the most commonly reported AEs during the IV treatment phase are "Gastrointestinal disorders" with fewer events occurring in the esomeprazole treatment group than in the placebo treatment group (12.3% and 19.8%, respectively).

Table 13. GI Related As, within 72 hrs

Overall AE	Esomeprazole (n=375)	Placebo (n=389)
Patients with any AE	147 (39.2%)	163 (41.9%)
Gastrointestinal Disorders	12.3%	19.8%
DU Bleeding	4.3%	4.1%
GU Bleeding	1.1%	3.3%
GI Bleeding	0.5%	0.5%
Rectal Bleeding	0.5%	0%
Melina	0.3%	0.3%
Hemetemesis	0.3%	0%

However, the esomeprazole treatment group had higher general and administrative site (27/375; 7.2%) events than that of placebo group (21/389; 5.1%). Esomeprazole treatment group also had higher vascular disorder (24/375; 6.4%) than that of placebo group (18/389; 4.1%).

2.3 Intrinsic Factors:

The intrinsic factor, e.g., gender differences within 2C19 genotypes, was also analyzed and shown below.

Table 14. Mean (± SD) PK Parameters of Esomeprazole Between Male and Female Subjects

Study D9615C00015*	**Esomeprazole**	
	Male	**Female**
Homo-EM (N = 17)	N=11	N=6
AUC_{0-24}	98.8 (±20.1)	114.7 (±11.2)
C_{max}	12.4 (±2.5)	16.7 (±1.5)
Hetreo-EM (N = 6)	N=6	N=0
AUC_{0-24}	123.2 (±31.5)	------
C_{max}	14.5 (±1.2)	------
Study D961DC00004[$]	**Esomeprazole**	
Homo-EM (N = 19)	N=9	N=10
AUC_{0-24}	86.4 (±13.7)	94.0 (±21.4)
C_{max}	11.2 (±1.1)	13.8 (±1.9)
Hetero-EM (N = 18)	N=13	N=5
AUC_{0-24}	110.4 (±26.9)	101.2 (±41.7)
C_{max}	14.0 (±3.8)	13.8 (±2.1)

*. PK data of subject # 20 (a male PM) not shown here.
[$]. PK data of subject # 7 (a male PM) not shown here.

No consistent results on gender differences within 2C19 genotypes of homo-EM and hetero-EM for esomeprazole are seen (Table 14 above) and it is also true for omeprazole (Study D961DC00004, not shown in Table 14).

2.4 Extrinsic Factors:

Drug interactions have not been specifically studied for esomeprazole IV at the proposed dosing regimen. Due to the higher dose and continuous infusion, a higher potential for interaction with drugs metabolized by CYP2C19 cannot be excluded with the proposed dosing regimen over 72 hrs. Furthermore, a higher potential for interaction with drugs with pH-sensitive absorption may be expected as the result of the more profound effect on intragastric pH.

2.5 General Biopharmaceutics:

The currently marketed Nexium (esomeprazole) IV dosage form for injection and infusion was employed.

2.6 Analytical Section

PK Measurement:
The sponsor reported that since the inversion of esomeprazole, the S-isomer of omeprazole, to the R-isomer of omeprazole is negligible, only stereo-unselective

bioanalytical methods have been used. The methods used in this clinical program are the same as used previously in the clinical programs for esomeprazole oral and esomeprazole IV.

For study D9615C00015, samples for determination of esomeprazole in plasma were analyzed at [redacted], using normal-phase liquid chromatography and UV-detection according to method No. AS M-002 ver3 [redacted] AstraZeneca method No BA-222). The standard curve covered the range of 25 to 8,000 nmole/L and the limit of quantification (LOQ) of esomeprazole was 25 nmole/L.

For study D961DC00004, samples for determination of esomeprazole or omeprazole were analyzed by [redacted] using normal-phase liquid chromatography and UV-detection according to method No AS M-002 version 3 [redacted] AstraZeneca method No BA-222). Eight calibration samples (25, 50, 200, 500, 1000, 2000, 6000 and 8000 nmol/L) were prepared in each batch for establishment of the calibration curve. The LLOQ of both esomeprazole and omeprazole was 25 nmole/L.

PD Measurements:

[redacted]

Q6. Is the assay methods adequately validated?

A6. The assay methods for determining plasma esomeprazole and omeprazole levels are adequately validated and the assay results of studies D9615C00015 and D961DC00004 are reviewed and found acceptable.

The assay performance results during the assay of esomeprazole (Study D9615C00015) are summarized below.

Table 15. Results of Inter-and Intra-assay Precision and Accuracy for Esomeprazole, batch 1-4

Batch	L1 nmol/l	L2 nmol/l	M1 nmol/l	M2 nmol/l	H1 nmol/l	H2 nmol/l
Number of duplicates		4		4		4
Nominal concentration		50.0		500		6000
Overall mean		49.4		501		6491
Mean accuracy %		-1.2		0.2		8.2
Intra-assay SD		1.91		21.8		509
Intra-assay CV %		3.9		4.4		7.8
Inter-assay SD		2.24		27.7		529
Inter-assay CV %		4.5		5.5		8.2

Table 16. Results of Inter-and Intra-assay Precision and Accuracy for Esomeprazole, batch 6-35

Batch	L1 nmol/l	L2 nmol/l	M1 nmol/l	M2 nmol/l	H1 nmol/l	H2 nmol/l
Number of duplicates		30		30		28
Nominal concentration		50.0		500		8000
Overall mean		50.1		515		8252
Mean accuracy %		0.1		3.0		3.1
Intra-assay SD		3.54		36.5		452
Intra-assay CV %		7.1		7.1		5.5
Inter-assay SD		3.68		38.7		454
Inter-assay CV %		7.4		7.5		5.5

Mean % accuracy ranged from 98.8% to 108.2%, intra-assay CV% reportedly ranged from 3.9% to 7.8%, and inter-assay CV%, 4.5% to 8.2%, respectively.

The assay performance results during the assay of esomeprazole and omeprazole (Study D961DC00004) are summarized below:

Table 17. Results of Inter-assay Precision and Accuracy for Esomeprazole and Omeprazole

Batch	L1 nmol/L	L2 nmol/L	M1 nmol/L	M2 nmol/L	H1 nmol/L	H2 nmol/L
Number of duplicate		n=17		n=17		n=17
Nominal concentration		50.0		500		6000
Overall mean		54.4		512		5960
Mean accuracy %		8.9		2.5		-0.6
Inter-assay SD		2.68		20.0		210
Inter-assay CV %		4.9		3.9		3.5

Mean % accuracy ranged from 99.4% to 108.9% and inter-assay CV% were reported to be 4.9%, 3.9% and 3.5%, respectively. However, the results of intra-assay precision and accuracy are missing.

For intragastric pH determination, the commercial kit was used. No actual calibration data was recorded and reported, however, the results appear acceptable.

3. Detailed Labeling Recommendations

No labeling revision is to be made for this review cycle.

4. Appendices

4.1 Proposed Package Insert (Original and Annotated)

4.2 Individual Study Review

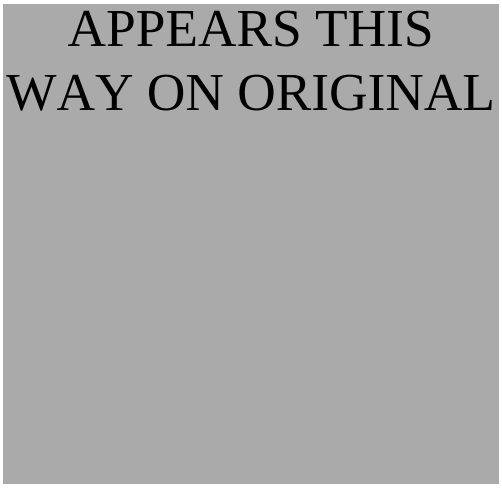
4.3 Cover Sheet and OCPB Filing/Review Form

NDA 21-689 (SE1) for Nexium IV

Appendix 4.1

Sponsor's Proposed Labeling

No Review of Sponsor's Proposed Package Insert will be made in this review cycle.



NDA 21-689 (SE1) for Nexium IV

Appendix 4.2

Individual Study Reports

NDA 21-689 (SE1) for Nexium IV

Appendix 4.3

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-689**	**Brand Name**	**Medium IV**
OCPB Division (I, II, III)	**DCP III**	**Generic Name**	**Esomeprazole Sod.**
Medical Division	**GI**	**Drug Class**	**PPI**
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	
OCPB Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Injection**
		Dosing Regimen	**80 mg Medium IV infusion for 0.5 hr followed by 8 mg/hr IV infusion over 3 days** (b) (4)
Date of Submission	**05/29/08**	**Route of Administration**	**IV** (b) (4)
Estimated Due Date of OCPB Review	**10/25/08**	**Sponsor**	**AstraZeneca**
Medical Division Due Date	**10/28/08**	**Priority Classification**	**P**
PDUFA Due Date	**11/28/08**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	**X**			
single dose:	**X**	**3**		One study in subjects with hepatic impairment
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**			**24-hr Intragastric pH values**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	**X**			**EM & PM for CYP2C19**
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. IRs will be sent to the sponsor.
QBR questions (key issues to be considered)		***1. Will PK and PD obtained from healthy subjects support the new dosing regimen for prevention of rebleeding in patients with gastric or duodenal ulcers?*** 2. Will PK of omeprazole obtained from subjects with hepatic impairment support the dose adjustment of esomeprazole in patients with hepatic impairment?
Other comments or information not included above		
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 07/14/08**	
Secondary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. 07/14/08**	

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/s/

Tien-Mien Chen
11/25/2008 05:53:37 PM
BIOPHARMACEUTICS

Sue Chih Lee
11/25/2008 07:15:56 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021689Orig1s014

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review
Addendum to July 12, 2013 Review

Date: September 10, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

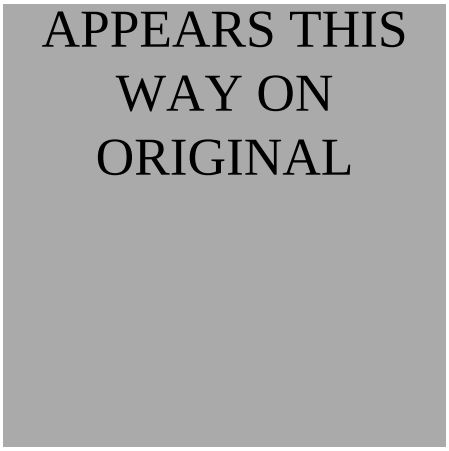
Drug: Nexium® IV (esomeprazole sodium) for injection

NDA: 21-689/S-014

Subject: Restructuring of the pregnancy and nursing mothers sections of labeling

In a review dated July 12, 2013, the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) provided suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling for Nexium IV (esomeprazole sodium) for injection in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements. In that review, PMHS-MHT recommended including epidemiologic data with regard to omeprazole use during pregnancy in Nexium IV pregnancy labeling to provide consistency between the Nexium labeling and the omeprazole labeling because esomeprazole is the S-isomer of omeprazole and omeprazole data already exist in the current approved Nexium IV pregnancy labeling. On July 22, 2013, the applicant requested the

removal of the omeprazole epidemiologic data from Nexium IV pregnancy labeling. PMHS-MHT concurs that the omeprazole epidemiologic data can be removed from Nexium IV pregnancy labeling as these data are not essential to assist with prescribing decisions for Nexium IV during pregnancy.



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/s/

CARRIE M CERESA
09/10/2013

JEANINE A BEST
09/10/2013

LYNNE P YAO
09/10/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: September 6, 2013

From: Alyson Karesh, MD, Medical Officer
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader
Lynne Yao, MD OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

NDA: 21689

Sponsor: AstraZeneca LP

Drug: Nexium IV (esomeprazole sodium)

Indication: Treatment of Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate.

Division Consult Request: DGIEP asked PMHS to assist with labeling and "insert animal data into the current Nexium IV efficacy supplement that derives from the recently approved NDA 202342 esomeprazole strontium label dated 8/6/13".[1]

Summary
After reviewing the approved esomeprazole strontium labeling, PMHS provided DGIEP with recommendations for the esomeprazole sodium (Nexium IV) labeling (Appendix I), and contributed to the labeling meeting on August 14, 2013. PMHS will continue to

[1] NDA 21680, Nexium IV, Pediatric and Maternal Health Staff Request for Consultation, August 7, 2013.

provide input as requested by DGIEP. Currently, PMHS suggestions are not likely to be incorporated into the Nexium IV labeling at this time; see final labeling for details.

Appendix I
PMHS Recommendations for Esomeprazole Sodium Labeling

Part of 6.1 – Clinical Trial Experience, Sx GERD and EE Trials

Pediatric

A randomized, open-label, multi-national study to evaluate the pharmacokinetics of repeated intravenous doses of once daily esomeprazole in pediatric patients 1 month to 17 years old, inclusive was performed. The safety results are consistent with the known safety profile of esomeprazole and no unexpected safety signals were identified. [*See Clinical Pharmacology (12.3)*]

8.4 Pediatric Use

The safety and effectiveness of NEXIUM I.V. for Injection have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis [*see Clinical Pharmacology, Pharmacokinetics (12.3)*]. However, effectiveness has not been established in patients less than 1 month of age.

(b) (4)

1 month to 17 years of age

Use of NEXIUM I.V. for Injection in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis is supported by: a) results observed from a pharmacokinetic (PK) study on NEXIUM I.V. for Injection performed in pediatric patients, b) predictions from a population PK model comparing I.V. PK data between adult and pediatric patients, and c) relationship between exposure and pharmacodynamic results obtained from adult I.V. and pediatric oral data and d) PK results already included in the current approved labeling and from adequate and well-controlled studies that supported the approval of NEXIUM I.V. for Injection for adults.

Neonates 0 to 1 month of age

Following administration of NEXIUM I.V. in neonates the geometric mean (range) for CL was 0.17 L/h/kg (0.04 L/h/kg- 0.32 L/h/kg).

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/s/

ALYSON R KARESH
09/06/2013

HARI C SACHS
09/09/2013

LYNNE P YAO
09/09/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 20, 2013

To: CDR Stacy Barley
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 021689
OPDP Comments for draft Nexium IV (esomeprazole sodium) for injection, for intravenous use, PI

OPDP has reviewed the proposed draft PI for Nexium IV (esomeprazole sodium) for injection, for intravenous use. We have reviewed the draft PI, last modified on August 15, 2013 and have the following comments.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/20/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: July 10, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Nexium® IV (esomeprazole sodium) for injection

NDA: 21-689/S-014

Subject: Restructuring of the pregnancy and nursing mothers sections of labeling

Applicant: AstraZeneca

Materials Reviewed:

- Nexium IV labeling submitted by the sponsor December 14, 2012.
- Prilosec® (omeprazole), approved labeling, May 15, 2013.

Consult Question: "Maternal health – Please assist with labeling to include the recommended structuring of the pregnancy subsection in the PLLR format."

INTRODUCTION

On December 14, 2012, AstraZeneca, submitted a complete response for Nexium IV (esomeprazole sodium) for injection, for the proposed indication of (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in response to the Complete Response Letter issued by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on June 16, 2011.

Nexium (esomeprazole sodium) was first approved on February 20, 2001, as a delayed release capsule for the healing of erosive esophagitis, maintenance of healing of erosive esophagitis and the treatment of symptomatic gastroesophageal reflux disease. Nexium (esomeprazole sodium) IV for injection was approved on March 31, 2005, for the short-term (up to 10 days) treatment of GERD patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with Nexium delayed-release capsules is not possible or appropriate. Details regarding the NDA complete response submission can be found in the Medical Officer's review in DARRTS.[1]

The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Nexium IV labeling.

This review provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion through inhibition of the H^+/K^+ – ATPase in the gastric parietal cell.[2] Esomeprazole blocks the final step in acid production through its action on the proton pump. Esomeprazole is the stereoisomer (S-isomer) of omeprazole which consists of the S- and R- isomers.[3] Prilosec (omeprazole) received initial approval in 1989 and is currently approved for the treatment of adults of duodenal ulcer and gastric ulcer, treatment in adults and children of gastroesophageal reflux disease (GERD) and maintainance of healing erosive esophagitis. Prilosec (omeprazole) and Nexium (esomeprazole) are both products marketed by AstraZeneca. Due to the chemical similarity between the two products, AstraZeneca has leveraged postmarketing data from both products to inform the labeling of both Prilosec and Nexium.

On April 16, 2013, PMHS-MHT provided a labeling review for Prilosec® (omeprazole) delayed release capsules. That review provided the basis for the revisions and restructuring of the pregnancy and nursing mothers labeling for Nexium IV (esomeprazole sodium).

[1] Aisha Peterson, Medical Officer, NDA 21-689/S-014 Clinical review.
[2] Approved Nexium (esomeprazole sodium) IV labeling, October 9, 2012.
[3] Ramakrishnan, A., Katz, P. (2002). Current Gastroenterology Reports. Pharmacological Management of Gastroesophageal Reflux Disease, 4:218-224.

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The Drugs and Lactation Database (LactMed)[4] was searched for available lactation data on with the use of Nexium IV, information was found regarding omeprazole levels in breast milk. Esomeprazole is the S-isomer of omeprazole. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

CONCLUSION

The pregnancy subsection of Nexium IV labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of the Nexium IV labeling was revised to comply with current labeling recommendations.

The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on June 26, 2013. The following PMHS- MHT recommendations reflect the discussions with the Division at that meeting.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below and are consistent with the May 15, 2013, approved Prilosec (omeprazole) labeling which contained PMHS-MHT recommendations and structuring.

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[4] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

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/s/

CARRIE M CERESA
07/10/2013

JEANINE A BEST
07/10/2013

LYNNE P YAO
07/12/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 18, 2013
Reviewer:	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Nexium I.V. (Esomeprazole Sodium) for Injection, 20 mg per vial and 40 mg per vial
Application Type/Number:	NDA 021689
Supplement:	S-014
Applicant:	AstraZeneca
OSE RCM #:	2013-440

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed insert labeling and container labels for Nexium I.V. (Esomeprazole Sodium for Injection), NDA 21689/S-014, for areas of vulnerability that could lead to medication errors. This prior approval efficacy supplement, submitted December 14, 2012, provides for an additional indication, (b) (4) (b) (4) risk reduction of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer".

1.1 REGULATORY HISTORY

Nexium I.V. was approved on March 31, 2005. On December 14, 2012, the Applicant submitted a supplement (S-014) for a new indication of use, (b) (4) (b) (4) risk reduction of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer". No other proton pump inhibitor (PPI) has this indication.

A Complete Response was issued by the Division during the first and second cycles secondary to insufficient and inadequate evidence to support the proposed indication. This is a class 2 resubmission submitted on December 14, 2012 in response to a CR letter issued June 16, 2011. Therefore, this is the third cycle for this supplement.

DMEPA previously reviewed the container label and carton labeling (S-023) as a part of a CBE-30 submission (OSE Review # 2012-311 dated March 19, 2012). Supplement 023 provided for revised container labels for Nexium I.V. for injection from a white background to a clear background to accommodate the manufacturing equipment used for the labeling operations. After an internal discussion with CMC, some of these recommendations were communicated in the action letter dated March 30, 2012. The revised labels were submitted April 24, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 14, 2012 submission.

- Active Ingredient: Esomeprazole Sodium
- Indication of Use for the approved and proposed indications and their respective recommended doses is in Table 1 below:

Table 1.
Approved and Proposed Indications for Nexium I.V. and the Recommended Dosing

Indication	Dose
Short term treatment of gastro esophageal reflux disease (GERD) with erosive esophagitis in adults and pediatric patients greater than 1 month of age, when oral therapy is not possible or appropriate (**approved indication**)	20 mg or 40 mg intravenously once daily over at least 3 minutes or given as an intravenous infusion over 10 minutes to 30 minutes (approved dosing)

[redacted] (b) (4) risk reduction of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer (**proposed indication**; adults only)	80 mg as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/hour for a duration of 72 hours (includes initial 30 minute dose plus 71.5 hours of constant rate infusion) [redacted] (b) (4)

- Route of Administration: Intravenous
- Dosage Form: Powder for injecton
- Strengths: 20 mg and 40 mg
- Dose and Frequency of Administration: see table above
- How supplied: freeze dried powder containing 20 mg or 40 mg
- Storage: Room temperature, protect from light
- Container and Closure Systems: 5 mL glass vial, sealed with a bromobutyl rubber stopper and an aluminum cap with plastic flip-off seals which have different colors for different strengths

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Nexium I.V. medication error reports. We also reviewed the approved container labels and the Nexium I.V. package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 2.

Table 2: FAERS Search Strategy	
Date of search with time limitations	February 10, 2012 to April 11, 2013 (date of last FAERS search in previous review was February 10, 2012)
Drug Names	Nexium Nexium IV
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT
Route of Administration:	IV, IV Bolus, IV Drip, IV infusion, Intravenously, Infusion, IVPB

The FAERS database search identified three cases. Cases that did not involve medication errors or involved an oral dosage form of Nexium were excluded from further analysis. Each case was reviewed for relevancy and duplication. After individual review, two cases were not included in the final analysis for the following reasons:

- No medication error occurred (e.g., patient reported that they were out of Nexium)

The remaining case was a wrong drug error where the healthcare provider administered Lasix at 8 mg per hour instead of Nexium at 8 mg/hour. The error resulted in dehydration, hypokalemia and hyponatremia with asymptomatic EKG changes requiring treatment with magnesium. Contributing factors, causality, and final outcome were not provided.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 24, 2012 (Appendix A)
- Insert Labeling submitted December 14, 2012 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the container label and carton labeling for Nexium I.V. in OSE Review # 2012-311 dated March 19, 2012. We considered the previous reviews to assess if any of the cases retrieved and the medication error risk assessment issues identified are relevant to our current assessment. We noted that none of the cases retrieved in our previous review was found relevant to this review. We also noted that all of our recommendations made in the previous reviews were implemented.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

We note that our recommendations were incorporated into the revised container labels submitted April 24, 2012. Additionally, we did not retrieve any medication error cases from FAERS which could be attributed to label or labeling.

The proposed additional indication for Nexium I.V. requires a different recommended dosing regimen from what has been utilized in the past (See Table 1). As such, the pharmacist or nurse will need step-wise instructions in the insert labeling to safely prepare a dose. We note that there are instructions for the loading dose, but not for the preparation of the subsequent continuous infusion making this section of the insert labeling incomplete. Additionally, the organization of Section 2.3 (titled (b) (4) (b) (4) under the heading, Full Prescribing Information Section) is

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

difficult to follow and may lead to misinterpretation of information. We attempt to address these deficiencies in Section 5 (Recommendations).

Finally, we note that the proposed loading dose and subsequent infusion do not require the use of strengths other than that which is currently marketed (20 mg and 40 mg). Therefore, the available strengths will be sufficient to prepare the dose for this indication.

4 CONCLUSIONS

DMEPA concludes that the preparation instructions associated with the additional indication can be better organized to safely prepare this product. Additionally, we note the preparation instructions do not address how to prepare the continuous infusion phase of the treatment regimen and therefore, this section (Preparation and Administration Instructions) is incomplete.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends revisions to the insert labeling for consideration by the Review Division prior to the approval of this NDA supplement. These revisions have been added as track changes to Section 2.3 in the Full Prescribing Information section of the insert labeling (see Appendix C).

If you have further questions or need clarifications, please contact Phong Do, OSE Project Manager, at (301) 796-4795.

REFERENCES

Tobenkin, A. Label and Labeling Review for Nexium (Esomeprazole Sodium) for Injection, 20 mg and 40 mg. OSE Review# 2012-311/S-023, March 19, 2012.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

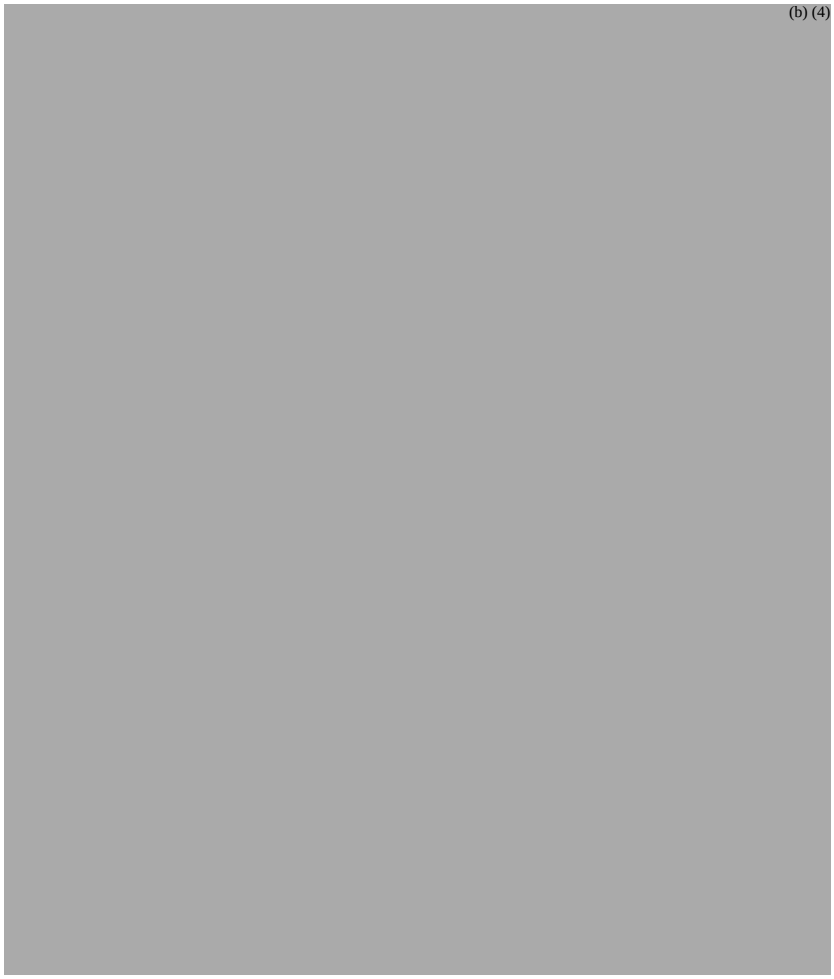
FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix B: Container Labels (20 mg and 40 mg), submitted April 24, 2012



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<u>Appendix C</u>. Proposed Revisions to the Insert Labeling (see attached insert labeling with track changes)

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/s/

DENISE V BAUGH
06/18/2013

LUBNA A MERCHANT
06/18/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: May 20, 2011

To: Stacy Barley, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Kathleen Klemm, Regulatory Review Officer
Twyla Thompson, Regulatory Review Officer
Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
DDMAC

Subject: NDA 021689/S-014
DDMAC labeling comments for Nexium® I.V. (esomeprazole sodium) for Injection, for intravenous use

---

We acknowledge receipt of your November 18, 2010, consult request for the proposed product labeling (Package Insert) for Nexium® I.V. (esomeprazole sodium) for Injection, for intravenous use, NDA 021689/S-014. DDMAC notes the email from Stacy Barley dated May 18, 2011, which indicated that DGP determined that labeling would not be finalized during the current review cycle and that a Complete Response letter would be issued. Therefore, DDMAC will provide comments regarding labeling for this supplemental application during a subsequent review cycle. DDMAC requests that DGP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at 301-796-5389 or Roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
05/20/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 7, 2011

TO: Stacy Barley, Regulatory Project Manager
Erica Wynn, Medical Officer
Division of Gastroenterology Products

FROM John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-689 / S-014

APPLICANT: AstraZeneca LP

DRUG: Nexium (esomeprazole) IV

NME: No

INDICATION: (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers

THERAPEUTIC CLASSIFICATION: Priority

CONSULTATION REQUEST DATE: December 14, 2010

INSPECTION SUMMARY GOAL DATE: April 25, 2011

DGP ACTION GOAL DATE: May 25, 2011

PDUFA DUE DATE: May 25, 2011

I. BACKGROUND

Hospitalization for acute upper gastrointestinal bleeding is associated with a 30-day mortality risk of 5 - 10%, a rate unchanged during the last 30 years despite new ulcer management drugs. Potential explanations for the unchanged rate include increased use of non-steroidal anti-inflammatory drugs and increasing population mean age with associated co-morbidity. High-risk patients typically receive endoscopic treatment to control bleeding and to reduce the risk of rebleeding. The literature supports the use of proton pump inhibitors (PPIs) in further reducing the risk of rebleeding, currently an off-label use gaining increased acceptance as standard therapy. Esomeprazole, the first PPI to be developed as an enantiomer, has been shown to be among the most effective PPIs (more effective than lansoprazole, pantoprazole and omeprazole) in reducing stomach acid secretion to manage erosive reflux esophagitis.

The applicant submitted this application for the use of esomeprazole as [redacted] (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. A single pivotal study, Study D961DC00001, was submitted in support of this application.

Synopsis of D961DC00001

Protocol: Study D961DC00001 was an international, randomized, double-blind, placebo-controlled study in 767 subjects with acute peptic ulcer bleeding (PUB). Esomeprazole was administered as a 72-hour intravenous infusion to reduce the risk of rebleeding after achieving endoscopic haemostasis of acute bleeding. Following the 72-hour infusion, all subjects received further oral therapy (40 mg esomeprazole daily) for 27 days. The primary objective was to compare, in patients with peptic ulcer bleeding after successful endoscopic haemostasis, the efficacy of 72 hours continuous intravenous infusion of either esomeprazole or placebo assessed by the primary endpoint defined as the rate of clinically significant rebleeding during the treatment period. Clinical significant rebleeding was to be either confirmed by endoscopy (recommended) or diagnosed using criteria A, B, or C as shown in the table below. Safety was assessed with adverse event monitoring, clinical laboratory tests, and physical examination.

Diagnosis of Rebleeding	Criteria
A: Endoscopy (A1 or A2), initiated by one of B1, B2, or B3	**A1:** Blood in stomach (this criterion cannot be used during the first 6 hours after primary endoscopic hemostasis). **A2:** A verified active bleeding from a peptic ulcer (Forrest Ia, Ib).
B: Clinical diagnosis based on two or more of B1, B2, and/or B3	**B1:** Vomiting of fresh blood or fresh blood in a gastric tube or haematochezia or melaena after a normal stool. **B2:** Decrease in Hb > 20 g/L (or Hct > 6%) during 24 hours or an increase in Hb < 10 g/L (or Hct < 3%) despite ≥ 2 units of blood transfused during 24 hours **B3:** Unstable circulation systolic blood pressure ≤ 90 mmHg or pulse ≥ 110 per min (after have had a stable circulation).
C: Hematemesis	**C:** Vomiting more than 200 mL of fresh blood (investigator estimate)

Results: The study results supported the efficacy of continuous intravenous infusion of esomeprazole. Rebleeding during the 72-hour infusion period was significantly less frequent for esomeprazole than for placebo ($p = 0.026$). Further, with continued oral therapy following intravenous infusion, esomeprazole therapy continued to reduce the rate of rebleeding (for up to 30 days, the duration of oral esomeprazole

therapy). Placebo was associated with surgical or second endoscopic intervention to control rebleeding at twice the rate for esomeprazole, both within the 72-hour infusion period and for up to 30 days. The safety profiles of esomeprazole and placebo were similar, with comparable rates of adverse events and serious adverse events and without significant laboratory or physical findings. No esomeprazole-associated safety concerns were identified, and the overall number of deaths was fewer for esomeprazole than for placebo. The results of study D961DC00001 appear to support the safety and efficacy of esomeprazole administered as a 72-hour intravenous infusion to reduce the rate of rebleeding following endoscopic control of acute peptic ulcer bleeding.

II. INSPECTION RESULTS

Only foreign data from a single study (D961DC00001) were submitted in support of this NDA. Site 102 (in Netherlands) with the largest treatment effect was inspected in support of this NDA review:

Clinical Investigator Site	Protocol (Site / Subjects)	Inspection Dates	Classification
Ernst J. Kuipers, MD, PhD Erasmus Medical Centre University Hospital Gastroenterology Department 40, 3015 GD Rotterdam, Netherlands	D961DC00001 Site 102 21 subjects	March 7 - 11, 2011	Pending Preliminary: NAI

Key to Classification: NAI = no deviation from regulations; VAI = deviation from regulations; OAI = significant deviation from regulations and/or data unreliable

Pending: Preliminary classification based on information on Form FDA 483 and communication with the field investigator; final establishment inspection report has not been received from the field office and DSI's complete review of the report remains pending as of this inspection summary

Ernst Kuipers (Site 102)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint, adverse events, subject randomization, concomitant medications, protocol deviations, subject discontinuations
- Subjects: 58 subjects were screened, 21 enrolled in study, and 19 completed the study. Complete records were reviewed for all 21 enrolled subjects.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
- Primary efficacy endpoint data reported in the NDA data listings were verifiable against source records and case report forms (CRFs). There was no evidence of adverse event underreporting.

- All subjects at this site were consented properly prior to study enrollment. The list of protocol violations matched the deviations noted in subject records. Source records appeared factual and complete, and matched corresponding CRFs.
- Two minor observations, both noted by the study monitor, were verbally discussed (not cited on a Form FDA 483):
  - One electrocardiogram for one subject was not available as part of subject records, although the results and interpretation were documented in the physician's progress notes and CRF
  - The test article box (containing drug vials, either empty or unused) for one subject was lost and not returned to sponsor as part of the procedures for final drug disposition and accountability.

  These minor deficiencies are unlikely to impact data reliability.

c. Assessment of data integrity: Data from this study site appear reliable.

Observations noted above are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In support of this NDA review, the conduct of Study D961DC00001 was inspected at a single clinical study site in Netherlands (Site 102, Ernst Kuipers).

No significant deficiencies were observed and a Form FDA 483 was not issued. The study appeared to have been conducted in accordance with the study protocol and applicable good clinical practice regulations, including data collection and assurance of subject safety and welfare. The study data from Site 102 appear reliable with respect to the study protocol as written and submitted in the NDA.

Note:

The final EIR from the field has not been received at DSI and the final classification remains pending. The observations noted above are based on preliminary communications with the field investigator.

An addendum to this clinical inspection summary will be forwarded to DGP if the final classification changes from the pending classification or if additional observations of clinical or regulatory significance are discovered after receipt and review of the EIR.

{See appended electronic signature page}

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CONCURRENCE:

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/s/

JONG-HOON LEE
04/08/2011

TEJASHRI S PUROHIT-SHETH
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

DATE: February 14, 2011

FROM: Amy M. Taylor, MD, MHS, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

THROUGH: Hari Cheryl Sachs, MD Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

TO: Donna Griebel, MD, Director
Division of Gastroenterology Products

DRUG: Nexium® I.V. (esomeprazole sodium) for Injection

SPONSOR: AstraZeneca LP

APPLICATION: NDA 21-689

CURRENT ADULT INDICATION: 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.

PROPOSED NEW ADULT INDICATION: (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

There are no approved pediatric indications for Nexium IV.

PROPOSED DOSING REGIMEN: Adult dose – 80 mg administered as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/hr given over 3 days (72 hours) [redacted] (b) (4)

CONSULT QUESTION: Does the indication [redacted] (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcer apply to pediatric patients? If so, what specific age groups?

Background

Nexium® I.V. was approved by the FDA on March 31, 2005 for use in adults for 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. The approval letter granted a deferral of pediatric studies required under PREA for the treatment of GERD in pediatric patients ages 0 to17 years until December 31, 2008. On December 19, 2006, AstraZeneca submitted a proposed pediatric development plan and a study design concept for a randomized, open-label study to evaluate the pharmacokinetics of repeated I.V. doses of esomeprazole in pediatric patients 0-17 years old inclusive.

A Written Request (WR) was issued for esomeprazole (oral formulation) on December 31, 2001 and amended four times, most recently on October 10, 2008. The WR outlines the following studies:

- A pharmacokinetic (PK) and safety study in neonates and preterm infants
- A PK/pharmacodynamic (PD) and safety study in infants aged 1 to 11 months
- An efficacy and safety study in infants 1 to 11 months
- A PK, exposure/response and safety study in pediatric patients aged 1 to 11 years
- A PK and safety study in pediatric patients aged 1 to 16 years

The sponsor submitted a complete response to the WR on December 18, 2008. Exclusivity was granted May 1, 2009.

Oral Nexium® is approved for short-term treatment of gastroesophageal reflux disease in pediatric patients 1 year and older:

- Healing of erosive esophagitis in pediatric patients 1 to 11 years
- Short-term treatment (up to 8 week) in pediatric patients 1 to 17 years

There are no approved indications for pediatric patients less than 1 year.

On November 26, 2008, FDA issued a complete response letter in response to a supplemental application for [redacted] (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. The primary reason for the CR was a lack of substantial evidence of efficacy. The CR letter noted the sponsor's request for a full waiver of pediatric studies due to the small number of pediatric patients and geographically widespread distribution of pediatric patients. The Division's response was as follows:

It is unlikely that a full waiver of pediatric studies will be granted on re-submission. The incidence of *H. pylori* related peptic ulcer disease in the pediatric population is low; however, peptic ulcers secondary to long term use of steroids, NSAIDs, and chronic renal failure are not uncommon. Pediatric patients are administered intravenous proton pump inhibitors (PPI) prophylactically before starting high dose steroids and for upper gastrointestinal bleeding.

Therefore, please submit a pediatric plan with your complete response.

The sponsor resubmitted the supplemental application on September 15, 2010.

Nexium® IV Treatment for GERD in Pediatric Patients

On March 31, 2010, the sponsor submitted a sNDA to provide pharmacokinetic, efficacy and safety information on the use of Nexium® I.V. as an alternative to oral formulation (b) (4) for the treatment of gastroesophageal reflux disease (GERD) in pediatric patients, ages 17 inclusive.

Reviewer's comment: The Division of Gastroenterology Products is currently reviewing the sNDA for the use of Nexium® IV for the treatment of GERD in pediatric patients ages (b) (4) *to 17. If approved, the approval will most likely be based on extrapolating efficacy om adults and matching pediatric drug exposure to adult drug exposure. Safety in pediatric patients will be supported by safety information obtained during clinical trials with oral Nexium®.*

Other PPI IV Formulations

Pantoprazole or Protonix® (NDA 20-988) was originally approved in March 22, 2001. The product is currently indicated in adults for short-term treatment (7-10 days) of patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis. The labeling states that safety and effectiveness in pediatric patients have not been established. Given at the time of approval, the following postmarketing requirements were rendered under the pediatric rule/PREA:

Deferred pediatric study under PREA for the treatment of short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative to oral therapy in patients who are unable to take Protonix (pantoprazole sodium) Delayed-Release Tablets in patients 2 to 16 years of age.

Deferred pediatric study under PREA for the treatment of GERD in pediatric patients ages 0 to 16.

According to the Postmarket Requirement and Commitments' database the final report for both requirements was submitted to FDA on March 21, 2004.

Safety of Nexium® IV

Oral and IV Nexium® are relatively safe. Frequent adverse reactions seen in adult GERD clinical trials with Nexium® IV include headache (10.9%), abdominal pain

(5.8%), flatulence (10.3%), dyspepsia (6.4%) nausea (6.4%) diarrhea (3.9%) and dry mouth (3.9%). A similar adverse reaction profile was seen with adult clinical trials with oral Nexium®. Pediatric patients in GERD clinical trials demonstrated a similar adverse reaction profile as adults. No new safety concerns were identified in pediatric patients.

Recently, a warning has been added to the labeling of PPIs concerning and increased risk for osteoporosis-related fractures of the hip wrist or spine. Several published observational studies suggest that the risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer).

The sponsor states in proposed labeling that adverse reactions seen in the peptic ulcer bleeding study in adults were similar to that of oral administration of Nexium® with the exception of injection site reactions including erythema, swelling, inflammation, pruritis, phlebitis, thrombophlebitis and superficial phlebitis.

Proposed indication in pediatric patients

Upper gastrointestinal (UGI) bleeding is an uncommon, but not rare condition in pediatric patients. Patients with hematemesis constitute 10 – 15% of referrals to pediatric gastroenterologist. (Bhatia 2009) In a study of pediatric patients undergoing an upper GI endoscopy, 8.1% of patients were found to have ulcers and/or erosions. Endoscopic signs bleeding were present in 16% of those patients with ulcers and/or bleeding. (Kalach 2010) Patients in a pediatric intensive care unit are at risk of UGI bleeding. A study of 1006 consecutive admissions to a pediatric ICU over 56 weeks reported 10.2% of participants had UGI bleeding and 1.6% had clinically significant bleeding. (Reveiz 2010)

Reviewer's comment: While UGI bleeding in pediatric patients is not rare, it may be difficult to find pediatric patients who meet the condition of the sponsor's proposed indication of (b) (4) *risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.*

Sponsor's request for a full waiver of pediatric studies

In the resubmission of the supplemental application, the sponsor again requested a full waiver of pediatric studies citing that the studies were not feasible. The sponsor states that the exact prevalence of PUB in a pediatric population is not known, due to the lack of pediatric prevalence studies reported in the literature.

The sponsor provided data from the literature estimating the number of pediatric patients with peptic ulcer disease and peptic ulcer bleeding. In one study, 6.4% of patients admitted to a pediatric ICU had upper GI bleeding with 0.4% with clinically significant bleeding. A second study found a higher rate of clinically significant bleeding of 1.6%. However, neither study described the rate of bleeding caused by peptic ulcers.

The sponsor provided incidence rates from Germany and Sweden for peptic ulcers in pediatric patients of 4.3/100,000 and 0.5/100,000 respectively. The sponsor noted that only a fraction of these patients would have bleeding from their peptic ulcer disease.

In order to estimate the prevalence of peptic ulcer bleeding, the sponsor reviewed data from two databases, Premier Perspective™ inpatient database and MarketScan® claims database. Based on these databases, the sponsor estimated the prevalence of pediatric patients with peptic ulcer bleeding to be between (b) (4) and (b) (4) patients. However, the sponsor noted, not all of these patients will fit wit the parameters of the indication. In addition, the patients will most likely be geographically dispersed.

The sponsor included a table from the Premier Perspective™ database with the projected number of hospitalized patients by age group and year with a primary discharge diagnosis of pediatric peptic ulcer bleeding (Table 1) and primary and secondary discharge diagnosis (Table 2).

Table 1 **US projected number of hospitalized patients with Pediatric PUB (primary discharge diagnosis only)**

Age group	2004	2005	2006	2007	2008
< 1	(b) (4)				
1 to 3					
4 to 11					
12 to 17					
Total					

Table 2 **US projected number of hospitalized patients with Pediatric PUB (primary and secondary discharge diagnoses)**

Age group	2004	2005	2006	2007	2008
< 1	(b) (4)				
1 to 3					
4 to 11					
12 to 17					
Total					

Discussion

PREA requires pediatric studies specific to the indication in the application triggering PREA. In the complete response letter on November 26, 2008, the Division suggested that a full waiver of pediatric studies was unlikely due to the fact that there are sufficient pediatric patients with peptic ulcer disease to study. However, broadening the proposed indication in adult to require pediatric studies in patients with peptic ulcer disease is not authorized under PREA. The sponsor is correct that there are too few pediatric patients to conduct studies for (b) (4) risk reduction of

rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

If the Division, through its review of the application, decides a broader indication in adults is appropriate (b) (4) studies in pediatric patients may feasible.

BPCA is designed to provide an incentive to sponsors to conduct pediatric studies that may not be required under PREA. In this case, the Division may be interested in studying peptic ulcer bleeding in pediatric patients. However, esomeprazole was granted pediatric exclusivity on May 1, 2009. Since esomeperazole is an enantiomer of omeprazole, the exclusivity granted to esomeprazole at that time was considered a second period of exclusivity for the moiety. Nexium is not eligible for any further periods of exclusivity.

Conclusion

A full waiver of required pediatric studies under PREA should be granted on the basis that necessary studies are impossible or highly impracticable because the number of patients is so small or the patients are geographically dispersed.

References

Bhatia V, Lodha R. Upper gastrointestinal bleeding. *Indian J Pediatr* 2010. Online publication

Chaibou M, Tucci M, Dugas M-A, et al. Clinically significant upper gastrointestinal bleeding acquired in a pediatric intensive care unit: a prospective study. *Pediatrics* 1998 102(4): 933-938

Kalach N, Bontems P, Koletzko S, et al. Frequency and risk factors of gastric and duodenal ulcers or erosions in children: a prospective 1-mont European multicenter study. *Eur J Gastroenterol Hepatol* 2010 22:1174-1181

Reveiz L, Guerrero-Lozano R, Camacho A, et al. Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. *Pediatr Crit Care Med* 2010; 11(1):124-132

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/s/

AMY M TAYLOR
03/01/2011

HARI C SACHS
03/01/2011
I agree with the recommendations in this consult.

LISA L MATHIS
03/02/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 11, 2011
Application Type/Number:	NDA 021689/S-014
To:	Donna Griebel, MD, Director Division of Gastroenterology Products
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Kellie Taylor, Pharm.D., MPH, Associate Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labeling Review
Drug Name(s):	Nexium I.V. (Esomeprazole Sodium) for Injection
Applicant/sponsor:	AstraZeneca LP
OSE RCM #:	2010-2448

CONTENTS

1 INTRODUCTION

This review evaluates the package insert labeling for Nexium I.V. (Esomeprazole) for Injection for the potential to contribute to the medication errors. The insert submitted under Efficacy Supplement-014, which allows for a new indication and dosing for (b) (4) (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

1.1 REGULATORY HISTORY

Nexium I.V.(Esomeprazole) for Injection was approved on March 31, 2005 for the indication short-term treatment of gastroesophageal reflux disease (up to 10 days) in patients with a history of esophagitis as an alternative therapy when therapy with oral Nexium is not possible or appropriate.

On May 28, 2008, the Applicant submitted an Efficacy Supplement (S-014) to expand Nexium I.V. indication for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. This indication includes a different dose of Nexium I.V. The proposed dose for Nexium I.V. is 80 mg as intravenous infusion over 30 minutes followed by 8 mg/hr for 71.5 hours.

On November 26, 2008, the Applicant received the Complete Response due to lack of clinical and statistical data. The Applicant re-submitted Efficacy Supplement (S-014) on September 15, 2010. The Applicant submitted the revised proposed package insert labeling for this supplement on November 16, 2010. This labeling is the subject of this review. There are no proposed revisions to the container label and carton labeling at this time.

2 METHODS AND MATERIALS

Since Nexium I.V. has been marketed since 2005, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors involving Nexium's I.V. labels and labeling.

Additionally, to evaluate potential medication errors involving the new dosing of Nexium IV DMEPA searched AERS for Protonix I.V. medication errors because Protonix I.V. has a similar dose and is available as 40 mg vial, which is similar to the product characteristics of Nexium I.V.

Duplicate reports were combined into cases. Those cases, not pertaining to medication errors (e.g., adverse drug reactions, allergic reactions) or pertaining to medication errors due to concomitantly administered drugs were excluded from further analysis. All cases of medication error were evaluated and grouped by the type of error. Each case was evaluated for the root cause.

Additionally, DMEPA evaluated the proposed package insert labeling for Nexium I.V. using Failure Mode and Effects Analysis[1] (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 NEXIUM I.V. ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA

The AERS search conducted on January 14, 2010 for Nexium I.V. used the following search terms: MedDRA High Level Group Terms (HLGT) "Medication Errors" and "product Quality Issues" along with the active ingredient name of "Esomeprazole", the trade name "Nexium I.V.",

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

and the verbatim terns “Nexi%” and “Esomepr%” without date limitations. The search used advanced product criteria of excluding oral route of administration.

2.2 PROTONIX I.V., ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA

The AERS search conducted on January 14, 2010 for Protonix I.V. used the following search terms: MedDRA High Level Group Terms (HLGT) “Medication Errors” and “product Quality Issues” along with the active ingredient name of “Pantoprazole”, the trade name “Protonix I.V.”, and the verbatim terns “Proton%” and “Pantopr%” without date limitations. The search used advanced product criteria of excluding oral route of administration.

2.3 PACKAGE INSERT LABELING RISK ASSESSMENT

For Nexium I.V. for Injection, the Applicant submitted the proposed package insert labeling on November 16, 2010.

3 RESULTS AND DISCUSSION

The following sections describe the results of the DMEPA’s medication error searches and labeling evaluation.

3.1 NEXIUM I.V. ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE RESULTS

In total, DMEPA evaluated four cases (n=4) of medication errors involving Nexium I.V. Three cases were (n=3) from the United Stated and one foreign case (n=1). The foreign case involved two medication errors of overdose and wrong rate of administration. The three U.S. cases each involved a single error only consisting of the wrong drug (n=2) and overdose (n=1). Thus, the total number of medication errors identified (n=5) is greater than the total number of cases (n=4). The following sections describe these cases in detail.

3.1.1 Overdoses (n=2)

Foreign Case (n=1)

One of the two cases that resulted in an overdose of Nexium I.V. was the foreign case from Switzerland. The case (ISR #6184035-7) reported an overdose due to an unspecified problem with the infusion pump. This error was related to the infusion pump itself and not caused by the labels and labeling of Nexium I.V.

Domestic Cases (n=1)

The US overdose case (ISR 6705226-X) was also due to an infusion pump error and not caused by the labels and labeling. This case reported that a patient received an overdose of Nexium I.V. as 80 mg/hour for 2 hours due to confusion with the pump. Although no additional details regarding contributing factors were provided, we suspect the error occurred at the time of the pump programming and we do not believe this error is related to Nexium I.V. labeling.

3.1.2 Wrong Rate of Administration (n=1)

The overdose case from Switzerland also involved the wrong rate of administration. The case (ISR #6184035-7) reported that *98 mg of Nexium I.V. was injected as bolus and 40 mg was given as drip infusion* due to unspecified problem with infusion pump. Since the error is related to the infusion pump and not to the labels and labeling of Nexium I.V., we did not evaluate the case further.

3.1.3 Wrong Drug (n=2)

Two US cases described administration of Lantus (Insulin Glargine) instead of Nexium I.V. Both cases reported that that error was made due to the similar looking shape and color of the vials. One case from April, 2007 (ISR #5372367-1) reported that patient received approximately 300 units of Lantus intravenously instead of Nexium, which resulted in low blood glucose. The patient was treated with dextrose and recovered. However, the error prolonged hospitalization. The second case from June, 2009 (ISR #6253923-5) reported that patient received approximately 20% of the contents of a Lantus vial instead of Nexium I.V. 20 mg; thus, approximately 200 units. No patient outcome was reported. The reporters stated that the confusion between Nexium I.V. and Lantus occurred due to the similarity in the shape and color of the vials. The new dosing due to the indication of (b) (4) risk reduction of rebleeding should not contribute to the wrong drug error between Nexium I.V. and Lantus since there were no changes to the container labels or packaging. Although this error occurred twice, DMEPA is reluctant to recommend revising the Nexium I.V. container label by changing the colors to avoid overlapping colors with Lantus at this time. However, the potentially serious outcomes of this error (e.g., severe hypoglycemia or death) warrant a further investigation and evaluation of the wrong drug error with Lantus outside the scope of this review. This will be evaluated through a separate postmarketing review.

3.2 PROTONIX I.V. ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE RESULTS

DMEPA evaluated two US cases (n=2) of relevant medication errors involving Protonix I.V. described in Section 2. One case described the wrong rate of administration and one case described the wrong concentration error. The following sections describe these cases in detail.

3.2.1 Wrong Rate of Administration (n=1)

One case (ISR #3855403-0) reported the 80 mg dose of Protonix I.V. was administered over an hour as continuous infusion instead of fifteen minute or two minute infusion as specified in the package insert labeling. The reporter stated that patient did not experience any adverse events. The case did not provide any additional details regarding the contributing factors. However, the insert labeling provides clear instructions for the correct administration of the product.

3.2.2 Wrong Concentration (n=1)

One case (ISR #3956172-6) reported that the Protonix I.V. preparation was over-diluted in 530 mL of Normal Saline. This hyper-diluted solution was administered to the patient and patient experienced pulmonary edema due to the extra fluid and compromised cardiac function. The patient was administered Protonix I.V. at the rate of 8 mg/hour in 53 mL of normal saline over 10 hours. Thus, patient received 80 mg dose of Protonix I.V. in 530 mL of normal saline over 10 hours instead of 80 mg dose in 100 mL of normal saline. The reporter stated that the pulmonary edema precipitated as a result of the infusion volume of the diluent. Although no additional details regarding the root cause of this error were reported, we suspect the error may have occurred during the dilution phase while preparing Protonix I.V. for administration. However, because no information regarding contributing factors has been identified in the case, we are unable to determine whether this error occurred due to unclear dilution instructions in the package insert labeling or other factors.

Since Nexium I.V. new indication of the (b) (4) risk reduction of rebleeding of gastric or duodenal ulcers proposes that an 80 mg dose be followed by 8 mg/hour for 71.5 hours is similar to Protonix I.V. in preparation and administration, it is important to ensure that preparation instructions are clear and comprehensive to help minimize the risk of medication errors involving the wring reconstitution or dilution.

3.3 PACKAGE INSERT LABELING RISK ASSESSMENT

Our evaluation of the package insert labeling identified the following deficiencies:

- Some of the information in the *Dosage and Administration* Section regarding reconstitution and dilution instructions as well as duration of intravenous infusion of 8 mg/hour is confusing and can be improved to be more comprehensive and contain clear and concise details
- Some information such as storage information can be relocated to a different subsection in the *Dosage and Administration* Section to improve clarity.

4 CONCLUSSIONS AND RECOMMENDATIONS

Our evaluation of the package insert labeling noted deficiencies in the insert labeling that can be improved upon to minimize the potential for medication errors. Thus, DMEPA recommends the package insert labeling revisions outlined below be implemented prior to approval of this supplement.

1. *Highlights of Prescribing Information and Full Prescribing Information, Dosage and Administration* Section

   The *Highlights of Prescribing Information and Full Prescribing Information, Dosage and Administration* Sections are inconsistent.

   For the proposed indication of (b) (4) risk reduction of rebleeding, the Dosage and Administration states "… followed by continuous infusion of 8 mg/hr (b) (4) (b) (4) However, in the *Full Prescribing Information*, Section 2.3 (b) (4) (b) (4) the duration of therapy for 8 mg/hr states This inconsistency in the duration of therapy for the continuous intravenous infusion of 8 mg/hour is confusing and misleading. Do not use the term (b) (4) as this term is imprecise; and thus, may be misinterpreted. Instead, define the correct duration of therapy (i.e. 71.5 hours or 72 hours) and use consistent terminology throughout the *Dosage and Administration* Sections in *Highlights of Prescribing Information* and *Full Prescribing Information*.

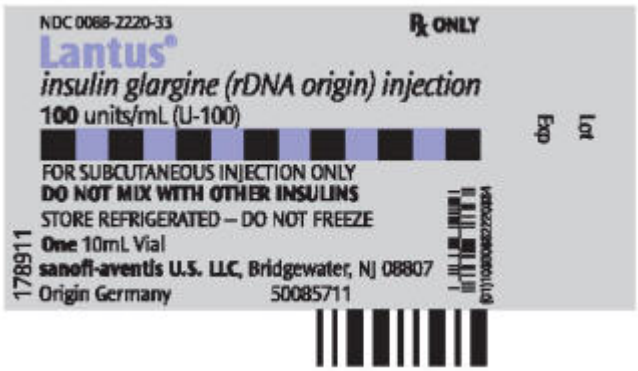
2. *Full Prescribing Information*, Section 2.3 (b) (4)

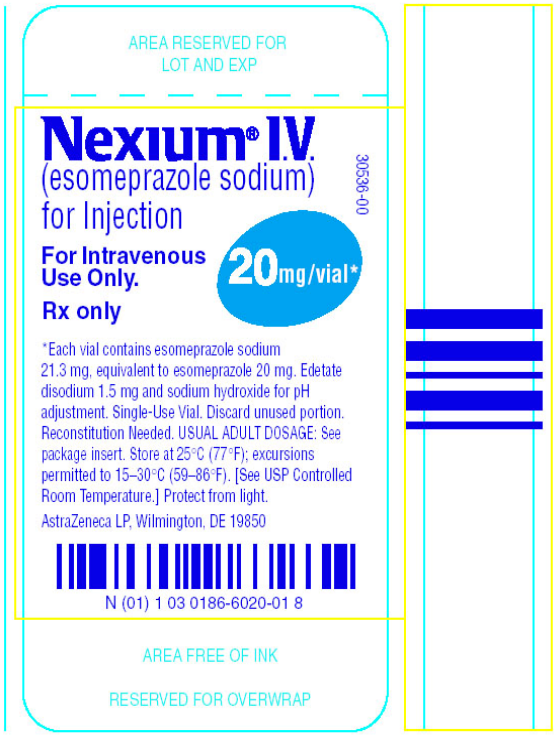
   a. Relocate the last subsection "Intravenous Infusion (20 or 40 mg) over 10 to 30 minutes" to the GERD subsection under the first paragraph describing preparation and administration of intravenous injection for no less than 3 minutes. As currently presented, this subsection is located in the section describing preparation and administration of Nexium I.V. for the new, proposed indication of (b) (4) risk reduction of rebleeding of gastric and duodenal ulcers, which is confusing and misleading since the subsection refers to the GERD indication.

   b. The name of the subheading (b) (4) in Section 2.3 (b) (4) is inconsistent with the wording for the proposed indication used throughout the remainder of the package inert labeling, which is confusing. Thus, revise this subheading to read (b) (4) Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers".

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix A: Container Labels of Lantus and Nexium I.V.





Appendix B: Nexium I.V. Case Number Listings

4108943	6458600	7177565	7373379	7418672	7627791
4112405	6624978	7190995	7373472	7421437	7627823
4115980	6983403	7239154	7374150	7596938	7628134
5864090	6983585	7252740	7374540	7466188	7630745
5917121	6989961	7295463	7374744	7611694	7638207
6128644	7050841	7322957	7374902	7632694	7674272
6245211	7131366	7372479	7375280	7627032	7305505
6373528	7146456	7372852	7375282	7627406	
6410985	7153499	7372853	7241090	7627627	

Appendix C: Protonix I.V. Case Number Listings

3724853	3887948	5935986	6704222	7352077	7598598
3735445	3945264	6044811	6647930	7321502	7624705
3782025	3952721	6044814	6724870	7359753	7645809
3782048	4004491	6044820	6899665	7386841	7657671
3812491	5966991	6089552	6925574	7458747	6893766
3810824	4221601	6097575	6920501	7535654	7650922
3825896	5727236	6239249	7012528	7579210	
3880977	5787030	6369949	7023893	7606974	
3884217	5846265	6538278	7219303	7598546	

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

/s/

YELENA L MASLOV
02/14/2011

ZACHARY A OLESZCZUK
02/14/2011

KELLIE A TAYLOR
02/14/2011

CAROL A HOLQUIST
02/15/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 28, 2011
To:	Donna Griebel, MD, Director Division of Gastroenterology Products Office of New Drugs, CDER
Through:	Solomon Iyasu, MD, MPH, Director Division of Epidemiology Office of Surveillance and Epidemiology, CDER
	Diane K. Wysowski, PhD, MPH, Acting Team Leader Division of Epidemiology Office of Surveillance and Epidemiology, CDER
From:	Julia Ju, PharmD, PhD, Pharmacoepidemiologist
	Patty Greene, PharmD, Drug Utilization Data Analyst
	Esther Zhou, MD, PhD, Epidemiologist Division of Epidemiology Office of Surveillance and Epidemiology, CDER
Subject:	Review of sponsor's epidemiology analysis titled "Upper GI bleeding in the US pediatric population: analysis and results" in support of their request for waiver of pediatric studies
Drug Name(s):	Nexium (esomeprazole magnesium) IV
Submission Number:	
Application Type/Number:	NDA 21-689
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2010-2688

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY

The Division of Gastroenterology Products (DGP) requested that the Division of Epidemiology (DEPI), Office of Surveillance and Epidemiology (OSE), review the sponsor's report titled "Upper GI bleeding in the US pediatric population: analysis and results" in support of the sponsor's request for a waiver of pediatric studies. The sponsor obtained estimates of the annual number of pediatric patients (age 0 through 17 years) diagnosed with peptic ulcer bleeding (PUB) to support this request.

The specific questions requested by DGP and addressed in this review were:
1) "Is there drug use and marketing data that supports the sponsor's argument? "
2) "Are the sponsor's epidemiology analysis and conclusion valid? "

From the sponsor's analyses using the Premier Perspective database, the projected annual numbers of pediatric patients hospitalized for PUB in the U.S. during 2004 through 2008 ranged from:

- (b) (4) to (b) (4) when only the primary (first-listed) discharge diagnosis was used
- (b) (4) to (b) (4) when all discharge diagnoses were used

From the sponsor's analyses using the MarketScan database which includes both inpatient and outpatient claims, the projected annual number of pediatric patients with PUB in the U.S. in 2008 was:

- (b) (4) among commercially insured pediatric patients
- (b) (4) among the general pediatric population (The sponsor assumed that the individuals with employer-sponsored health insurance coverage and those without such health insurance have a similar incidence of pediatric PUB)

The sponsor concluded that the total number of pediatric patients treated in U.S. hospitals for PUB is no more than (b) (4) per year.

To verify the estimates provided by the sponsor, the DEPI reviewers used the SDI inpatient healthcare utilization system database, the National Inpatient Sample (NIS) of the HealthCare Cost and Utilization Project (HCUP), and the National Hospital Discharge Survey (NHDS), to estimate the annual number of hospitalized pediatric patients with PUB in the U.S in comparison to the estimates provided by the sponsor.

Results from the SDI inpatient data showed that the projected annual number of hospitalized pediatric patients with PUB in the U.S. during 2005 through 2009 ranged from:

- (b) (4) to (b) (4) when only the primary discharge diagnosis was used
- (b) (4) to (b) (4) when all discharge diagnoses were used

When upper GI ulcer codes were added to the list of PUB codes to obtain a more conservative estimate of the annual number of hospitalized patients who might have PUB, the numbers ranged from

- (b) (4) to (b) (4) when only the primary discharge diagnosis was used
- (b) (4) to (b) (4) when all discharge diagnoses were used

Results from the HCUP data showed that the national hospital discharges with pediatric PUB were consistent with the estimates from the SDI data. Similarly, results from the NHDS data showed that the projected average annual number of hospitalized pediatric PUB during 2005 through 2008 was:

- (b) (4) when only PUB codes were used in all discharge diagnoses
- (b) (4) when both PUB and upper GI ulcer codes were used in all discharge diagnoses

Results from the DEPI's analyses of three different databases showed that the annual number of hospitalized pediatric patients with discharge diagnoses of PUB in the U.S. is likely to be no more than (b) (4), based on the conservative estimates from the SDI inpatient data when both PUB and upper GI ulcer codes were used in all discharge diagnoses. Since PUB usually requires inpatient treatment, the estimated number of hospitalized pediatric PUB is expected to be similar to the total number of pediatric PUB in the general pediatric population in the U.S. This conservative estimate of (b) (4) is very close to the high end estimate of (b) (4) from the sponsor's analyses.

In conclusion, the sponsor's projected estimates of the annual number of pediatric patients with PUB in the U.S. using the Premier and the MarketScan data were similar to those of DEPI's using three different databases. The sponsor's estimates are acceptable in considering the pediatric waiver request.

1 BACKGROUND/HISTORY

The Division of Gastroenterology Products (DGP) requested that the Division of Epidemiology (DEPI), Office of Surveillance and Epidemiology (OSE), review the sponsor's estimates of the annual number of pediatric patients with PUB in the U.S. to support their request for a waiver of pediatric studies for Nexium IV. The report titled "Upper GI bleeding in the US pediatric population: analysis and results" was reviewed.

Nexium (esomeprazole) IV is a proton pump inhibitor indicated as an alternative to oral therapy for the short-term treatment of gastroesophageal reflux disease (GERD) in patients with a history of erosive esophagitis. Oral esomeprazole is approved for use in patients 1 year of age and older for the treatment of GERD, healing of erosive esophagitis, and short-term treatment (up to 8 weeks) in pediatric patients 1-17 years old. On September 15, 2010, the sponsor submitted a request for the indication of (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute gastric or duodenal ulcer bleeding. The sponsor also submitted a waiver request to conduct pediatric studies in patients under 18 years of age based on their estimates which demonstrated a low prevalence of peptic ulcer bleeding (PUB) in this population.

2 MATERIALS REVIEWED

The sponsor's analyses titled "Upper GI bleeding in the US pediatric population: analysis and results" was reviewed. To verify the sponsor's estimates, DEPI obtained estimates of the annual number of pediatric patients with PUB using the SDI Inpatient Healthcare Utilization System data, the Healthcare Cost and Utilization Project (HCUP) data, and the National Hospital Discharge Survey (NHDS) data. The projected annual numbers of pediatric patients hospitalized with PUB were compared with the estimates provided by the sponsor. The specific questions addressed by this review were:

1) "Is there drug use and marketing data that supports the sponsor's argument?"

2) "Are the sponsor's epidemiology analysis and conclusion valid?"

3 RESULTS OF REVIEW OF SPONSOR'S ANALYSES

3.1 STUDY SYNOPSIS

AstraZeneca, the sponsor of Nexium IV, estimated the annual number of pediatric patients with PUB in the U.S. using two databases: the Premier Perspective inpatient database and the MarketScan claims database. From the Premier Perspective database, the projected annual numbers of pediatric patients hospitalized with PUB in the U.S. ranged from (b) (4) to (b) (4) during 2004 through 2008 when only the primary (first-listed) discharge diagnosis was used. The numbers were (b) (4) to (b) (4) when all discharge diagnoses were used.

From the MarketScan database which includes both inpatient and outpatient claims, the projected number of commercially insured patients with pediatric PUB was (b) (4) in 2008. The sponsor assumed that the individuals with employer-sponsored health insurance coverage and those without such health insurance have a similar incidence of pediatric PUB. Thus, the estimated total number of pediatric PUB was (b) (4) in 2008 in the U.S.

3.2 OSE COMMENTS

3.2.1 Study Objective

Study Objective:

The study objective stated in the report was to estimate the number of pediatric patients who are diagnosed with PUB each year in the U.S.

Reviewer Comments:

The reviewer agrees that the proposed study objective is appropriate to provide an estimate so that a decision can be made on whether there are a substantial number of pediatric patients with PUB to conduct pediatric studies in the U.S.

3.2.2 Study Design

Study Design:

The sponsor's analysis is a cross-sectional study to examine the annual number of pediatric patients with PUB in the U.S.

Reviewer Comments:

This reviewer agrees that the cross-sectional study design is appropriate to estimate the annual number of pediatric patients with PUB in the U.S.

3.2.3 Data Sources

Data Sources Used in the Sponsor's Analyses:

The sponsor's analyses used the Premier Perspective inpatient database (2004-2008) and the MarketScan Commercial claims and encounters database (2008). The Premier database is one of the nation's largest inpatient drug utilization and discharge databases providing patient level data that can be projected to the national hospitalized patient population. The MarketScan data contains both inpatient and outpatient claims for patients with commercial health plans. The healthcare information in the MarketScan database is from 125 large employers and 13 additional health plans across the U.S. The 2008 data covered (b) (4) patients. Among them, (b) (4) were 0 through17 years of age, accounting for (b) (4)% of the total pediatric population of (b) (4) million in the U.S.Estimates from this database can be projected to the national commercially insured population using the MarketScan National Weights.

Reviewer Comments:

This reviewer agrees that estimates from an inpatient database provide reasonable reflection of the annual number of pediatric patients with PUB since PUB usually requires inpatient treatment. However, the ***Premier*** data may not be representative of hospitalized pediatric patients in the U.S. The Premier database is a large hospital drug utilization and financial database. Information is available from over (b) (4) acute care and pediatric facilities and includes approximately (b) (4) million inpatient records. On an annual basis, this constitutes roughly (b) (4) out of every (b) (4) inpatient discharges in the United States.[1] The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and are not necessarily representative of all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, bed size, population served, payers and

teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.[2] Although Premier Network hospitals appear representative of all U.S. acute short stay hospitals in general, it is not clear whether they are representative of pediatric inpatient care in the U.S.

The ***MarketScan*** data can be used to support the estimates from the Premier data. MarketScan data provided estimated number of pediatric patients with PUB based on both inpatient and outpatient claims. Since the indication being investigated for Nexium IV is (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding peptic ulcers", the estimates based on inpatient and outpatient claims are expected to be less relevant than estimates based only on inpatient claims.

3.2.4 Study Time Period

Study Time Period:

The Premier data from January 1, 2004 to December 31, 2008, and the MarketScan data from January 1, 2008 to December 31, 2008 were used in the analyses.

Reviewer Comments:

This reviewer agrees that the analyses with the study time of 2004 through 2008 can provide a reflection of the trend of pediatric PUB diagnoses in the U.S in recent years.

3.2.5 Study Population

Study Population:

All children from 0 up to 17 years of age, inclusive, who were discharged from hospitals between 1/1/2004 and 12/31/2008 were included in the analysis of the Premier data. All infants less than 1 year of age regardless of length of enrollment, and children from age 1

through 17 years who were continuously enrolled in a MarketScan covered insurance plan for the entire 2008 calendar year were included in the MarketScan analysis.

Reviewer Comments:

The inclusion criteria for children 1 to 17 years of age with continuous enrollment for the entire 2008 calendar year in the MarketScan data analysis may cause underestimation of the number of pediatric patients with PUB. Newly enrolled patients with PUB without continuous enrollment for the entire 2008 calendar year and those PUB patients who died before 12/31/2008 were not captured in the analysis. Although the number of such patients were not provided, the number is likely to be small.

3.2.6 Disease Outcome of Interest

Disease Outcome of Interest:

The patient population of interest in this analysis is pediatric PUB. The following ICD 9-CM codes were used to identify relevant patients: gastric ulcer with bleed/perforation (531.0x, 531.1x, 531.2x, 531.4x, 531.5x, 531.6x), duodenal ulcer with bleed/perforation (532.0x, 532.1x, 532.2x, 532.4x, 532.5x, 532.6x), gastrojejunal ulcer with bleed/perforation (534.0x, 534.1x, 534.2x, 534.4x, 534.5x, 534.6x), peptic ulcer with bleed/perforation (533.0x, 533.1x, 533.2x, 533.4x, 533.5x, 533.6x), and esophageal ulcer with bleed (530.21).

Reviewer Comments:

This reviewer agrees that the diagnoses above were appropriate to identify pediatric PUB patients. These ICD 9-CM codes were checked and were consistent with the ICD 9-CM manual.

3.2.7 Analyses

Sponsor's Analyses:

The analysis with the Premier data projected the number of hospitalized pediatric PUB patients within the database to the total U.S hospitalized pediatric population using hospital-specific projection weights. Those weights are based on geographic region, urban/rural location, teaching status, hospital ownership, and bed size.

The analysis with the MarketScan data projected the number of pediatric PUB patients in the database to the pediatric population with employer-sponsored health insurance coverage using the MarketScan National Weights. The rate of pediatric PUB was estimated by dividing the projected number of pediatric patients with PUB who had employer-sponsored health insurance coverage by the total projected number of the insured pediatric population in 2008. Under the assumption that individuals who have and don't have employer-sponsored health insurance coverage have a similar rate of pediatric PUB, the sponsor's analysis calculated the total number of pediatric PUB patients in the U.S in 2008 by multiplying the estimated rate for patients with employer-sponsored health insurance coverage with the total number of people 0 through 17 years in the U.S in 2008.

Reviewer Comments:

The assumption that individuals with or without employer-sponsored health insurance coverage have a similar incidence of pediatric PUB may not be true. Instead, the incidence of PUB may be higher in those without employer-sponsored health insurance coverage since many of the independent risk factors of PUB in adults (e.g. previous peptic ulcer, diabetes, heart failure, current smoking) are associated with lower socioeconomic status[3]. Therefore, the total number of pediatric patients with PUB in the U.S. may be underestimated when assuming the rate of PUB is similar in insured and uninsured pediatric patients.

3.2.8 Study Results

Study Results:

From the Premier Perspective database, the projected numbers of pediatric patients hospitalized with PUB per year ranged from (b) (4) to (b) (4) during 2004 to 2008 when only the primary discharge diagnosis was used. These numbers were (b) (4) to (b) (4) when all discharge diagnoses were used.

From the MarketScan database which includes both inpatient and outpatient claims, the projected number of commercially insured pediatric patients with PUB was (b) (4) in 2008. The sponsor assumed that the individuals with employer-sponsored health

insurance coverage and those without such health insurance have a similar incidence of pediatric PUB and estimated that the total number of pediatric patients with diagnoses of PUB was (b) (4) in 2008 in the U.S.

Reviewer Comments:

As mentioned in the Reviewer's Comments sections of Study Population and Study Analyses, the estimated total number of pediatric PUB in the U.S. may be under-estimated. Newly enrolled patients with PUB and those PUB patients who died before 12/31/2008 were not captured because they did not meet the inclusion criteria of continuous enrollment for the entire 2008 calendar year to be included in the MarketScan data analysis. Another source of under-estimation is introduced by the assumption that individuals with or without employer-sponsored health insurance coverage have similar incidence of pediatric PUB. In reality, those without employer-sponsored health insurance coverage may have higher incidence of PUB.

4 ESTIMATES OF PEDIATRIC PUB FROM DATABASES ACCESSED BY DEPI

To verify the estimates provided by the sponsor, the DEPI reviewers used the SDI inpatient healthcare utilization system database, the NIS of the HCUP, and the NHDS, to estimate the annual number of hospitalized pediatric patients with PUB in the U.S. Each of the databases was described in Section 4.1 and the results were provided in Section 4.2.

4.1 DESCRIPTION OF DATABASES USED IN DEPI'S ANALYSES

*The **SDI's Inpatient HealthCare Utilization System*** provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. This robust data set includes more than (b) (4) hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include over (b) (4) million annual hospital inpatient encounters and ove (b) (4) million annual hospital outpatient encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their

associated hospital emergency departments. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. SDI's datasets are geographically representative, and unlike the Premier and MarketScan data, include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The SDI Hospital sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals, and does not necessarily represent all acute care hospitals in the U.S. in all markets. However, validations of SDI's Hospital data using both the National Hospital Discharge Survey (NHDS) and the HCUP data have shown SDI's patient level data to be representative and accurate across multiple therapeutic areas (provided by the SDI in the description of the SDI Inpatient HealthCare Utilization System).

The second database used to verify the sponsor's estimates, the ***NIS*** is part of the ***HCUP***, sponsored by the U.S. Agency for Healthcare Research and Quality (AHRQ)[4]. The NIS is the largest all-payer inpatient care database that is publicly available in the United States, containing data from 5 to 8 million hospital stays from about 1,000 hospitals sampled to approximate a 20-percent stratified sample of U.S. community hospitals. The NIS is drawn from those States participating in HCUP, which for 2008, comprise 95 percent of the U.S. population. Weights are provided to calculate national estimates. The NIS is the only national hospital database with charge information on all patients, regardless of payer, including persons covered by Medicare, Medicaid, private insurance, and the uninsured. The large sample size of NIS enables analyses of rare conditions, such as pediatric PUB, and special patient populations, such as the uninsured.

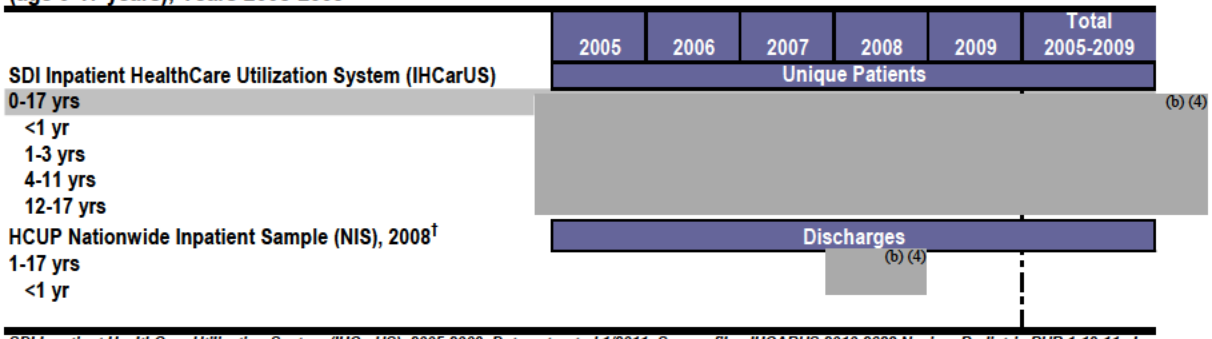
The ***NHDS*** is an annual national probability sample survey of discharges from non-federal, general and short-stay hospitals in the U.S. to collect information on inpatient care. Public data is available for the years 1965-2008. Up to 7 listed diagnoses and up to 4 listed procedures codes are available for each patient discharge. From 1988-2007 the NHDS collected data from a sample of approximately 270,000 inpatient records acquired

from a national sample of about 500 hospitals. Beginning in 2008 the number of hospitals was reduced to 239.[5] Because the data are obtained from a national probability sample, the data are considered to be a national representative sample of hospital discharges in the U.S.

4.2 DEPI's Study Results

The DEPI's analyses using the SDI inpatient data showed that the projected annual number of hospitalized pediatric patients with PUB ranged from (b) (4) to (b) (4) during 2005 through 2009 when only the primary discharge diagnosis was used (Table 1). The numbers were (b) (4) to (b) (4) when all discharge diagnoses were used (Table 2). When upper GI ulcer codes were added to the list of PUB codes to get a more conservative estimate of the number of pediatric patients who might have PUB, the annual numbers were from (b) (4) to (b) (4) when only the primary discharge diagnosis was used (Table 3) and from (b) (4) to (b) (4) when all discharge diagnoses were used (Table 4) during 2005 through 2009.

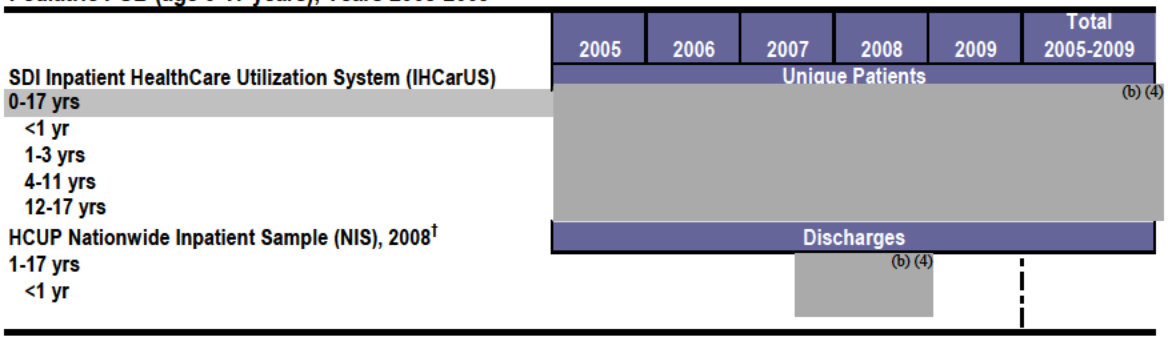
Table 1. US projected number of hospitalized patients with primary discharge diagnosis of Pediatric PUB (age 0-17 years), Years 2005-2009



SDI Inpatient HealthCare Utilization System (IHCarUS), 2005-2009. Data extracted 1/2011. Source file: IHCARUS 2010-2688 Nexium Pediatric PUB 1-19-11.xls

†*Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2008, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = (b) (4) tatistics based on 10 or fewer weighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).*

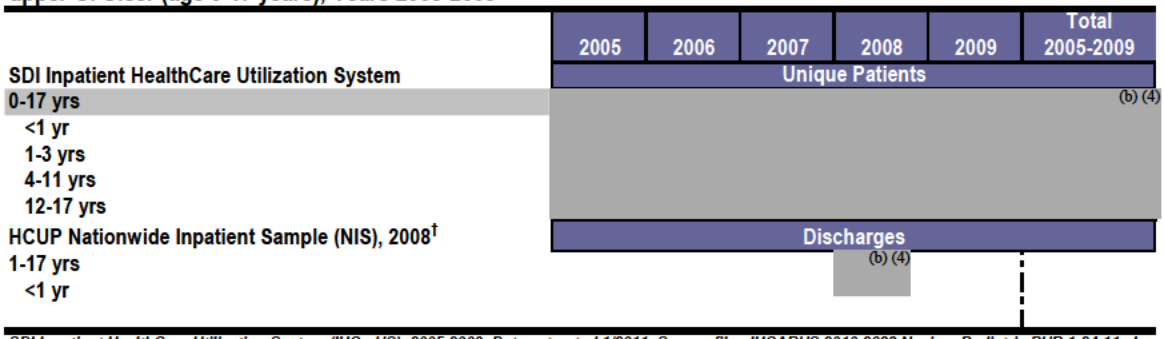
Table 2. US projected number of hospitalized patients with primary and secondary discharge diagnoses of Pediatric PUB (age 0-17 years), Years 2005-2009



SDI Inpatient HealthCare Utilization System (IHCarUS), 2005-2009. Data extracted 1/2011. Source file: IHCARUS 2010-2688 Nexium Pediatric PUB 1-19-11.xls

†Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2008, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = (b) (4) *Statistics based on 10 or fewer weighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).*

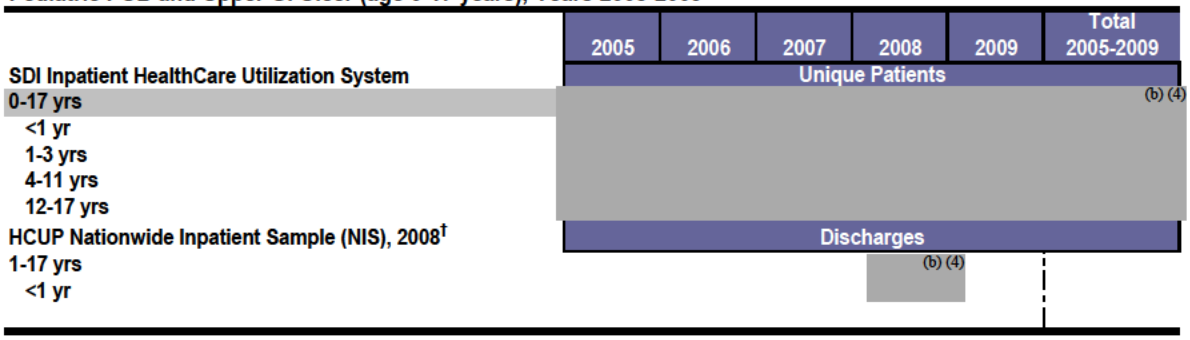
Table 3. US projected number of hospitalized patients with primary discharge diagnosis of Pediatric PUB and upper GI Ulcer (age 0-17 years), Years 2005-2009



SDI Inpatient HealthCare Utilization System (IHCarUS), 2005-2009. Data extracted 1/2011. Source file: IHCARUS 2010-2688 Nexium Pediatric PUB 1-24-11.xls

†Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2008, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = (b) (4) *Statistics based on 10 or fewer weighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).*

Table 4. US projected number of hospitalized patients with primary and secondary discharge diagnoses of Pediatric PUB and Upper GI Ulcer (age 0-17 years), Years 2005-2009



SDI Inpatient HealthCare Utilization System (IHCarUS), 2005-2009. Data extracted 1/2011. Source file: IHCARUS 2010-2688 Nexium Pediatric PUB 1-24-11.xls

†Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2008, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = (b) (4) *Statistics based on 10 or fewer weighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).*

The annual number of hospitalized pediatric PUB patients was also estimated from the NHDS data using all discharge diagnoses. The results are shown in Table 5. The annual number of pediatric PUB was too small to obtain stable weighted estimates (the NHDS data require crude cell counts of more than 30 for national projections). For the calendar year 2008, the crude count of pediatric PUB was less than 30. To overcome the restriction of crude count of 30 or more, four years of data (2005 through 2008) were combined to get a projected average annual number (b) (4) of hospital discharges in 0 through 17 years old patients with PUB. The estimated average annual number of hospital discharges with pediatric PUB and upper GI ulcers during 2005 through 2008 was (b) (4).

Table 5. Crude count and projected number of hospitalized pediatric PUB using the NHDS data, 2005 through 2008

	Pediatric PUB		Pediatric PUB and Upper GI Ulcers	
YEAR	Frequency*	Weighted-Frequency**	Frequency*	Weighted-Frequency**
2005-08	(b) (4)			

* Cumulative number of hospitalizations from year 2005-2008

** Projected **average annual number** of hospitalizations for year 2005-2008

5 DISCUSSION

The projected annual number of hospitalized pediatric patients with diagnoses of PUB in the U.S. during 2004 through 2008 based on the SDI inpatient data ranged from (b) (4) to (b) (4) when only the primary discharge diagnosis was used, and from (b) (4) when all discharge diagnoses were used. These numbers are slightly higher than the numbers provided by the sponsor ((b) (4) when only the primary discharge diagnosis was used; (b) (4) when all discharge diagnoses were used). When both PUB codes and upper GI ulcer codes were used to obtain more conservative estimates of pediatric patients who may have PUB based on the SDI inpatient data, the annual numbers ranged from (b) (4) to (b) (4) when only the primary discharge diagnosis was used, and from (b) (4) to (b) (4) when all discharge diagnoses were used. The (b) (4) number is close to the high end estimate of (b) (4) in the sponsor's analysis using the MarketScan data in which both inpatient and

outpatient diagnoses of PUB were counted. The projected annual number of hospitalizations for pediatric PUB based on the HCUP data is consistent with the estimates from the SDI inpatient data.

Based on the NHDS data, the average annual number of pediatric PUB discharges in the U.S. during 2005 through 2008 was (b) (4) when the PUB codes were used and (b) (4) when both PUB and upper GI ulcer codes were used. The (b) (4) number is within the range of (b) (4) from the SDI data when all discharge diagnoses were used for PUB. The (b) (4) number is within the range of (b) (4) from the SDI data when all discharge diagnoses were used for both PUB and upper GI ulcer codes. However, the results from the NHDS should be interpreted with caution because it provides an average annual number for year 2005 through 2008. As shown in the SDI inpatient data analyses, the annual number of pediatric PUB varied year by year.

Based on the conservative estimates from the SDI inpatient data when both PUB and upper GI ulcer codes were used in all discharge diagnoses, the annual number of pediatric patients hospitalized with PUB in the U.S. is likely to be no more than (b) (4). Since active PUB usually requires inpatient treatment, the estimated number of pediatric patients hospitalized with PUB is expected to be similar to the total number of pediatric patients with PUB in the general pediatric population in the U.S.

Of note, neither the data used in the sponsor's analyses nor those used in DEPI's analyses were validated by medical records. Because of this, the estimates provided may be overestimates of the true number since provisional diagnoses may have been included. This further supports the idea that annual number of hospitalized pediatric patients with PUB in the U.S. is likely to be no more than (b) (4).

As stated in the sponsor's report, even those with PUB would not all be indicated to receive Nexium IV for (b) (4) risk reduction of rebleeding in patients following therapeutic endoscopy for (b) (4) Therefore, the number of pediatric PUB patients who are eligible to participate in a study is very limited and would be difficult to identify and enroll in clinical trials.

6 CONCLUSIONS

In conclusion, compared to the DEPI's results, the sponsor's estimates of the annual number of pediatric patients diagnosed with PUB were generally similar. The sponsor's estimates are acceptable in considering the pediatric waiver request.

7 REFERENCES

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