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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s) Farrokh Sohrabi, M.D.
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Established Name Esomeprazole magnesium
(Proposed) Trade Name Nexium 24HR
Therapeutic Class Proton pump inhibitor
Applicant AstraZeneca

Formulation(s) Delayed-release capsule
Dosing Regimen 20 mg once daily for 14 days (14-day course may be repeated every 4 months)

Indication(s) Treatment of frequent heartburn
(occurs 2 or more days per week)
Intended Population(s) Adults (≥18 years old)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical efficacy standpoint, this reviewer recommends that esomeprazole magnesium delayed release capsules (20 mg) for over the counter (OTC) use be approved at a dosage of 20 mg per day for 14 days for the relief of frequent heartburn (occurring two or more days a week) in adults 18 years and older pending the clinical safety findings and revisions to the proposed labeling. The information in this submission provides substantial evidence to support the proposed indication, and there are data to provide adequate directions for use.

This reviewer's recommendation is contingent upon the findings of other reviewers that include the pharmacology reviewer and clinical reviewer from the Division of Nonprescription Clinical Evaluation (DNCE), the statistics reviewer from the Office of Biostatistics (OB), and the reviewers from the Office of New Drug Quality Assessment (ONDQA).

1.2 Risk Benefit Assessment

Esomeprazole magnesium 20 mg has been prescribed by physicians in the United States since 2001. There are extensive efficacy data for esomeprazole magnesium for the treatment of heartburn in NDA 21-153 for prescription esomeprazole magnesium. In addition, the efficacy results in this submission demonstrate the efficacy of esomeprazole magnesium 20 mg for the treatment of frequent heartburn (occurring two or more days a week) in adults (≥ 18 years of age); treatment is for 14 days and a 14-day course may be repeated (if needed) every 4 months. No major safety signals emerged from the clinical trials in this submission [see review performed by Dr. Jane Filie in DNCE under the same NDA (NDA 204-655)]. Therefore, given the combined evidence of efficacy for the treatment of frequent heartburn and the lack of major new safety signals in the clinical trials submitted to NDA 204-655, the use of esomeprazole magnesium for OTC use over a 14-day course is warranted.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended for this NDA.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements or commitments are recommended for this NDA.

Pediatrics

The safety and effectiveness of esomeprazole magnesium 20 mg (or any other proton pump inhibitor) for OTC use for the indication of frequent heartburn have not been established for pediatric patients. Pediatric gastroenterologists recommend that children with symptoms of heartburn should be under the direction of a healthcare provider.¹ Children differ from adults with regard to how much physiologic reflux, or asymptomatic episodes of acid reflux, is normal.^{1,2} In the pediatric population, heartburn may be caused by diseases other than gastroesophageal reflux. The complications of gastroesophageal reflux (e.g., esophagitis), and/or other causes of chest pain (e.g., cardiac and respiratory etiologies), may be serious clinical conditions. Furthermore, symptom reporting in the pediatric age groups may not be reliable depending on the reporter.²

Accordingly, the Sponsor is requesting a full waiver for pediatric studies for all pediatric age groups required under the Pediatric Research Equity Act (PREA) for the indication of frequent heartburn. Granting this waiver would be consistent with the Agency's decision to waive pediatric studies for other drugs in the same class and marketed for the same proposed indication (e.g., OTC lansoprazole, OTC omeprazole). The Pediatric Review Committee (PeRC) PREA subcommittee meeting was held on January 22, 2014. The PeRC agreed with a full waiver because the product would be ineffective and/or unsafe for pediatric patients (a learned intermediary is needed).

2 Introduction and Regulatory Background

2.1 Product Information

Nexium (esomeprazole magnesium) is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. Esomeprazole is the S-enantiomer of omeprazole.

For oral use, Nexium is currently available as delayed-release capsules (20 mg, 40 mg) and as granules for delayed release oral suspension (2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg). Subjects in the studies submitted in support of the current NDA received Nexium delayed release capsules at a dosage of 20 mg once daily over 14 days.

¹ Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. G Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49(4):498-547.

² Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol.* 2009;104(5):1278-1295.

2.2 Currently Available Treatments for Proposed Indications

There are other currently available medical treatments for the Sponsor's proposed OTC indication of frequent heartburn. These include the OTC PPIs omeprazole magnesium (Prilosec OTC), omeprazole delayed release tablets, omeprazole/sodium bicarbonate (Zegerid OTC), and lansoprazole (Prevacid 24HR). Omeprazole OTC and lansoprazole OTC are currently marketed for use in adults 18 years of age and older, used once a day for 14 days; this treatment course maybe repeated every 4 months if necessary.

There are other OTC products available for the treatment of other acid-related gastrointestinal disorders such as episodic heartburn. These include H₂-receptor antagonists (e.g., ranitidine, cimetidine, famotidine, and nizatidine), and antacids (e.g., aluminum and/or magnesium hydroxide, calcium bicarbonate, and sodium bicarbonate).

2.3 Availability of Proposed Active Ingredient in the United States

Nexium (esomeprazole magnesium) is available in the U.S. as a prescription drug for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD) in adult and pediatric patients. Additional indications include risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. For details of approved indications, see current product labeling. Nexium is marketed by AstraZeneca (AZ).

[Table 1](#) outlines the regulatory history pertaining to the approval of Nexium for various formulations, populations, and indications.

Table 1. Overview of Nexium Regulatory History

| Date | Application | Population | Approved Indication(s) |
|--------------|------------------|--|---|
| Feb 20, 2001 | NDA 21-153 | Adults | <u>Delayed-Release Capsules (20 mg, 40 mg)</u> • Healing of EE • Maintenance of healing of EE • Treatment of symptomatic GERD |
| Feb 20, 2001 | NDA 21-154 | Adults | • <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence (joint action with the Division of Special Pathogens) |
| Nov 22, 2004 | NDA 21-153/S-019 | Adults | • Risk reduction of NSAID-associated gastric ulcers |
| Mar 31, 2005 | NDA 21-689 | Adults | <u>New formulation approval: I.V.</u> • Short-term treatment (up to 10 days) of GERD with EE as an alternative to oral therapy when oral Nexium is not possible or appropriate |
| Apr 28, 2006 | NDA 21-153/S-022 | Pediatric patients 12-17 years of age | • Short-term treatment of GERD |
| Oct 11, 2006 | NDA 21-153/S-023 | Adults | • Treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome |
| Oct 20, 2006 | NDA 21-957 | Adults and pediatric patients 12-17 years of age | <u>New formulation approval: Delayed-Release Oral Suspension (20 mg, 40 mg)</u> • All previously approved indications |
| Feb 27, 2008 | NDA 22-101* | Pediatric patients 1-11 years of age | <u>Delayed-Release Oral Suspension (10 mg)</u> • Short-term treatment of GERD symptoms and healing of EE |
| Jun 18, 2009 | NDA 21-957/S-004 | Infants (b) (4) 11 months | • Complete Response for treatment of GERD |
| Apr 29, 2011 | NDA 21-689/S-017 | Pediatric patients 1 month to 17 years | • Short-term treatment (up to 10 days) of GERD with EE as an alternative to oral therapy when oral Nexium is not possible or appropriate |
| Dec 15, 2011 | NDA 21-957/S-004 | 1 month to 11 months, inclusive | • Short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD |

Abbreviations: EE, erosive esophagitis; GERD, gastroesophageal reflux disease; I.V., intravenous.

* NDA 22-101 was submitted prior to the approval of NDA 21-957 (delayed-release oral suspension formulation); therefore, it was given a unique NDA number. Had the submission of NDA 22-101 occurred after the approval of NDA 21-957, it would have been a supplement to NDA 21-957.

Source: Summarized from Dr. Jessica Lee's Clinical Review of NDA 21-957 dated October 20, 2011, Section 2.3.

2.4 Important Safety Issues with Consideration to Related Drugs

PPIs are widely used and have been found to be generally safe and well-tolerated. The current Nexium labeling includes the following as warnings and precautions:

- Symptomatic response to Nexium 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 Nexium should be avoided due to the inhibition of CYP2C19 activity. CYP2C19 is necessary for the metabolism of clopidogrel to its active metabolite.
- Long-term and multiple daily dose PPI therapy may be associated with an increased risk of osteoporosis-related fractures of the hip, wrist, or spine.
- Hypomagnesemia, symptomatic and asymptomatic, has been reported in patients treated with a PPI.
- The concomitant use of St. John's Wort and rifampin with Nexium should be avoided due to the induction of CYP2C19 or CYP3A4 which can lead to decreased Nexium concentrations.
- 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.
- Concomitant use of PPIs with methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- May 16, 2011: Planned **Type B, pre-IND meeting** between DNCE, DGIEP and Sponsor to discuss the development program for Nexium OTC. In advance of the planned meeting, the Sponsor submitted a briefing package on April 4, 2011 that indicated its plans to conduct two identical, 14-day, randomized, double-blind, placebo-controlled trials with 20 mg Nexium delayed-release capsules in subjects with frequent heartburn. The Sponsor indicated that the trial design would generally follow the design that facilitated the approval of Prevacid 24HR for OTC status (NDA 22-327). In written responses dated May 13, 2011, FDA agreed that the proposed clinical study design is adequate and appears appropriate to support the OTC indication. Subsequent to receipt of written responses from FDA on May 13, 2011, the Sponsor cancelled the face-to-face meeting.
- June 2, 2011: AZ submitted the protocols for the two proposed phase 3 trials, D961RC00001 and D961RC00002, to the IND.
- January 18, 2013: Planned **Type B pre-NDA meeting** between DNCE, DGIEP and Sponsor to seek FDA guidance. In advance of the planned meeting, the Sponsor submitted a briefing package on November 26, 2012 that included a summary of the completed trials D961RC00001 and D961RC00002 and questions for FDA. Subsequent to receipt of written responses from FDA on January 15, 2013, the Sponsor cancelled the face-to-face meeting. Key comments from FDA included:

- The clinical program appears, as outlined in the briefing package, to be sufficient for filing and review.
- AZ's plan to request a waiver of the requirement for pediatric studies in patients less than 18 years of age appears reasonable.
- The Agency agrees with the approach that the NDA will include draft labeling that is based on the current approved OTC PPI labeling, with product specific information.
- AZ's proposed cut-off date of December 31, 2012 appears reasonable for data that will be presented in the Summary of Clinical Safety (Section 2.7.4), provided that the NDA is submitted within the first two quarters of 2013. Data acquired since esomeprazole approval from all postmarketing safety databases (from all formulations) should be summarized and analyzed by dose and duration of use. Data should also be analyzed according to gender, race, and age subgroups. A list of countries in which esomeprazole is marketed OTC, English translations of OTC labeling, and a list of countries in which the drug has been withdrawn for safety reasons should be included.

Interactions between the Sponsor and FDA regarding various aspects of phase 3 trial design and conduct are summarized below.

- Primary endpoint: The proposed primary endpoint of percentage of heartburn-free 24-hour days during 14 days of double-blind treatment is identical to that used in the trials that supported approval of Prevacid 24HR for OTC status.
- Secondary endpoints:
 - April 4, 2011: In its briefing package, the Sponsor proposed a minor change relative to the secondary endpoints used in the Prevacid 24HR phase 3 program. Instead of using percentage of nights without heartburn during 14 days of treatment and percentage of subjects without heartburn on day 1, the Sponsor proposed to evaluate the proportion of days with no heartburn over days 1 to 4 as a secondary endpoint. According to the Sponsor, this secondary endpoint would allow examination of potential early heartburn response and thus support the use of the following PPI class labeling (included in the Use section): "Not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect."
 - May 13, 2011: In its written responses, FDA indicated that the proposed secondary objectives appear acceptable, but asked the Sponsor to also add a secondary endpoint of the proportion of consumers who have a resolution of frequent heartburn as defined by entry criteria (less than 2 days per week).
 - May 16, 2011: In a clarification request from the Sponsor regarding responses from FDA, AZ proposed to add the proportion of subjects reporting heartburn 2 days or less during the final week of the treatment phase of the study as a secondary endpoint. The final week is defined as the consumer's last 7 days while taking study medication.

- June 9, 2011: In an Advice Letter to AZ, FDA responded that the definition of the proposed endpoint seemed reasonable. FDA requested that AZ also include a 2-week responder analysis with an endpoint of the proportion of subjects reporting heartburn two days or less during both weeks of the treatment phase of the study.
 - July 22, 2011: In an Advice Letter to AZ, FDA clarified that AZ should also analyze the proportion of subjects who achieve clinical response (i.e., report heartburn less than 2 days per week) at the end of Week 1 and at the end of Week 2 of the active treatment phase. FDA recommended that the protocol be modified to reflect this endpoint.
 - October 3, 2011: In an Advice Letter to AZ, FDA emphasized that as previously agreed, AZ agreed to add as a secondary endpoint an overall 2-week responder analysis with an endpoint of the proportion of subjects reporting heartburn 2 days or less during both week 1 and 2 of the treatment phase of the study combined. FDA asked AZ to revise the protocols as agreed.
 - December 2, 2011: AZ submitted revised study protocols (amendment #2) to include an additional secondary endpoint for overall evaluation of heartburn resolution during the 14-day randomized treatment period (both weeks 1 and 2).
- Definition of heartburn:
- April 4, 2011: In its briefing package, the Sponsor proposed using the Montreal definition of heartburn [i.e., a burning sensation in the retrosternal area (behind the breastbone)]. This definition is more current than the one used in the Prevacid 24HR phase 3 clinical program (i.e., an upward-moving, uncomfortable sensation behind the breastbone, frequently accompanied by a burning feeling).
 - May 13, 2011: In its written responses, FDA indicated that the proposed Montreal definition of heartburn appears acceptable.
 - July 22, 2011: In an Advice Letter to AZ, FDA indicated that the Montreal definition of heartburn and a definition of “daytime” and nighttime” should be provided for participants in the self-assessment daily diary.
- Self-assessment diary:
- April 4, 2011: In its briefing package, the Sponsor noted that measures of efficacy will be assessed by subject data recorded daily in an interactive voice response system (IVRS) self-assessment diary. The diary will collect information on the occurrence of overall (24-hour) heartburn to support the primary variable, as well as daytime and nighttime heartburn episodes, maximum heartburn severity, and study rescue medication consumption. Nighttime will specifically refer to the time between going to bed until the next day’s morning daily dose. Subjects will be asked to respond to the following statements each morning:
 - Rate overall heartburn severity over the past 24 hours using the following scale: 0=none; 1=mild (heartburn present but easily

tolerated); 2=moderate (heartburn sufficient to cause interference with normal daily activity or sleep); and 3=severe (incapacitating heartburn, with the subject unable to perform normal daily activities or sleep).

- Rate heartburn severity during the day (0 to 3).
- Rate heartburn severity during the night (0 to 3).
- How much Gelusil (rescue medication) have you taken over the previous 24 hours?

The Sponsor asked if the proposed daily questions for subjects were adequate to assess heartburn.

- May 13, 2011: In its written responses, FDA responded that these questions are not adequate and noted that the endpoint should assess if the consumer has an episode of heartburn in the prior 24 hours (yes/no). The analysis should be percentage of heartburn-free 24-hour days over the 14-day period. Severity could be evaluated as an exploratory endpoint but would not result in labeling claims.
 - May 16, 2011: In a clarification request from the Sponsor regarding responses from FDA, AZ indicated that it had always been AZ's intent to analyze the daily questions as a yes/no response for the primary endpoint, where a response of none is mapped as "No" and a response of Mild, Moderate, or Severe is mapped as "Yes". AZ indicated that it worded the questions this way to not bias the responders to answer "No" in order to avoid having to respond to further questions. AZ indicated that it understands that any analysis of severity will be exploratory in nature and not result in labeling claims.
 - June 9, 2011: In an Advice Letter to AZ, FDA responded that AZ's proposal seemed reasonable.
- Inclusion/exclusion criteria:
- May 13, 2011: In its written responses, FDA recommended that subjects with a history of GERD diagnosed by a physician and confirmed by endoscopy should be excluded from the study. The Sponsor's final protocol excludes subjects with a history of GERD diagnosed by a physician, but does not require endoscopic confirmation of the GERD diagnosis.
 - July 22, 2011: In an Advice Letter to AZ, FDA provided the following recommendations to AZ:
 - Study participants should not be allowed any new prescription, OTC, or herbal/nutritional therapies that may confound the outcome results. In the final protocol, the Sponsor excludes any subjects receiving "concomitant therapy which could interfere with the evaluation of heartburn treatment."
 - Clarify whether subjects who have required more than one 14-day course of treatment within the past 4 months will be excluded or if subjects who have had a 14-day course of treatment for heartburn

- ≥3 times within the past year will be excluded. In the final protocol, the Sponsor has listed both of these situations as exclusion criteria.
- Subjects currently taking greater than the standard approved PPI doses for any GERD indication (e.g., BID dosing) (Item 7) could be deleted from the exclusion criteria as it is redundant with Item 5. In the final protocol, the Sponsor has removed Item 7.
 - Item 8: Iron salts and digoxin should be added to the list of excluded concomitant medications. In the final protocol, the Sponsor has made the recommended revisions.
 - Item 10: “Clinically significant and/or unstable renal or hepatic disease” may be deleted. The prescription label states that the pharmacokinetics of esomeprazole in subjects with renal impairment is not expected to be altered relative to healthy volunteers, and in subjects with severe hepatic insufficiency, a dose not exceeding 20 mg once daily is recommended. In the final protocol, the Sponsor has made the recommended revisions.
- Other elements of study design:
- April 4, 2011: In its briefing package, the Sponsor asked if FDA had any comments concerning any elements of the study design.
 - May 13, 2011: In its written responses, FDA noted that the proposed Nexium OTC label directs consumers to “swallow one capsule before eating in the morning”; however in the proposed efficacy trials, volunteers are directed to take Nexium [REDACTED] ^{(b) (4)}. FDA noted that the proposed efficacy trials should support the labeling of the proposed OTC product. For example, the directions for use in the label (for OTC marketing) should reflect the way the product was taken in the clinical efficacy trials. FDA noted that a Label Comprehension (LC) study is not needed unless portions of the label are significantly different from the approved OTC PPI label. FDA also noted that an Actual Use study would not be needed for the proposed product if the label does not present new elements that might impact consumer use.
 - October 3, 2011: In an Advice Letter to AZ, FDA asked AZ to clarify if the placebo run-in period is considered to be the first week of treatment. If not, then AZ should distinguish between the “final week of treatment” and the “second week of treatment” On December 2, 2011, AZ submitted revised study protocols (amendment #2) clarifying the parameters of the treatment periods being evaluated and analyzed.

Reviewer comments: *Based on this medical officer’s review of the recent relevant regulatory history, it appears that the Sponsor has addressed adequately the Agency’s pre-submission recommendations and concerns regarding general study design, inclusion/exclusion criteria, and efficacy endpoints. The Sponsor’s final protocol excludes subjects with a history of GERD diagnosed by a physician, but does not require endoscopic confirmation of the GERD diagnosis. Thus, the Sponsor’s definition*

of GERD for this exclusion criterion is less stringent than the definition recommended by FDA. In this medical officer's assessment, however, the overall enrolled population represented appropriately the intended use population of adults with frequent heartburn.

2.6 Other Relevant Background Information

The Sponsor developed Nexium for partial OTC switch under IND 111,185.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Methods used to evaluate data quality and integrity included:

- Review of possible bias based on financial ties
- Seeking source documentation for efficacy analyses
- Review of Sponsor's compliance with Good Clinical Practices
- Advanced Methods for Risk-based Prioritization of Clinical Trial Inspections Site Selection Tool version 2.4 (March 27, 2013)

The Sponsor submitted the application in electronic modular format. The application was generally well organized and navigable.

3.2 Compliance with Good Clinical Practices

According to the Sponsor, all of the trials were conducted in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). Per the Sponsor, the two trials submitted for this NDA were conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonisation, and the FDA.

A request for Office of Scientific Investigations (OSI) audit was not placed for this NDA. A review of the study protocols, clinical study reports, summary of clinical efficacy, summary of clinical safety, and Advanced Methods for Risk-based Prioritization of Clinical Trial Inspections Site Selection Tool (reviewed in conjunction with OSI) did not generate any findings about the clinical sites that, in this medical officer's assessment, warranted inspection.

3.3 Financial Disclosures

The Sponsor provided a signed copy of FDA Form 3454 certifying that it has not entered into any financial arrangements with its clinical investigators, whereby the value

of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts. See [Appendix 4: Clinical Investigator Financial Disclosure](#) for additional details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The active substance for OTC Nexium is esomeprazole (20 mg) and under NDA 21-153, this was approved for prescription use. The Sponsor references NDA 21-153 for the CMC information. Please refer to the reviews by ONDQA for further details.

4.2 Clinical Microbiology

See review by Dr. Stephen Langille, dated November 8, 2013. Briefly, per Dr. Langille's review, the Sponsor submitted information regarding the conversion of a previously approved prescription version of esomeprazole magnesium delayed-release capsules to an OTC version. Dr. Langille identified no microbiology deficiencies based upon the information provided.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were submitted with this NDA. The animal data and toxicology studies were referenced from NDA 21-153 that had already been submitted and approved by FDA. See review by the pharmacology reviewer from DNCE.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Esomeprazole is a PPI that inhibits gastric acid secretion through irreversible inhibition of the H⁺/K⁺ ATPase in the gastric parietal cell.

4.4.2 Pharmacodynamics

No new pharmacodynamics studies were submitted as part of this NDA.

4.4.3 Pharmacokinetics

No new pharmacokinetics studies were submitted as part of this NDA.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The efficacy of esomeprazole 20 mg per day over a 14-day course for the treatment of frequent heartburn was evaluated in two clinical efficacy trials, D961RC00001 and D961RC00002. Hereafter, Study D961RC00001 will be referred to as Study 1 and Study D961RC00002 will be referred to as Study 2. A total of 681 subjects were randomized into these placebo-controlled, randomized studies. The primary efficacy endpoint in Study 1 and Study 2 was the percentage of heartburn-free 24-hour days during 14 days of placebo-controlled, double-blind treatment. [Table 2](#) provides an overview of the clinical trials included in this NDA submission.

Table 2. Overview of Phase 3 Clinical Studies Submitted to Support NDA

| Parameters | Study D961RC00001 (Study 1) | Study D961RC00002 (Study 2) |
|---------------------------------|---|---|
| No. Trial Sites | 10 (U.S.) | 10 (U.S.) |
| No. Subjects Randomized/Treated | 340/331 | 341/326 |
| Objective | Efficacy/safety in subjects with frequent heartburn | Efficacy/safety in subjects with frequent heartburn |
| Trial Design | Multicenter, double-blind, randomized, parallel group, placebo-controlled study in a population of patients with frequent heartburn (≥ 2 episodes per week) | Multicenter, double-blind, randomized, parallel group, placebo-controlled study in a population of patients with frequent heartburn (≥ 2 episodes per week) |
| Treatment | <p>7-day placebo run-in period</p> <p>↓</p> <p>Randomized 1:1 to esomeprazole 20 mg or placebo (orally before eating in the morning)</p> <p>↓</p> <p>14-day double-blind treatment period</p> <p>↓</p> <p>7-day placebo follow-up period</p> | <p>7-day placebo run-in period</p> <p>↓</p> <p>Randomized 1:1 to esomeprazole 20 mg or placebo (orally before eating in the morning)</p> <p>↓</p> <p>14-day double-blind treatment period</p> <p>↓</p> <p>7-day placebo follow-up period</p> |
| Efficacy Endpoints | <ul style="list-style-type: none"> • <i>Primary:</i> proportion of days with no heartburn over 14 days • <i>Secondary:</i> <ol style="list-style-type: none"> a) Proportion of subjects reporting heartburn 2 days or less during the 14-day randomized period (both Weeks 1 and 2) b) Proportion of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase c) Proportion of subjects with heartburn 1 day or less during the final week of treatment d) Proportion of subjects with heartburn 1 day or less during the second week of treatment e) Proportion of subjects with heartburn 1 day or less during the first week of treatment | <ul style="list-style-type: none"> • <i>Primary:</i> proportion of days with no heartburn over 14 days • <i>Secondary:</i> <ol style="list-style-type: none"> a) Proportion of subjects reporting heartburn 2 days or less during the 14-day randomized period (both Weeks 1 and 2) b) Proportion of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase c) Proportion of subjects with heartburn 1 day or less during the final week of treatment d) Proportion of subjects with heartburn 1 day or less during the second week of treatment e) Proportion of subjects with heartburn 1 day or less during the first week of treatment |

Source: Reviewer's table, derived from CSRs and Summary of Clinical Efficacy.

5.2 Review Strategy

This review will evaluate the efficacy of esomeprazole 20 mg for OTC use by reviewing the efficacy data obtained through the two trials as submitted by the Sponsor. Dr. Wen

Jen Chen is the statistical reviewer for this NDA. Dr. Jane Filie, Medical Officer, DNCE, is the clinical reviewer of the safety information in this NDA.

5.3 Discussion of Individual Studies/Clinical Trials

Two phase 3, multicenter (U.S. sites), randomized, double-blind, placebo-controlled, parallel group efficacy and safety trials of identical design were conducted, comprising a total of 681 randomized subjects. Each trial consisted of a 14-day screening and washout period, a 7-day single-blind placebo run-in period, a double-blind treatment period of 14 days, and a 7-day single-blind placebo follow-up period.

Key inclusion criteria included the following:

- Presence of heartburn ≥ 2 days a week over the preceding 4 weeks
- Discontinuation of antacids, H₂ receptor antagonists (H₂RAs), and/or PPI treatment prior to the start of the run-in period (washout period of ≥ 1 day for antacids and ≥ 7 days for H₂RAs and/or PPIs)

Key exclusion criteria included the following:

- History of GERD diagnosed by a physician
- History of erosive esophagitis verified by endoscopy
- History of pathologic intraesophageal pH monitoring
- Use of any medication prescribed for GERD
- More than one 14-day course of PPI treatment within the past 4 months
- 14-day course of PPI treatment for heartburn ≥ 3 times within the past year

Reviewer comments: *In written responses dated May 13, 2011, FDA recommended that subjects with a history of GERD diagnosed by a physician and confirmed by endoscopy should be excluded from the study. The Sponsor's final protocol excludes subjects with a history of GERD diagnosed by a physician, but does not require endoscopic confirmation of the GERD diagnosis. Thus, the Sponsor's definition of GERD for this exclusion criterion is somewhat less stringent than the definition recommended by FDA. Overall, however, in this medical officer's assessment, the enrolled population represents adequately the intended use population of adults with frequent heartburn.*

Subjects not meeting eligibility criteria at the screening visit or placebo run-in visit were considered screen failures.

At the beginning of the screening/washout period, antacids, H₂RAs, and PPIs were discontinued. The washout period was ≥ 1 day for antacids and ≥ 7 days for H₂RAs and/or PPIs. Subjects meeting all inclusion/exclusion criteria, satisfactorily completing screening assessments, and successfully washing out from any antacid, H₂RA, or PPI use entered a single blind, one-week placebo run-in period (Day -8 to Day -1)

completing a daily diary via IVRS to document heartburn symptoms during the previous 24-hour period. At the end of the placebo run-in period (Day 0), subjects returned to the investigational site for possible randomization.

The treatment period began with the first dose of study medication (randomization visit) and ended upon completion of the end of treatment visit or upon administration of the last dose. Eligible subjects [i.e., subjects reporting at least 1 episode of heartburn during 2 separate 24-hour periods (at least 2 days with heartburn during the run-in period) and compliant in reporting symptoms via IVRS on at least 5 of 7 days] were randomly assigned to blinded doses of esomeprazole (20 mg) daily or matching placebo in a 1:1 ratio. Subjects were to record daily heartburn symptoms via IVRS for the previous 24-hour period during the 14-day treatment regimen. Subjects began taking study drug on Day 1 and began reporting symptoms on Day 2 and at each subsequent 24-hour period through Day 15. The first week of treatment was defined as the first 7 consecutive days subjects were on randomized study drug [between Visit 3 (V3) and V4; Days 1 through 7]. The second week of treatment was defined as the second 7 consecutive days subjects were on randomized study drug (between V3 and V4; Days 8 through 14). The final week of treatment was defined as the last 7 consecutive days subjects were on randomized study drug (between V3 and V4).

Upon the end of the 14-day treatment regimen, subjects returned to the investigational site for assessments on Day 15. At this visit (Visit 4), subjects were to answer additional global assessment questions (GASTQ) to measure satisfaction with the study medication. Subjects then entered a single blind, one-week placebo follow-up period. Subjects continued to record heartburn symptoms via IVRS during the follow-up period. Subjects began taking placebo on Day 16 and began reporting heartburn symptoms on Day 17 and at each subsequent 24-hour period through Day 23.

For all phases of the two studies, study drug was taken once daily. The capsules were swallowed whole (not chewed or crushed) with a glass of water once a day before eating in the morning. Subjects were instructed to eat breakfast daily.

The sole permitted rescue medication was Gelusil. Subjects were to chew one tablet of Gelusil for heartburn symptoms as needed and allowed to repeat hourly if symptoms returned.

The patient populations used for efficacy and safety analyses were:

- Safety analysis set: all randomized subjects who took at least one dose of study medication. Erroneously treated subjects (e.g., those randomized to treatment A but actually given treatment B) were accounted for in the actual treatment group.
- Full analysis set (FAS): all randomized subjects who took at least one dose of randomized treatment and had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment. Subjects were classified

according to randomized treatment. This analysis set was used for all efficacy analyses.

- Per-protocol (PP) analysis: a subset of the FAS excluding data from subjects with certain protocol deviations (determined by study team prior to unblinding of the data). Subjects were classified according to actual treatment received. According to the Sponsor, this analysis set was used in sensitivity analyses to examine the robustness of FAS results for the primary variable and secondary efficacy endpoints.

Reviewer comments: *Although in the statistical analysis plan (SAP) the Sponsor pre-defined the population for the efficacy analyses as all randomized subjects who had one dose of randomized treatment and had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment (i.e., the FAS population), the statistical reviewer (Dr. Wen Jen Chen) noted in his Filing Review that the “valid” requirement may not be assessed impartially. As such, the FAS population may be a biased representation of the target population. Accordingly, the statistical reviewer requested the Sponsor perform analyses of the primary and secondary endpoints using a modified ITT (MITT) population, defined as all randomized subjects who took at least one dose of randomized treatment.*

Because the FAS population was pre-specified as the analysis population in the SAP for both studies used to support the current NDA, this medical officer will present all efficacy results using the FAS population. Additionally, for comparison, the primary analysis results using the MITT population will be presented in section 6.1.10

[Additional Efficacy Issues/Analyses](#). The results of the primary analysis using the MITT population are nearly identical with the primary analysis findings using the Sponsor’s pre-specified FAS population.

For historical comparison, it should be noted that in the trials conducted to support approval of Prevacid 24HR for OTC use in 2009, the primary analysis was similarly in a pre-specified ITT population defined as all randomized subjects who took at least one dose of study medication, and had at least one post-baseline efficacy assessment.

Measures of efficacy were assessed by data recorded by subjects in an IVRS daily self-assessment diary. Each 24-hour time period began when the subject took a dose of the study medication and ended just prior to the subject taking the next dose on the following day (i.e., treatment started at Day 1 and ended at Day 14, endpoint collection started at Day 2 and ended at Day 15).

The pre-specified primary efficacy endpoint was percentage of heartburn-free 24-hour days during 14 days of double-blind treatment, which was defined as the number of days when the subject had a heartburn severity score of zero (None) during Days 1 to 14 of the treatment period divided by 14. For example, if a subject has 5 heartburn-free

24-hour days during 14 days then the percentage of heartburn-free 24-hour days is $(5/14)*100 = 35.75\%$.

Pre-specified secondary efficacy endpoints included the following:

- Proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both Weeks 1 and 2 between V3 and V4)
- Proportion of days with no heartburn over Days 1-4; (the first 4 consecutive days subjects are on randomized treatment, between V3 and V4)
- Proportion of subjects with heartburn 1 day or less during the final week of treatment; the final week of treatment is defined as the last 7 consecutive days subjects are on randomized study drug (between V3 and V4)
- Proportion of subjects with heartburn 1 day or less during the second week of treatment; The second week of treatment is defined as the second 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 8 through 14)
- Proportion of subjects with heartburn 1 day or less during the first week of treatment; the first week of treatment is defined as the first 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 1 through 7)

For the secondary endpoints, when calculating the proportion of subjects who were heartburn-free for a given day, subjects without data for that day were assumed to have had heartburn.

6 Review of Efficacy

Efficacy Summary

The clinical development program of esomeprazole 20 mg for short-term OTC use consisted of two phase 3 placebo-controlled trials conducted in the United States in subjects with frequent heartburn.

The design and objectives of the two studies, D961RC00001 (Study 1) and D961RC00002 (Study 2), were identical. The primary objective of these two studies was to demonstrate that esomeprazole 20 mg once daily dosed in the morning is superior to placebo in reducing the frequency of heartburn episodes during the 14-day double-blind treatment period. The study cohorts consisted of subjects with a history of frequent heartburn, defined as ≥ 2 days of heartburn a week.

The pre-specified primary endpoint in both studies was the percentage of 24-hour days with no heartburn during 14 days of double-blind treatment. The pre-specified primary analysis population in both studies was the full analysis set (FAS) population, defined as all randomized subjects who took at least one dose of randomized treatment and had a valid baseline heartburn assessment and at least one valid post-baseline heartburn

assessment. In Study 1, for the primary endpoint, the treatment difference favoring esomeprazole over placebo was 13.1% ([95% confidence interval, 7.4-18.7]; $p < 0.0001$). In Study 2, the treatment difference favoring esomeprazole over placebo was 15.3% ([95% confidence interval, 9.9-20.6]; $p < 0.0001$).

Reviewer comments: *It should be noted that at the time of completion of this medical officer's primary review, the statistical team's review of efficacy is still pending. However, this medical officer notes that as of this writing, no major issues have been raised by the statistical review team that would be expected to affect the clinical review team's recommendations on approval of Nexium 24HR from an efficacy standpoint.*

6.1 Indication

The Sponsor is seeking approval to market esomeprazole magnesium 20 mg delayed release capsules for OTC use in adults 18 years and older for the treatment of frequent heartburn (occurring two or more days a week) and is not intended for immediate relief of heartburn.

6.1.1 Methods

The efficacy and safety of esomeprazole 20 mg for short-term OTC use was investigated in the target population (adults 18 years of age or older with a history of frequent heartburn) over a 14-day period. Two randomized, double-blind, placebo-controlled, parallel group, phase 3 studies (Study 1 and Study 2) involving 657 subjects with frequent heartburn were conducted to support the current application; of these 657 treated subjects, 333 received esomeprazole 20 mg and 324 received placebo for 14 consecutive days. Efficacy evaluation was based on the subject's daily self-assessment (collected using an IVRS) regarding the occurrence of heartburn episodes during the 14-day treatment period.

6.1.2 Demographics

[Table 3](#) and [Table 4](#) present key baseline demographic and disease characteristics data for the two efficacy trials.

Table 3. Demographic Characteristics at Baseline – Study 1 and Study 2 (FAS Population)

| Variable | Study 1 | | Study 2 | |
|----------------------------------|----------------------|-----------------|----------------------|-----------------|
| | Esomeprazole (N=168) | Placebo (N=163) | Esomeprazole (N=162) | Placebo (N=158) |
| Age (Years) | | | | |
| Mean ± Standard Deviation | 43.6 ± 12.2 | 45.9 ± 12.6 | 41.6 ± 14.0 | 42.8 ± 13.2 |
| Median (Minimum, Maximum) | 43.0 (19, 73) | 46.0 (19, 85) | 41.0 (19, 90) | 42.5 (18, 84) |
| Age Group, n (%) | | | | |
| <65 Years | 161 (95.8) | 152 (93.3) | 153 (94.4) | 152 (96.2) |
| ≥65 Years | 7 (4.2) | 11 (6.7) | 9 (5.6) | 6 (3.8) |
| Sex, n (%) | | | | |
| Female | 104 (61.9) | 95 (58.3) | 86 (53.1) | 82 (51.9) |
| Male | 64 (38.1) | 68 (41.2) | 76 (46.9) | 76 (48.1) |
| Race, n (%) | | | | |
| White | 101 (60.1) | 108 (66.3) | 107 (66.0) | 111 (70.3) |
| Black or African American | 64 (38.1) | 53 (32.6) | 48 (29.6) | 46 (29.1) |
| Asian | 0 (0.0) | 1 (0.6) | 0 (0.0) | 0 (0.0) |
| Native Hawaiian/Pacific Islander | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| American Indian/Alaska Native | 1 (0.6) | 0 (0.0) | 3 (1.9) | 0 (0.0) |
| Other | 2 (1.2) | 1 (0.6) | 3 (1.9) | 1 (0.6) |
| Ethnic Group, n (%) | | | | |
| Hispanic or Latino | 34 (20.2) | 25 (15.3) | 24 (14.8) | 21 (13.3) |
| All Other | 134 (79.8) | 138 (84.7) | 138 (85.2) | 137 (86.7) |

Source: Reviewer's table, adapted from Sponsor's Table 5, page 26, Summary of Clinical Efficacy and subject level datasets.

Reviewer comments: The placebo and esomeprazole arms within each of the two double-blind trials were generally well matched with regard to gender, race, and age. When comparing baseline demographics across trials, Study 2 enrolled fewer black/African-American and Hispanic/Latino subjects than Study 1. Given what is known about the mechanism of action of esomeprazole, no substantial differences in efficacy findings between the two trials would be expected despite these demographic differences. Overall, the demographic subsets of subjects were limited by the inadequate percentage of geriatric subjects; however, consistency therein was generally well maintained across the study groups.

Table 4. Disease Characteristics at Baseline – Study 1 and Study 2 (FAS Population)

| Variable | Study 1 | | Study 2 | |
|--|-------------------------|--------------------|-------------------------|--------------------|
| | Esomeprazole (N=168) | Placebo (N=163) | Esomeprazole (N=162) | Placebo (N=158) |
| Days with Heartburn in the Last Month | | | | |
| Mean ± Standard Deviation | 14.2 ± 5.5 | 15.7 ± 5.9 | 14.0 ± 7.1 | 13.6 ± 6.9 |
| Median (Minimum, Maximum) | 12.0 (5, 30) | 15.0 (8, 30) | 12.0 (2, 30) | 12.0 (2, 30) |
| Rating of Most Intense Heartburn, n (%) | | | | |
| Mild | 15 (8.9) | 12 (7.4) | 13 (8.0) | 11 (7.0) |
| Moderate | 95 (56.6) | 95 (58.3) | 93 (57.4) | 97 (61.4) |
| Severe | 58 (34.5) | 56 (34.4) | 56 (34.6) | 50 (31.7) |
| Heartburn Caused by Food/Beverage, n (%) | | | | |
| Yes | 162 (96.4) | 158 (96.9) | 154 (95.1) | 153 (96.8) |
| Heartburn Caused by Stress/Anxiety, n (%) | | | | |
| Yes | 81 (48.2) | 83 (50.9) | 68 (42.0) | 73 (46.2) |
| Heartburn Caused by Lying Down, n (%) | | | | |
| Yes | 103 (61.3) | 89 (54.6) | 84 (51.9) | 95 (60.1) |
| Heartburn Caused by Physical Activity, n (%) | | | | |
| Yes | 26 (15.5) | 26 (16.0) | 20 (12.4) | 24 (15.2) |
| Heartburn Caused by Hectic Lifestyle, n (%) | | | | |
| Yes | 42 (25.0) | 38 (23.3) | 22 (13.6) | 31 (19.6) |
| Heartburn Caused by Medication, n (%) | | | | |
| Yes | 4 (2.4) | 8 (4.9) | 6 (3.7) | 14 (8.9) |
| Received OTC/Prescribed Heartburn Medication in Past 5 Years, n (%) | | | | |
| Yes | 147 (87.5) | 148 (90.8) | 151 (93.2) | 146 (92.4) |

Source: Reviewer's table, adapted from Sponsor's Table 6, pages 28-29, Summary of Clinical Efficacy.

Reviewer comments: The placebo and esomeprazole arms within each of the two double-blind trials were generally well matched with regard to disease characteristics at baseline. However, these data are of very limited value because the validity of the assessment to actually capture a causal relationship has not been established. It is not clear what the difference is between heartburn due to “stress/anxiety” vs. “hectic lifestyle” or what psychological state that is actually capturing.

6.1.3 Subject Disposition

In Study 1, a total of 486 subjects were screened (enrolled), of whom 146 were screen failures. Thus, 340 subjects were randomized at 10 sites in the United States. In Study 2, a total of 526 subjects were screened (enrolled), of whom 185 were screen failures. Thus, 341 subjects were randomized at 10 sites in the United States.

Screen failures were determined at the time of the screening visit and at the time of the placebo run-in visit (see schedule for studies in Table 26). Table 5 summarizes reasons for the 331 screen failures in the two efficacy studies.

Table 5. Reason for Screen Failures (Subjects Enrolled But Not Randomized) in Efficacy Studies

| Reasons for Screen Failures | Study 1 (N=146) n (%) | Study 2 (N=185) n (%) | Total (N=331) n (%) |
|---|-----------------------------|-----------------------------|---------------------------|
| Eligibility criteria not fulfilled | 139 (95.2) | 181 (97.8) | 320 (96.7) |
| Withdrawn due to adverse event ¹ | 1 (0.7) | 3 (1.6) | 4 (1.2) |
| Withdrawn due to death ² | 0 | 1 (0.5) | 1 (0.3) |
| Withdrawn due to subject decision | 2 (1.4) | 0 | 2 (0.6) |
| Withdrawn due to other ³ | 4 (2.7) | 0 | 4 (1.2) |

¹ In Study 1, one subject (E7808144, a 24-year-old female) had adverse events (AEs) of hypertension and migraine. In Study 2, one subject (E7802279, 60-year-old male) had an AE of myocardial infarction, one subject (E7805243, 28-year-old female) had an AE of nausea, and one subject (E7810208, 18-year-old female) had an AE of depression.

² At the start of the placebo run-in period (Visit 2 on (b) (6) in Study 2, subject E7808221, a 45-year-old male, died due to a reported acute cardiac arrest (arrest occurred on (b) (6) and death occurred on (b) (6)). The subject had not yet taken a dose of the placebo medication and was never exposed to esomeprazole 20 mg.

³ Three subjects were lost to follow-up despite meeting all inclusion/exclusion criteria and one subject was, according to the Sponsor, "unable to complete study requirements."

Source: Reviewer's table, adapted from Sponsor's Table 3, page 22, Summary of Clinical Efficacy; Appendix 12.2.1; and Appendix 12.2.7.7.

The most common reasons cited for not randomizing enrolled subjects (i.e., screen failures) in both studies included the following:

- Met exclusion criterion #11: Inability to take study medication or complete the study and all procedures
 - Failure to return for Visit 2 (to begin placebo run-in period)
 - Failure to return for Visit 3 (randomization visit)
- Diary randomization criteria not met
 - Noncompliant in reporting heartburn symptoms via IVRS for at least 5 of 7 days during the run-in period
 - Fewer than 2 episodes of heartburn reported via IVRS during the 7 day run-in period

Reviewer comments: *The placebo and esomeprazole arms within each of the two double-blind trials were generally well matched with regard to reasons for screen failure. The principal reasons for screen failure across the two studies related to noncompliance with study procedures (i.e., failure to report symptoms via IVRS, failure to return for follow up visits) and not meeting pre-specified requirements for frequent heartburn during the 7-day run-in period. Overall, the study population appears generalizable to the actual population who may use esomeprazole magnesium OTC.*

Table 6 summarizes subject disposition for the two efficacy studies. The table legend includes additional details (where available) on reasons for discontinuation from the studies.

Table 6. Subject Disposition – Study 1 and Study 2 (Randomized Subjects)

| Disposition | Study 1 | | Study 2 | |
|--|----------------------|-----------------|----------------------|-----------------|
| | Esomeprazole (N=171) | Placebo (N=169) | Esomeprazole (N=170) | Placebo (N=171) |
| Randomized subjects, n (%) | 171 (100.0) | 169 (100.0) | 170 (100.0) | 171 (100.0) |
| Safety analysis set, n (%) | 168 (98.2) | 163 (96.4) | 165 (97.1) | 161 (94.2) |
| Full analysis set, n (%) | 168 (98.2) | 163 (96.4) | 162 (95.2) | 158 (92.4) |
| Completed subjects, n (%) | 163 (95.3) | 158 (93.5) | 151 (88.8) | 152 (88.9) |
| Per-protocol analysis set, n (%) | 150 (87.8) | 149 (88.2) | 142 (83.5) | 153 (81.9) |
| Discontinued subjects, n (%) | 8 (4.7) | 11 (6.5) | 19 (11.2) | 19 (11.1) |
| Reason for Discontinuation From Study, n (%) | | | | |
| Subject decision ¹ | 2 (1.2) | 3 (1.8) | 3 (1.8) | 2 (1.2) |
| Eligibility criteria not fulfilled ² | 2 (1.2) | 0 (0.0) | 0 (0.0) | 1 (0.6) |
| Adverse event ³ | 0 (0.0) | 1 (0.6) | 1 (0.6) | 0 (0.0) |
| Severe non-compliance to protocol ⁴ | 2 (1.2) | 1 (0.6) | 8 (4.7) | 5 (2.9) |
| Development of study-specific withdrawal criteria ⁵ | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (0.6) |
| Other ⁶ | 2 (1.2) | 6 (3.6) | 6 (3.5) | 10 (5.8) |

¹ Subject decision: In Study 1, of the 3 placebo subjects, 1 discontinued from the study due to “patient unable to commit to completing study,” 1 discontinued due to “subject’s mother died, could not continue due to personal issues at home.” For the other placebo subject, no additional information was available. Of the 2 esomeprazole subjects, one discontinued from the study due to “left town emergently, death in family.” For the other esomeprazole subject, no additional information was available. In Study 2, for the 2 placebo subjects, no additional information was available. Of the 3 esomeprazole subjects, one discontinued from the study due to “subject moved.” For the other 2 esomeprazole subjects, no additional information was available.

² Eligibility criteria not fulfilled: In Study 1, of the 2 esomeprazole subjects, 1 was discontinued due to “received medical records that showed subject was diagnosed with GERD previously,” and 1 was “inadvertently randomized, but not meet inclusion criterion #2.” In Study 2, the placebo subject met exclusion criterion #4.

³ Adverse events (AEs): In Study 1, one placebo subject (E7802129) had a reported AE of cholelithiasis on study day 7. In Study 2, one esomeprazole subject (E7802201) had a reported AE of sinusitis on study day 7.

⁴ Severe non-compliance to protocol: In Study 1, the placebo subject “did not want to continue taking medication.” Of the 2 esomeprazole subjects, 1 “lost medication” and 1 was “lost to follow-up.” In Study 2, of the 5 placebo subjects, 1 was “lost to follow-up,” 1 was “unable to return for study visits,” and 3 had no additional information available. Of the 8 esomeprazole subjects, 2 were “lost to follow-up,” 1 “missed four IVRS calls,” and 5 had no additional information available.

⁵ Development of study-specific withdrawal criteria: In Study 2, the placebo subject “took a new concomitant medication” and the esomeprazole subject was diagnosed with GERD followed endoscopy based on record review.

⁶ Other: In Study 1, 7 of the 8 subjects that discontinued due to “other” discontinued due to “lost to follow-up.” One placebo subject discontinued due to “started new concomitant medication.” In Study 2, of the 10 placebo subjects, 5 were “lost to follow-up,” 1 was “randomized in error,” 1 “only took about 2 doses of study drug and did not make any calls since the day of visit 3,” 1 was “unable to make calls after visit 3 due to fires in the area,” 1 was “out of window due to being on vacation,” and 1 was “out of window and has not returned calls.” Of the 6 esomeprazole subjects, 2 were “randomized in error,” 1 was “lost to follow-up,” 1 “withdrew consent,” 1 was “out of window and has not returned calls,” and 1 “decided to move out of town.”

Source: Reviewer’s table, adapted from Sponsor’s Table 3, pages 22-23, Summary of Clinical Efficacy; Appendix 12.2.7; Table 8 and 9, pages 17-21, Response to information request in 74-day letter.

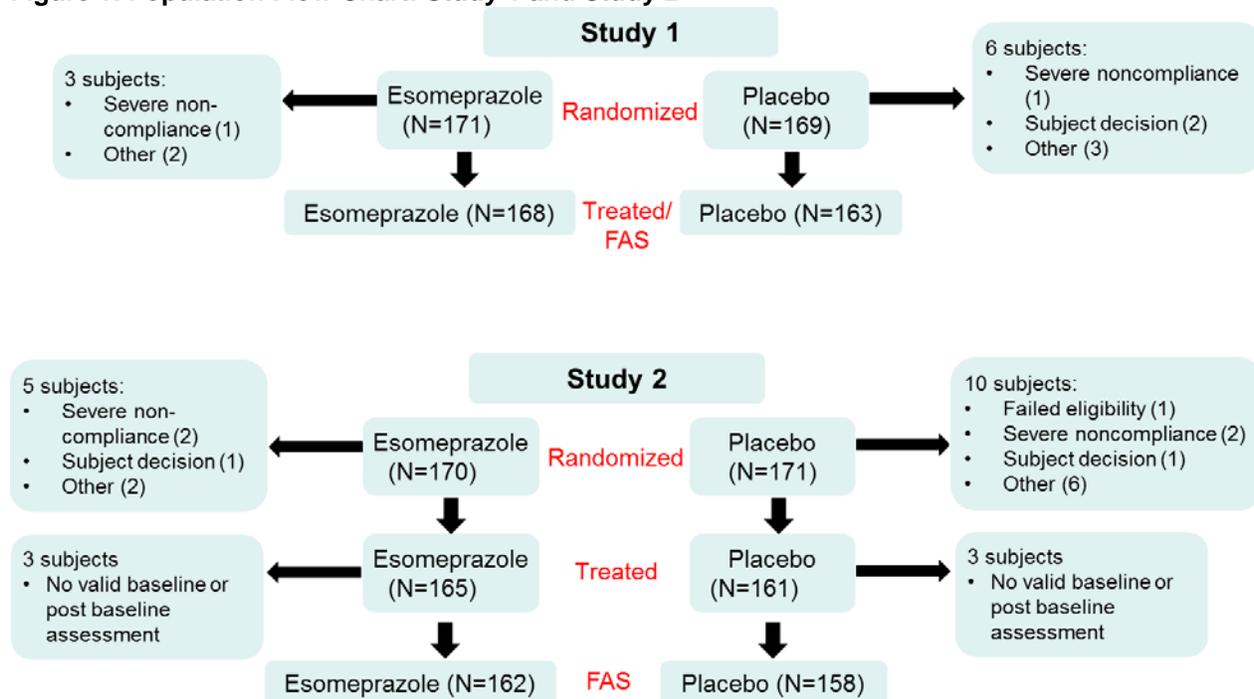
Reviewer comments: *Although discontinuation rates were higher in Study 2 than in Study 1, the placebo and esomeprazole arms within each of the two double-blind trials*

were generally well matched with regard to the percentage that discontinued from the study.

Randomized Population versus FAS Population

As noted previously, the full analysis set (FAS) consisted of all randomized subjects who took at least one dose of randomized treatment and had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment. The FAS population was pre-specified in the SAP as the analysis population for the primary endpoint. Figure 1 shows the population flow in Study 1 and Study 2.

Figure 1. Population Flow Chart: Study 1 and Study 2



Treated patients = Modified intent-to-treat (MITT) = All randomized subjects who took at least one dose of randomized treatment

Source: Reviewer's figure.

In Study 1 the treated (i.e., MITT) and FAS populations are exactly the same (i.e., there were no randomized subjects who took drug and did not have post-baseline data). In Study 2, there were 6 subjects in total (3 subjects in each treatment arm) who were randomized and treated, but did not have post-baseline data (FAS=320 subjects, MITT=326 subjects).

Determination of Per-Protocol Population

Protocol violators were excluded from the per-protocol analyses. Criteria used to determine protocol violations included:

1. Not in the FAS population

2. Violated any of the following inclusion criteria: 1, 2, 4, 5 or 6
3. Violated any of the exclusion criteria: 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13 or 14
4. Not compliant with study drug during the randomized double-blind study period (intake of study drug outside the range of 75-125%)
5. Visit 4 window outside of range (<12 days)
6. Received any new prescriptions, OTC medications, or herbal/nutritional therapies during the study, which could affect, or interfere with the subject's ability to evaluate, the efficacy of the drugs during the double-blind treatment period
7. Received treatment with any H₂RAs, PPIs (except for study medication), gastric prokinetic drugs or drugs that may affect symptoms/pathophysiology during the trial
8. Failed to meet either of the two specific randomization criteria during the run-in phase:
 - Subjects must experience and report via IVRS at least 1 episode of heartburn during 2 separate 24-hour periods (2 episodes of heartburn in total) during the run-in period. If a subject was in the run-in phase for longer than 7 days, at least 2 of their heartburn episodes must have occurred during the first 7 days.
 - Subjects must be compliant in reporting heartburn symptoms via IVRS during the run-in period. Compliance is defined as reporting in at least 5 of the first 7 days during their run-in period.

Table 7 lists the protocol violations for each efficacy trial.

Table 7. Summary of Protocol Violations (FAS Population)

| Protocol Violation * | Study 1 | | Study 2 | |
|--|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | Esomeprazole (N=168) n (%) | Placebo (N=163) n (%) | Esomeprazole (N=162) n (%) | Placebo (N=158) n (%) |
| Disallowed medication | 10 (4.5) | 7 (3.2) | 35 (16.1) | 37 (16.7) |
| Excluded previous medical history | 8 (3.6) | 8 (3.7) | 1 (0.5) | 2 (0.9) |
| Did not experience heartburn ≥2 days a week over the past 4 weeks | 10 (4.5) | 13 (5.9) | 13 (6.0) | 13 (5.9) |
| Visit 4 occurred at <12 days | 6 (2.7) | 6 (2.7) | 9 (4.1) | 7 (3.2) |
| Noncompliant in reporting heartburn symptoms via IVRS 5 of 7 days during run-in period | 2 (0.9) | 0 | 5 (2.3) | 10 (4.5) |
| Treatment noncompliance | 7 (3.2) | 5 (2.3) | 11 (5.1) | 17 (7.7) |
| History of physician-diagnosed GERD | 0 | 3 (1.4) | 1 (0.5) | 0 |
| Total | 45 (20.5) | 43 (19.6) | 77 (35.5) | 86 (38.9) |

*A subject might have multiple protocol violations. Subjects who met multiple violations were counted once in each category.
 Source: Reviewer's table, adapted from Sponsor's Table 4, page 24, Summary of Clinical Efficacy.

Reviewer comments: Overall, protocol violations were less frequent in Study 1 than Study 2. The number of violations was generally balanced across the treatment arms

within each trial, with a few exceptions. Noncompliance, both with treatment and with symptom reporting, was more frequent among placebo subjects than esomeprazole subjects in Study 2. However, the overall numbers of protocol violations were relatively small and the higher frequency of treatment noncompliance in the placebo arm compared with the esomeprazole arm might be a reflection of an expected lack of improvement in frequent heartburn symptoms with placebo. In this medical officer's assessment, the small imbalances in specific protocol violations across treatment arms in the two studies would not be expected to affect substantially the efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

Percentage of heartburn-free 24-hour days during 14 days of treatment

The pre-specified primary efficacy endpoint in Study 1 and Study 2 was the percentage of 24-hour days with no heartburn during 14 days of treatment. The assessment of efficacy was based on the subject's daily self-assessment regarding the occurrence of heartburn episodes during the 14-day double-blind treatment period. The pre-specified primary analysis was based on the FAS. The percentage of heartburn-free 24-hour days during 14 treatment days was defined as the number of days when the subject had a heartburn severity score of zero (None) during Days 1 to 14 of the treatment period divided by 14. According to the Sponsor, missing data were imputed based on the run-in phase according to pre-specified rules in the SAP. The proportion of 24-hour days with no heartburn during the run-in phase was used as follows:

$$y = [(number\ of\ 24\text{-hour}\ days\ with\ no\ heartburn) + m * (proportion\ of\ 24\text{-hour}\ days\ with\ no\ heartburn\ during\ the\ run\text{-in}\ phase)]/14$$

Where m = the number of days with missing data

Reviewer comments: *It should be noted that although the above equation for handling of missing data was provided in the Summary of Clinical Efficacy (section 1.2.8, page 16), the final version of the SAP for both studies presented a slightly different formula, with the differences emphasized in red text:*

$$y = [(number\ of\ 24\text{-hour}\ days\ or\ nighttimes\ with\ no\ heartburn) + m * (proportion\ of\ 24\text{-hour}\ days\ or\ nighttimes\ with\ no\ heartburn\ during\ the\ run\text{-in}\ phase)]/14$$

In an information request, the Sponsor was asked to clarify this apparent discrepancy. The Sponsor's response, reproduced below, explains adequately the discrepancy:

"The imputation rules used for the primary endpoint are the ones indicated in section 1.2.8 (page 16) of the Summary of Clinical Efficacy in Module 2.7.3. The apparent discrepancy in the statistical analysis plans (SAP) and protocols arises from an attempt to generalize the formula for both the primary endpoint and an exploratory endpoint of nighttime heartburn. In other words when evaluating

nighttime heartburn, missing nighttime values should be imputed using the proportion of nighttime heartburn-free days during the run-in phase, instead of the 24-hour heartburn-free days from the run-in phase. AZ recognizes this was awkwardly worded in the protocol and SAPs. There was never any intention to incorporate nighttime heartburn into the imputation of missing data for the primary endpoint and the wording in the Clinical Summary Efficacy is just a clearer statement of the intended imputation rules for the primary endpoint.”

When calculating the proportion of 24-hour days or nighttimes with no heartburn during the run-in phase, the denominator was the number of days the subject actually was in the run-in phase. The calculation was based on only non-missing values (e.g., if a subject had only 5 days in the run-in phase and of those 2 days with heartburn, then the proportion of 24-hour days or nighttimes with no heartburn during the run-in phase for this subject is: $(5-2)/5 = 3/5$). The Sponsor contends that because there were slightly more values missing in the active treatment group than the placebo group, these imputation rules tended to bias the results against an effective active treatment.

The percentage of 24-hour days with no heartburn over 14 days of treatment, analyzed as a continuous variable, was analyzed using analysis of covariance (ANCOVA) model including treatment and center as factors and frequency of heartburn during the run-in phase as a covariate. Model-based point estimates, 95% confidence intervals, and two-sided p-value were reported.

Reviewer comments: *The above primary analysis approach is congruent with the primary analysis employed in the trials conducted to support approval of Prevacid 24HR for OTC use in 2009. In those trials, the proportion of 24-hour days with no heartburn over 14 days of treatment, expressed as percentages, was also analyzed using ANCOVA model including treatment and center as factors and frequency of heartburn during the run-in phase as a covariate.*

Table 8 shows results of the pre-specified primary efficacy analysis for Study 1 and Study 2.

Table 8. Percentage of Heartburn-Free 24-Hour Days During 14 Days of Treatment (FAS Population)

| Study | Esomeprazole | | Placebo | | Treatment Difference ¹ | | |
|-------|--------------|--------------|---------|--------------|-----------------------------------|---------------|---------|
| | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean (SE) | 95% CI | P-value |
| 1 | 168 | 46.13 (2.24) | 163 | 33.07 (2.26) | 13.06 (2.86) | (7.44, 18.68) | <0.0001 |
| 2 | 162 | 48.00 (1.96) | 158 | 32.75 (1.99) | 15.25 (2.73) | (9.88, 20.62) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square; SE, standard error

¹Obtained from ANCOVA with centers and treatment as fixed effects and heartburn frequency during the run-in phase as covariate.

Note: Missing values for the treatment phase were imputed based on the run-in phase data.

Source: Reviewer's table, adapted from Sponsor's Table 10, page 34, Summary of Clinical Efficacy.

Reviewer comments: *The treatment differences favoring esomeprazole over placebo in Study 1 (13%) and Study 2 (15%) for the current NDA submission are comparable to the treatment effect of lansoprazole 15 mg in the Prevacid 24HR trials. In two of the three phase 3 trials used to support approval of Prevacid 24HR for the OTC treatment of frequent heartburn, the primary endpoint was also proportion of 24-hour days with no heartburn over 14 days of treatment. The treatment difference favoring lansoprazole 15 mg over placebo was approximately 14% in one trial and approximately 20% in the second trial. A treatment difference of 13% to 15% favoring esomeprazole translates to approximately 2 fewer days of heartburn over a 14-day period when taking esomeprazole than when taking placebo. Given the aforementioned considerations, in this reviewer’s opinion, a treatment difference of 13% to 15% favoring esomeprazole represents a clinically meaningful treatment effect in adults with frequent heartburn and offers another OTC treatment option for frequent heartburn in this patient population.*

The Sponsor also performed a pre-specified supportive analysis of the primary endpoint (percentage of heartburn-free 24-hour days during 14 days of treatment) in the per-protocol population, the results of which were similar to the results for the FAS population (treatment difference of 13% favoring esomeprazole in Study 1; treatment difference of 16% favoring esomeprazole in Study 2).

A pre-specified sensitivity analysis was performed where subject missing data were assumed to be days with heartburn. When calculating the proportion of subjects who were heartburn-free for a given day, subjects without data for that day were assumed to have had heartburn. [Table 9](#) summarizes the results of the sensitivity analysis.

Table 9. Percentage of Heartburn-Free 24-Hour Days During 14 Days of Treatment (FAS Population) – Subjects Assumed to Have Heartburn on Days with Missing Data

| Study | Esomeprazole | | Placebo | | Treatment Difference ¹ | | |
|-------|--------------|--------------|---------|--------------|-----------------------------------|---------------|---------|
| | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean (SE) | 95% CI | P-value |
| 1 | 168 | 43.47 (2.28) | 163 | 30.97 (2.30) | 12.50 (2.91) | (6.77, 18.22) | <0.0001 |
| 2 | 162 | 44.52 (2.03) | 158 | 29.97 (2.06) | 14.55 (2.82) | (9.00, 20.09) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square; SE, standard error

¹Obtained from ANCOVA with centers and treatment as fixed effects and heartburn frequency during the run-in phase as covariate.

Note: Missing values for the treatment phase were considered as days with heartburn.

Source: Reviewer’s table, adapted from Sponsor’s Table 12, page 36, Summary of Clinical Efficacy.

Reviewer comments: *The treatment differences favoring esomeprazole in Study 1 (13%) and Study 2 (15%) remain essentially unchanged in the sensitivity analysis wherein subjects with missing data for a day were assumed to have had heartburn on that day. This sensitivity analysis supports the primary efficacy analysis.*

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints pre-specified in the final SAP for Study 1 and Study 2 included the following:

- Proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both Weeks 1 and 2 between V3 and V4)
- Proportion of days with no heartburn over Days 1-4; (the first 4 consecutive days subjects are on randomized treatment, between V3 and V4)
- Proportion of subjects with heartburn 1 day or less during the final week of treatment; the final week of treatment is defined as the last 7 consecutive days subjects are on randomized study drug (between V3 and V4)
- Proportion of subjects with heartburn 1 day or less during the second week of treatment; The second week of treatment is defined as the second 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 8 through 14)
- Proportion of subjects with heartburn 1 day or less during the first week of treatment; the first week of treatment is defined as the first 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 1 through 7)

Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission outlines discussions between FDA and the Sponsor that culminated in the above list of pre-specified secondary endpoints.

In adjusting for multiplicity, the Sponsor employed a hierarchical testing procedure to control the type I error. As pre-specified in the SAP, the primary and secondary efficacy endpoints were analyzed sequentially in the following order:

1. The percentage of 24-hour days with no heartburn during 14 days of treatment (primary endpoint)
2. The resolution of frequent heartburn, defined as heartburn 2 days or less during the 14-day randomized period (both weeks 1 and 2)
3. The percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase
4. The percentage of subjects with heartburn 1 day or less during the final week of treatment
5. The percentage of subjects with heartburn 1 day or less during the second week of treatment
6. The percentage of subjects with heartburn 1 day or less during the first week of treatment

When a test resulted in statistically insignificant result, the next test in the sequence was not carried out.

Analysis of all secondary endpoints was performed on the FAS population. When calculating the proportion of subjects who were heartburn-free for a given day, subjects without data for that day were assumed to have had heartburn.

Percentage of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both weeks 1 and 2)

As the first secondary endpoint in the analysis hierarchy, the Sponsor evaluated the percentage of subjects reporting heartburn ≤ 2 days during the 14-day randomized treatment period. The Sponsor described subjects reporting heartburn ≤ 2 days during the 14-day randomized treatment period as having resolution of frequent heartburn. Table 10 shows results of the first secondary endpoint analysis for Study 1 and Study 2.

Table 10. Percentage of Subjects Reporting Heartburn 2 Days or Less During the 14-Day Randomized Treatment Period (FAS Population)

| Study | Esomeprazole | | Placebo | | Comparison Between Groups ¹ | | |
|-------|--------------|---|---------|---|--|---------------|---------|
| | N | Number (%) of Subjects Reporting ≤ 2 Days of Heartburn | N | Number (%) of Subjects Reporting ≤ 2 Days of Heartburn | Relative Risk | 95% CI | P-value |
| 1 | 168 | 27 (16.07) | 163 | 7 (4.29) | 3.74 | (1.68, 8.35) | 0.0004 |
| 2 | 162 | 27 (16.67) | 158 | 2 (1.27) | 13.17 | (3.18, 54.44) | <0.0001 |

Abbreviations: CI, confidence interval

¹Proportion of subjects with ≤ 2 days of heartburn by treatment were compared by using a chi-square test. A relative risk >1 shows esomeprazole to have a favorable outcome compared to placebo.

Source: Reviewer's table, adapted from Sponsor's Table 14, page 38, Summary of Clinical Efficacy.

Reviewer comments: *For this secondary endpoint, the SAP for Study 1 and Study 2 indicates that the proportion of subjects with resolution of frequent heartburn (i.e., reporting heartburn ≤ 2 days during the 14-day treatment period) by treatment will be compared by using a chi-square test. The SAP, however, does not pre-specify if the treatment difference between the two arms will be presented as a risk difference or as a relative risk. Although the Sponsor's rationale for presenting relative risk instead of risk difference is unclear, the decision to present relative risk instead of risk difference is not contradictory with the SAP. This medical officer discussed further this issue with the statistical reviewer (Dr. Wen Jen Chen). Dr. Chen noted (via personal communication) that although the size of risk differences is easier to capture and understand than relative risk, it is acceptable to use relative risk to assess the effect of the drug. Moreover, Dr. Chen noted (via personal communication) that the p-values presented in the table are calculated based on the risk difference and not the relative risk. However, because the statistical review was not finalized at the time of completion of this clinical review, we defer the ultimate acceptability of this approach to the statistical reviewer.*

Because a lower bound of the 95% confidence interval (CI) of the relative risk >1 indicates that subjects receiving esomeprazole had a favorable outcome (i.e., ≤ 2 days of heartburn during the 14-day treatment period) compared with subjects receiving placebo, the relative risk for Study 1 (3.7) and Study 2 (13.2) both favor the esomeprazole group by a statistically significant margin. This medical officer notes, however that the 95% CI for this endpoint in Study 2 is wide (lower bound 3.2, upper

bound 54.4). Because sample size was similar for both studies, the wide 95% CI in Study 2 is likely due to greater variability in the data for Study 2 and not due to insufficient data. The wide interval indicates that the relative risk of 13.2 in Study 2 is not a precise estimate. The relative risk calculated for Study 1 (3.7) is more precise and likely a better estimate of the true relative risk.

Percentage of days with no heartburn over Days 1-4; (the first 4 consecutive days subjects are on randomized treatment)

As pre-specified in the final SAP, the count of 24-hour days with no heartburn over Days 1 to 4 was analyzed using a proportional odds model (i.e., cumulative logit model) for ordinal outcomes with treatment as factor and the baseline results as a covariate. The results were expressed in terms of an odds ratio and its associated CI. Table 11 presents the comparison of the percentage of subjects with heartburn-free 24-hour days over 1 to 4 days between the 2 treatment groups in Study 1 and Study 2 using a proportional odds model.

Table 11. Comparison of Percentage of Subjects with 0, 1, 2, 3, or 4 Days (24-hour Days) with No Heartburn Over Days 1-4 of the 14-Day Randomized Treatment Period Using Proportional Odds Model (FAS Population)

| Study/Group | N | Number (%) of Subjects | | | | | Comparison Between Groups ¹ | |
|----------------|-----|------------------------|------------|------------|------------|------------|--|---------|
| | | 0 Day | 1 Day | 2 Days | 3 Days | 4 Days | Odds Ratio (95% CI) | P-value |
| Study 1 | | | | | | | | |
| Esomeprazole | 168 | 64 (38.10) | 25 (14.88) | 36 (21.43) | 25 (14.88) | 18 (10.71) | 1.81 (1.19, 2.74) | 0.0053 |
| Placebo | 163 | 76 (46.63) | 36 (22.09) | 18 (11.04) | 21 (12.88) | 12 (7.36) | | |
| Study 2 | | | | | | | | |
| Esomeprazole | 162 | 55 (33.95) | 32 (19.75) | 22 (13.58) | 37 (22.84) | 16 (9.88) | 2.54 (1.66, 3.88) | <0.0001 |
| Placebo | 158 | 77 (48.73) | 34 (21.52) | 29 (18.35) | 16 (10.13) | 2 (1.27) | | |

Abbreviations: CI, confidence interval

¹Proportional odds model with treatment as a factor and frequency of heartburn during the run-in phase as a covariate. An odds ratio >1 shows esomeprazole to have a favorable outcome compared to placebo.

Source: Reviewer's table, adapted from Sponsor's Table 15, page 39, Summary of Clinical Efficacy.

Reviewer comments: *In Study 1, in the placebo group, 51 (31%) of subjects experienced ≥2 heartburn-free days during the first 4 days of treatment compared to 79 (47%) of esomeprazole subjects. In Study 2, in the placebo group, 47 (30%) of subjects experienced ≥2 heartburn-free days during the first 4 days of treatment compared to 75 (46%) of esomeprazole subjects.*

In both studies, there was a statistically significant difference between the esomeprazole and placebo groups in the proportion of subjects who experienced at least one heartburn-free 24-hour day in the first 4 days of treatment (odds ratio 1.8 in Study 1; odds ratio 2.5 in Study 2), but according to the Sponsor, when the proportional odds assumption for this analysis was tested, the assumption was not met. Therefore, as pre-specified in the SAP, analysis using the same model with few response categories (i.e., merging categories) was performed to confirm the validity of the results. When the categories were dichotomized (0 or 1 heartburn-free days versus >1 heartburn-free days) the results remained statistically significant in Study 1 (odds ratio 2.8, 95% CI 1.6 to 4.8; p=0.0003) and Study 2 (odds ratio 2.3, 95% CI 1.4 to 3.8; p=0.0015).

Proposed labeling for esomeprazole OTC states that “it may take 1 to 4 days for full effect, (b) (4).” In this medical officer’s assessment, the first part of the statement (i.e., “it may take 1 to 4 days for full effect”) is supported by the data from the pre-specified analysis in [Table 11](#). Strictly speaking, the analysis in [Table 11](#) indicates that the odds of having at least 1 day with no heartburn over the first 4 days is 1.8 times higher and 2.5 times higher in Study 1 and Study 2, respectively, on esomeprazole than on placebo. However, the data also indicate that over the first 4 days in Study 1, the percentage of esomeprazole subjects who had 4 heartburn-free days (10.7%) was comparable to the percentage of placebo subjects who had 4 heartburn-free days (7.4%). Therefore, given the similarity across treatment arms in the proportion of subjects with 4 heartburn-free days over the first 4 days of treatment, it does appear to take up to 4 days for full drug effect. Moreover, although exploratory, additional analyses, presented in [Table 20](#) and [Figure 2](#) of section 6.1.9 [Discussion of Persistence of Efficacy and/or Tolerance Effects](#), and in [Table 22](#) of section 6.1.10 [Additional Efficacy Issues/Analyses](#), also support the statement that “it may take 1 to 4 days for full effect.” The statement that “it may take 1 to 4 days for full effect” is also included in the current labeling for lansoprazole OTC and omeprazole OTC.

In this reviewer’s assessment, however, the second part of the proposed labeling statement (i.e., (b) (4)”) is not supported by data from any of the pre-specified analyses. None of the pre-specified secondary endpoints in Study 1 or Study 2 directly assessed “relief of symptoms” (i.e., heartburn-free status) (b) (4). An exploratory analysis of the percentage of subjects with heartburn-free 24-hour days by diary day during the 14-day treatment period (missing days assumed to be days with heartburn), presented in (b) (4). (b) (4). The reader is referred to section 6.1.9 [Discussion of Persistence of Efficacy and/or Tolerance Effects](#) for a more detailed discussion of these data.

Proportion of subjects with heartburn 1 day or less during the final week of treatment

For this secondary endpoint, the final week of treatment was defined as the last 7 consecutive days subjects were on randomized study drug. [Table 12](#) summarizes results for Study 1 and Study 2.

Table 12. Percentage of Subjects Reporting Heartburn 1 Day or Less During the Final Week of Treatment of the 14-Day Randomized Treatment Period (FAS Population)

| Study | Esomeprazole | | Placebo | | Comparison Between Groups ¹ | | |
|-------|--------------|--|---------|--|--|--------------|---------|
| | N | Number (%) of Subjects Reporting ≤1 Day of Heartburn | N | Number (%) of Subjects Reporting ≤1 Day of Heartburn | Relative Risk | 95% CI | P-value |
| 1 | 168 | 43 (25.60) | 163 | 17 (10.43) | 2.45 | (1.46, 4.12) | 0.0003 |
| 2 | 162 | 40 (24.69) | 158 | 17 (10.76) | 2.29 | (1.36, 3.87) | 0.0011 |

Abbreviations: CI, confidence interval

¹Proportion of subjects with ≤1 day of heartburn by treatment were compared by using a chi-square test. A relative risk >1 shows esomeprazole to have a favorable outcome compared to placebo.

Source: Reviewer's table, adapted from Sponsor's Table 16, page 40, Summary of Clinical Efficacy.

Reviewer comments: *Because a lower bound of the 95% CI of the relative risk >1 indicates that subjects receiving esomeprazole had a favorable outcome (i.e., ≤1 days of heartburn during the final week of treatment of the 14-day treatment period) compared with subjects receiving placebo, the relative risk for Study 1 (2.5) and Study 2 (2.3) both favor the esomeprazole group by a statistically significant margin. The narrow 95% CIs for both studies support the precision of the estimated relative risk. Overall, the findings support the durability of efficacy over the entire course of the 14-day treatment period.*

Proportion of subjects with heartburn 1 day or less during the second week of treatment

For this secondary endpoint the second week of treatment was defined as the second 7 consecutive days subjects were on randomized study drug. [Table 13](#) summarizes results for Study 1 and Study 2.

Table 13. Percentage of Subjects Reporting Heartburn 1 Day or Less During the Second Week of Treatment of the 14-Day Randomized Treatment Period (FAS Population)

| Study | Esomeprazole | | Placebo | | Comparison Between Groups ¹ | | |
|-------|--------------|--|---------|--|--|--------------|---------|
| | N | Number (%) of Subjects Reporting ≤1 Day of Heartburn | N | Number (%) of Subjects Reporting ≤1 Day of Heartburn | Relative Risk | 95% CI | P-value |
| 1 | 168 | 43 (25.60) | 163 | 16 (9.82) | 2.61 | (1.53, 4.44) | 0.0002 |
| 2 | 162 | 38 (23.46) | 158 | 13 (8.23) | 2.85 | (1.58, 5.15) | 0.0002 |

Abbreviations: CI, confidence interval

¹Proportion of subjects with ≤1 day of heartburn by treatment were compared by using a chi-square test. A relative risk >1 shows esomeprazole to have a favorable outcome compared to placebo.

Source: Reviewer's table, adapted from Sponsor's Table 17, page 41, Summary of Clinical Efficacy.

Reviewer comments: Results for the analysis of the percentage of subjects reporting ≤1 days of heartburn during the second week of treatment of the 14-day treatment period were similar to results for the final week of treatment. The relative risk for Study 1 (2.6) and Study 2 (2.9) both favor the esomeprazole group by a statistically significant margin. These data support the durability of efficacy of esomeprazole 20 mg daily for the OTC treatment of frequent heartburn over 14 days.

Proportion of subjects with heartburn 1 day or less during the first week of treatment

For this secondary endpoint the first week of treatment was defined as the first 7 consecutive days subjects were on randomized study drug. Table 14 summarizes results for Study 1 and Study 2.

Table 14. Percentage of Subjects Reporting Heartburn 1 Day or Less During the First Week of Treatment of the 14-Day Randomized Treatment Period (FAS Population)

| Study | Esomeprazole | | Placebo | | Comparison Between Groups ¹ | | |
|-------|--------------|--|---------|--|--|--------------|---------|
| | N | Number (%) of Subjects Reporting ≤1 Day of Heartburn | N | Number (%) of Subjects Reporting ≤1 Day of Heartburn | Relative Risk | 95% CI | P-value |
| 1 | 168 | 26 (15.48) | 163 | 10 (6.13) | 2.52 | (1.26, 5.06) | 0.0064 |
| 2 | 162 | 32 (19.75) | 158 | 7 (4.43) | 4.46 | (2.03, 9.80) | <0.0001 |

Abbreviations: CI, confidence interval

¹Proportion of subjects with ≤1 day of heartburn by treatment were compared by using a chi-square test. A relative risk >1 shows esomeprazole to have a favorable outcome compared to placebo.

Source: Reviewer's table, adapted from Sponsor's Table 18, page 42, Summary of Clinical Efficacy.

Reviewer comments: Because a lower bound of the 95% CI of the relative risk >1 indicates that subjects receiving esomeprazole had a favorable outcome (i.e., ≤1 days of heartburn during the first week of treatment of the 14-day treatment period) compared with subjects receiving placebo, the relative risk for Study 1 (2.5) and Study 2 (4.5) both favor the esomeprazole group by a statistically significant margin. The wider 95% CI in Study 2 indicates the relative risk of 4.5 is a less precise estimate than the relative risk

of 2.5 estimated by Study 1. The findings support the efficacy of esomeprazole in the first 7 days of treatment. Overall, the analysis results are generally consistent for the first week, second week, and final week of treatment of the 14-day randomized treatment period. The totality of these data supports the efficacy of esomeprazole 20 mg daily for the OTC treatment of frequent heartburn over 14 days.

6.1.6 Other Endpoints

No other efficacy endpoints were pre-specified in the SAP for the two efficacy studies submitted as part of this NDA. Exploratory efficacy analyses pertaining to durability of efficacy are presented in section [6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects](#). Additional exploratory endpoints are discussed in section [6.1.10 Additional Efficacy Issues/Analyses](#).

6.1.7 Subpopulations

Age

As shown in [Table 15](#), for Study 1 the treatment difference favored esomeprazole in subjects aged <65 years (12%) and in subjects aged ≥65 years (41%), but there were only 18 subjects aged ≥65 years (~5% of FAS population). For Study 2 the treatment difference also favored esomeprazole in subjects aged <65 years (15%) and in subjects aged ≥65 years (11%), but there were only 15 subjects aged ≥65 years (~5% of FAS population).

Table 15. Percentage of Heartburn-free 24-hour Days During 14 Days of Treatment by Age Group (FAS Population)

| Study/Group | Esomeprazole | | Placebo | | Treatment Difference | |
|----------------|--------------|-------------------|---------|-------------------|----------------------|---------|
| | N | LS Mean (95% CI) | N | LS Mean (95% CI) | LS Mean (95% CI) | P-value |
| Study 1 | | | | | | |
| <65 Years | 161 | 45.5 (41, 49.9) | 152 | 33.9 (29.3, 38.5) | 11.6 (5.8, 17.3) | <0.0001 |
| ≥65 Years | 7 | 63.5 (43.7, 83.4) | 11 | 23.1 (7.3, 38.8) | 40.5 (15.4, 65.6) | 0.0016 |
| Study 2 | | | | | | |
| <65 Years | 153 | 47.5 (43.5, 51.4) | 152 | 32.2 (28.2, 36.2) | 15.3 (9.8, 20.8) | <0.0001 |
| ≥65 Years | 9 | 56 (39.6, 72.4) | 6 | 45.3 (25.2, 65.5) | 10.7 (-15.4, 36.7) | 0.4215 |

Abbreviations: CI, confidence interval; LS, least square

Source: Reviewer's table, adapted from Sponsor's Table 6 and 7, pages 15-16, Response to information request in 74-day letter.

Reviewer comments: *The percentage of subjects aged ≥65 years in Study 1 (5%) and Study 2 (5%) was probably too small to draw any meaningful conclusions.*

Gender

As shown in [Table 16](#), for Study 1 the treatment difference favored esomeprazole in male subjects (14%) and in female subjects (13%). For Study 2 the treatment difference also favored esomeprazole in male subjects (14%) and in female subjects (17%).

Table 16. Percentage of Heartburn-free 24-hour Days During 14 Days of Treatment by Gender (FAS Population)

| Study/Group | Esomeprazole | | Placebo | | Treatment Difference | |
|----------------|--------------|-------------------|---------|-------------------|----------------------|---------|
| | N | LS Mean (95% CI) | N | LS Mean (95% CI) | LS Mean (95% CI) | P-value |
| Study 1 | | | | | | |
| Male | 64 | 47.8 (41, 54.6) | 68 | 33.7 (27.1, 40.3) | 14.1 (5.1, 23.2) | 0.0023 |
| Female | 104 | 45.1 (39.7, 50.5) | 95 | 32.6 (27, 38.3) | 12.5 (5.1, 19.8) | 0.0009 |
| Study 2 | | | | | | |
| Male | 76 | 47.6 (42.1, 53.2) | 76 | 33.8 (28.1, 39.4) | 13.9 (6, 21.8) | 0.0006 |
| Female | 86 | 48.3 (43, 53.6) | 82 | 31.8 (26.3, 37.3) | 16.5 (9, 24) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square

Source: Reviewer's table, adapted from Sponsor's Table 6 and 7, pages 15-16, Response to information request in 74-day letter.

Reviewer comments: *The treatment effect favoring esomeprazole appears comparable in both genders across both studies.*

Race

As shown in [Table 17](#), in both Study 1 and Study 2, the treatment effect favoring esomeprazole is ~5% in Black or African American subjects, as compared with ~18% to 20% among white subjects. In both studies, Black or African American subjects comprised an adequate percentage of the overall study population (38% in Study 1 and 33% in Study 2).

Table 17. Percentage of Heartburn-free 24-hour Days During 14 Days of Treatment by Race (FAS Population)

| Study/Group | Esomeprazole | | Placebo | | Treatment Difference | |
|---------------------------|--------------|-------------------|---------|-------------------|----------------------|---------|
| | N | LS Mean (95% CI) | N | LS Mean (95% CI) | LS Mean (95% CI) | P-value |
| Study 1 | | | | | | |
| White | 101 | 51 (45.5, 56.5) | 108 | 32.9 (27.7, 38.2) | 18.1 (11, 25.1) | <0.0001 |
| Black or African American | 64 | 37 (29.7, 44.3) | 53 | 32.3 (24.5, 40) | 4.7 (-4.7, 14.2) | 0.3245 |
| Other | 3 | 54.6 (24.6, 84.7) | 2 | 37.7 (0.3, 75.1) | 21 (-27.3, 69.2) | 0.3930 |
| Study 2 | | | | | | |
| White | 107 | 53 (48.3, 57.7) | 111 | 32.9 (28.3, 37.5) | 20 (13.6, 26.5) | <0.0001 |
| Black or African American | 48 | 36.1 (28.8, 43.4) | 46 | 31.2 (23.7, 38.8) | 4.9 (-4.9, 14.7) | 0.3294 |
| Other | 7 | 48.8 (30.7, 67) | 1 | 43.1 (-4.8, 90.9) | 5.8 (-45.1, 56.6) | 0.8231 |

Abbreviations: CI, confidence interval; LS, least square
 Source: Reviewer's table, adapted from Sponsor's Table 6 and 7, pages 15-16, Response to information request in 74-day letter.

Reviewer comments: *Treatment differences among subjects of other race are not consistent across the studies (likely due to small sample sizes), with a treatment difference of 21% favoring esomeprazole in Study 1 and a treatment difference of 6% favoring esomeprazole in Study 2. The smaller treatment effect favoring esomeprazole in Black or African American subjects as compared with white subjects, however, was consistent across the two studies (~5% in both studies). The etiology of this differential effect among races is not entirely clear. Because the studies were not powered to compare individual subgroups, however, these findings should be interpreted with caution. Additional discussion is provided below, following the presentation of treatment differences by ethnicity.*

Ethnicity

As shown in [Table 18](#), for Study 1 the treatment difference favored *placebo* in Hispanic or Latino subjects (-5%) and favored esomeprazole in subjects of other ethnicity (17%). This observation was not consistent across the two studies. Namely, in Study 2, the treatment difference favored esomeprazole in Hispanic or Latino subjects *and* in subjects of other ethnicity, and the magnitude of the treatment difference (15%) was consistent in both groups.

Table 18. Percentage of Heartburn-free 24-hour Days During 14 Days of Treatment by Ethnicity (FAS Population)

| Study/Group | Esomeprazole | | Placebo | | Treatment Difference | |
|--------------------|--------------|-------------------|---------|-------------------|----------------------|---------|
| | N | LS Mean (95% CI) | N | LS Mean (95% CI) | LS Mean (95% CI) | P-value |
| Study 1 | | | | | | |
| Hispanic or Latino | 34 | 33.9 (22.3, 45.4) | 25 | 38.7 (25.2, 52.2) | -4.8 (-18.2, 8.6) | 0.4803 |
| All Other | 134 | 48.9 (44.1, 53.7) | 138 | 31.7 (27.1, 36.4) | 17.2 (11, 23.3) | <0.0001 |
| Study 2 | | | | | | |
| Hispanic or Latino | 24 | 50.7 (40.3, 61) | 21 | 35.5 (24.5, 46.4) | 15.2 (0.6, 29.7) | 0.0410 |
| All Other | 138 | 47.6 (43.4, 51.8) | 137 | 32.4 (28.2, 36.6) | 15.2 (9.4, 21) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square

Source: Reviewer's table, adapted from Sponsor's Table 6 and 7, pages 15-16, Response to information request in 74-day letter.

To explore further this inconsistency between the two studies, the Sponsor examined treatment effect at each clinical site. This investigation determined that 48 of the 59 Hispanic subjects in Study 1 came from a single site, site 7808, which showed a low treatment effect overall. The Sponsor performed an analysis of the data from site 7808, and concluded that the reasons for the unexpected efficacy pattern observed at this site are unclear. With regard to important protocol deviations and premature discontinuation, the proportions at this site were similar to the proportions in the study overall. Aside from a predominance of Hispanic subjects, other baseline characteristics for subjects at site 7808 were similar to those at other sites in Study 1 and Study 2. According to the Sponsor, the pattern of IVRS call-in frequency was also consistent with that at other sites. This examination of site 7808 data along with an on-site review of study records led the Sponsor to conclude that the data at site 7808 "support the integrity of the overall data for use in primary efficacy analyses."

Reviewer comments: *Following careful review of site details in the Advanced Methods for Risk-based Prioritization of Clinical Trial Inspections Site Selection Tool and discussion with OSI, this medical officer determined that site 7808 from Study 1 did not warrant OSI inspection.*

To examine further a potential effect of ethnic subgroup on efficacy of oral esomeprazole, this medical officer reviewed findings of subgroup analyses from the phase 3 studies used to support approval of Prevacid 24HR for OTC use. In the two phase 3 studies that assessed percentage of 24-hour days with no heartburn over 14 days of treatment with lansoprazole 15 mg (Study 301 and Study 302), subgroup analysis was performed not by ethnicity (i.e., Hispanic vs. other as done in Study 1 and Study 2 of the current NDA for esomeprazole), but rather by race [i.e., Caucasian,

Hispanic, and other (includes Black, Asian, or other races)]. [Table 19](#) summarizes results for the primary analysis by race for Study 301 and Study 302.

Table 19. Percentage of Heartburn-Free 24-Hour Days During 14 Days of Treatment (ITT Population)¹ in Phase 3 Prevacid 24HR Trials (NDA 22-327)

| Study/Race | Lansoprazole 15 mg | | Placebo | | P-value ² |
|-------------------------|--------------------|-------------------|---------|-------------------|----------------------|
| | N | Mean (95% CI) | N | Mean (95% CI) | |
| Study 301 | | | | | |
| Caucasian | 195 | 63.2 (59.1, 67.3) | 195 | 45.6 (41.6, 49.5) | <0.0001 |
| Hispanic | 39 | 48.3 (37.5, 59.0) | 39 | 43.5 (34.3, 52.8) | 0.5251 |
| Black, Asian, and Other | 48 | 56.0 (47.7, 64.2) | 48 | 47.8 (39.2, 56.3) | 0.2065 |
| Study 302 | | | | | |
| Caucasian | 218 | 68.0 (64.1, 71.9) | 209 | 44.6 (40.7, 48.5) | <0.0001 |
| Hispanic | 34 | 51.6 (38.8, 64.5) | 39 | 37.6 (28.7, 46.5) | 0.1497 |
| Black, Asian, and Other | 36 | 56.6 (47.1, 66.1) | 34 | 55.6 (44.6, 66.6) | 0.0800 |

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least square; SE, standard error

¹The ITT population was defined as all randomized subjects who took at least one dose of study medication, and had at least one post-baseline efficacy assessment. The ITT population was the pre-specified primary analysis population in Studies 301 and 302.

²Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

Source: Reviewer's table, adapted from Table 4.1, pages 27-29, Statistical Review and Evaluation of NDA 22-327 (Prevacid OTC) by Dr. Freda Cooner, dated April 6, 2009.

In Study 301, the treatment effect favoring Prevacid 24HR was ~17% among Caucasian subjects, ~5% among Hispanic subjects, and ~8% among Black, Asian, and other subjects. In Study 302, the treatment effect favoring Prevacid 24HR was ~23% among Caucasian subjects, ~14% among Hispanic subjects, and ~1% among Black, Asian, and other subjects. Based on these findings, it appears that subgroup analyses were not consistent between Study 301 and Study 302 with respect to the magnitude of the treatment effect among Hispanic and Black, Asian, and other subjects. In some ways, the discordant results between Study 301 and Study 302 with respect to treatment difference among Hispanic subjects echo the findings for treatment difference among Hispanic subjects in Study 1 and Study 2 of the Nexium OTC trials. The statistical reviewer for the Prevacid 24HR NDA, Dr. Freda Cooner, noted the following in her review (dated April 6, 2009):

“Although the p-values across the subgroups may look different, the differences were mainly caused by the sample size differences among the subgroups. There were some noticeable treatment effect differences across subgroups that could not be explained by the sample size differences; however, there was no consistent trend across the studies and they might be purely random incidences.

In general, the treatment group statistics are similar across the various subgroups.”

This medical officer also reviewed the findings of subgroup analyses by race for NDA 21-153, which led to the initial approval of Nexium in February 2001 for the prescription treatment of erosive esophagitis and symptomatic GERD. Although the subgroup analyses performed for the studies submitted as part of the original NDA 21-153 did not include analysis by ethnicity, subgroup analyses did assess efficacy by race (i.e., Caucasian, Black, Asian, and others). In his review of the studies used to support approval of prescription Nexium for the aforementioned indications (review dated October 3, 2000), the statistical reviewer, Dr. Yi Tsong, noted that treatment arms were well balanced with respect to race, and noted that there were no meaningful differences between races with respect to the assessed efficacy endpoints.

Reviewer comments: Given the lack of a known or plausible theoretical intrinsic factor that might cause Hispanic or Black patients to have a blunted response to PPIs, and in light of the findings of the race subgroup analyses for NDA 21-153 (Nexium) and NDA 22-327 (Prevacid 24HR) discussed above, this medical officer finds no consistent evidence to suggest differential response to esomeprazole for the OTC treatment of frequent heartburn among various races or ethnicities. Moreover, because the studies were not powered to compare individual subgroups, these differences in treatment effect in certain subgroups should be interpreted with caution. In this medical officer's assessment, the Sponsor's explanation of the role of results from a single clinical site (site 7808) in Study 1 in blunting the overall treatment effect among subjects of Hispanic ethnicity appears reasonable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosage (20 mg) recommended by the Sponsor for OTC esomeprazole for the treatment of heartburn for a 14-day period is consistent with the lowest dose of esomeprazole that was initially approved in 2001 for the treatment of symptomatic GERD. This dose is currently available through prescription in the United States.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

According to the Sponsor, because the application for OTC status of oral esomeprazole magnesium specifies a 14-day dosing regimen for treatment of frequent heartburn in adults, not long-term treatment, a discussion of persistence of efficacy and/or tolerance effects is not directly applicable.

As an exploratory analysis, the Sponsor determined the percentage of subjects with heartburn-free 24-hour days by diary day during the 14-day treatment period. The analysis, presented in [Table 20](#), assumes days with missing data to be days with heartburn.

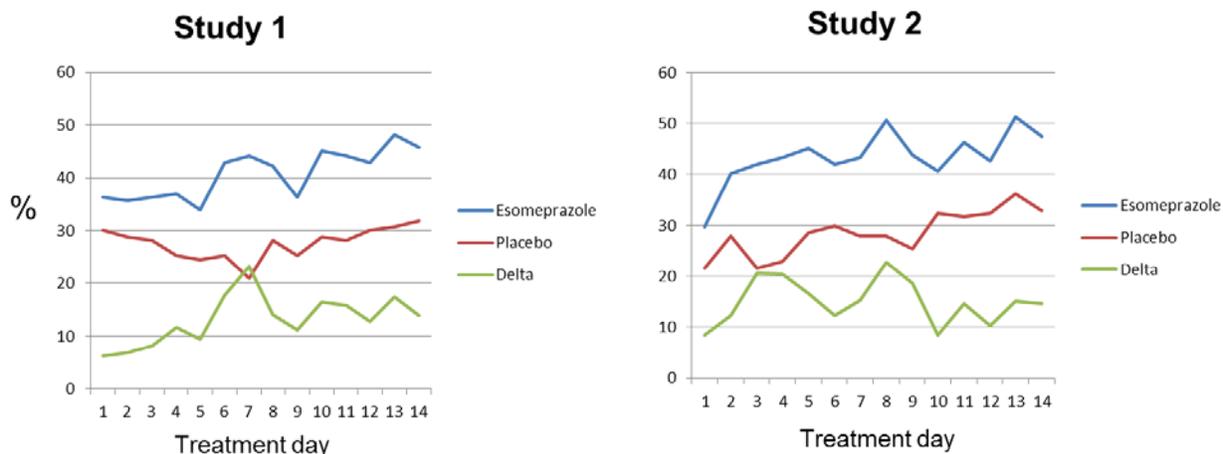
Table 20. Number (%) of Subjects with Heartburn-free 24-hour Days by Diary Day During 14 Days of Treatment (FAS Population)

| Diary Day | Study 1 | | Study 2 | |
|-----------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | Esomeprazole (N=168) n (%) | Placebo (N=163) n (%) | Esomeprazole (N=162) n (%) | Placebo (N=158) n (%) |
| 1 | 61 (36.3) | 49 (30.1) | 48 (29.6) | 34 (21.5) |
| 2 | 60 (35.7) | 47 (28.8) | 65 (40.1) | 44 (27.9) |
| 3 | 61 (36.3) | 46 (28.2) | 68 (42.0) | 34 (21.5) |
| 4 | 62 (36.9) | 41 (25.2) | 70 (43.2) | 36 (22.8) |
| 5 | 57 (33.9) | 40 (24.5) | 73 (45.1) | 45 (28.5) |
| 6 | 72 (42.9) | 41 (25.2) | 68 (42.0) | 47 (29.8) |
| 7 | 74 (44.1) | 34 (20.9) | 70 (43.2) | 44 (27.9) |
| 8 | 71 (42.3) | 46 (28.2) | 82 (50.6) | 44 (27.9) |
| 9 | 61 (36.3) | 41 (25.2) | 71 (43.8) | 40 (25.3) |
| 10 | 76 (45.2) | 47 (28.8) | 66 (40.7) | 51 (32.3) |
| 11 | 74 (44.1) | 46 (28.2) | 75 (46.3) | 50 (31.7) |
| 12 | 72 (42.9) | 49 (30.1) | 69 (42.6) | 51 (32.3) |
| 13 | 81 (48.2) | 50 (30.7) | 83 (51.2) | 57 (36.1) |
| 14 | 76 (45.2) | 51 (31.2) | 74 (45.7) | 47 (29.8) |

Note: Days with missing values are handled as days with heartburn.
 Source: Reviewer's table, adapted from Sponsor's Table 55, page 253, CSR of Study 1; Table 55, page 234, CSR of Study 2; Table 1 and Table 2 of Appendix 1, Response to November 18, 2013 information request.

Figure 2 below provides a graphical representation of the data in Table 20. In the graphs, the delta equals the percentage of esomeprazole subjects with heartburn-free 24-days minus percentage of placebo subjects with heartburn-free 24-days.

Figure 2. Percentage of Subjects with Heartburn-free 24-hour Days by Diary Day During 14 Days of Treatment (FAS Population)



Source: Reviewer's graphs, derived from data in Table 20.

Reviewer comments: Numerically, a larger proportion of esomeprazole subjects than placebo subjects demonstrated heartburn-free days during each of the 14 days of treatment in both studies. Although the interpretability of this exploratory analysis is

limited by the lack of statistical validity, the numerical trend does support durability of efficacy over the 14-day treatment period.

Notably, the largest treatment differences numerically favoring esomeprazole over placebo generally occurred after the first 4 days of treatment in both studies. This finding, although based on an exploratory endpoint, supports the Sponsor's proposed labeling claim that states "it may take 1 to 4 days for full effect." The pre-specified endpoint that supported this claim was presented previously in [Table 11](#). An additional exploratory analysis that also supports the assertion that "it may take 1 to 4 days for full effect" is presented in [Table 22](#).



The current labeling for lansoprazole OTC also includes the claim that (b) (4) in the 2 principal studies (301 and 302) that showed a statistically significant treatment difference favoring lansoprazole 15 mg over placebo. In Study 301, the treatment difference favoring lansoprazole 15 mg over placebo (b) (4) and in Study 302, the treatment difference favoring lansoprazole 15 mg over placebo was (b) (4). For additional details, see Statistical Review and Evaluation of the lansoprazole OTC NDA (see Dr. Freda Cooner's review of NDA 22-327 in DARRTS, dated April 6, 2009). (b) (4)

Clinical Review

Farrokh Sohrabi, MD

NDA 204-655

Nexium (esomeprazole magnesium) Delayed-Release Capsules OTC 20 mg

(b) (4)
The primary efficacy endpoint in the studies that supported approval of omeprazole for OTC use (Study 171 and Study 183) was proportion of subjects with no heartburn (b) (4)

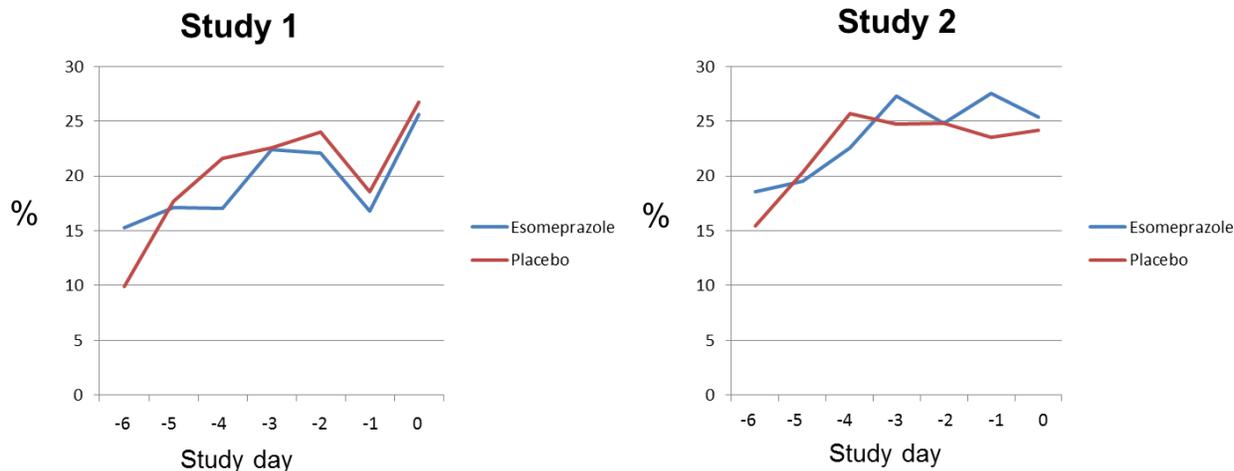
The results of the primary analysis in both studies showed a statistically significant treatment difference favoring omeprazole 20 mg over placebo. In Study 171, the treatment difference favoring omeprazole 20 mg over placebo (b) (4) and in Study 183, the treatment difference favoring omeprazole 20 mg over placebo was (b) (4)

For additional details, see Division Director review of the omeprazole OTC NDA (see Dr. Robert Justice's review of NDA 21-229 in DARRTS, dated June 19, 2003). The treatment differences favoring esomeprazole 20 mg over placebo (b) (4) are numerically smaller than the treatment differences favoring omeprazole 20 mg over placebo (b) (4).

In this medical officer's assessment, because no pre-specified, statistically valid endpoints in Study 1 or Study 2 directly assessed "relief of symptoms" (i.e., heartburn-free status) (b) (4) and because the magnitude of the treatment difference favoring esomeprazole over placebo (b) (4) in both studies was small, the Sponsor's proposed labeling claim that (b) (4) does not appear to be supported.

This medical officer requested that for each of the two studies, the Sponsor also provide the number and percentage of subjects (by treatment arm during the randomized phase) with heartburn-free 24-hour days by diary day during the placebo run-in period, on the day of randomization (day 0), and during the placebo follow-up period. The data for the run-in period and the day of randomization are presented in graph form in [Figure 3](#) and the data for the follow-up period are presented in graph form in [Figure 4](#). See [Table 27](#) and [Table 28](#) for the tabular summary of the number and percentage of subjects (by treatment arm) with heartburn-free 24-hour days by diary day in Study 1 and Study 2, respectively.

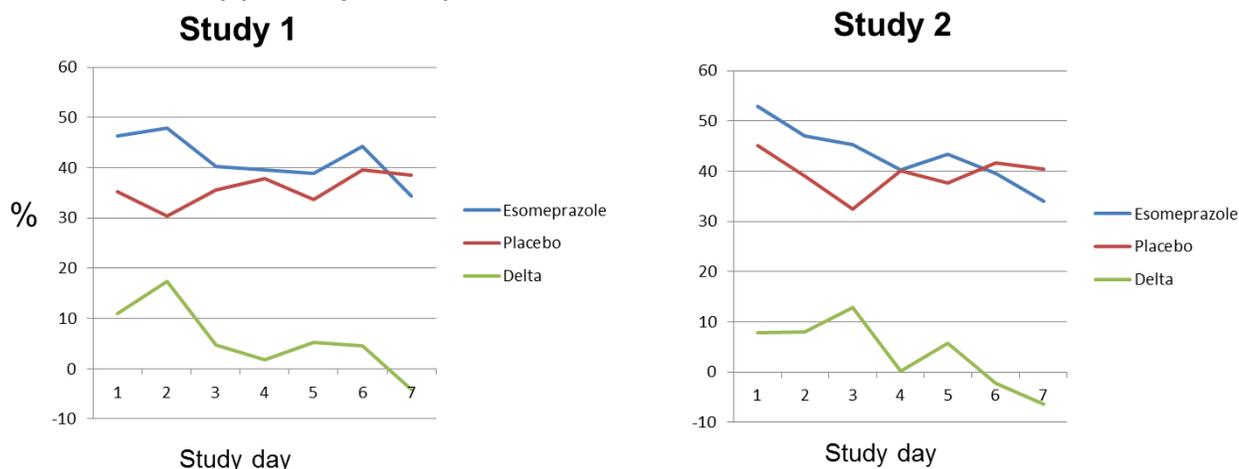
Figure 3. Percentage of Subjects with Heartburn-free 24-hour Days by Diary Day During the Placebo Run-in Period (Day -6 to -1) and on Day of Randomization (Day 0) (FAS Population)



Source: Reviewer's graphs, derived from data in [Table 27](#) and [Table 28](#).

Reviewer comments: *There is evidence of a regression-to-the-mean effect during the placebo run-in period (i.e., percentage of subjects with heartburn-free 24-hour days generally increases from day -6 to day -1), but the percentage of subjects with heartburn-free 24-hour days was generally similar across both treatment arms in Study 1 and Study 2. Moreover, subjects were well matched across treatment arms in both studies with regard to percentage reporting a heartburn-free 24-hour day on the day of randomization (day 0). Overall, the findings reassure this medical officer that the treatment differences favoring esomeprazole during the 14-day double-blind treatment period (see [Table 20](#) and [Figure 2](#)) were driven by the drug itself and not imbalances across the treatment arms.*

Figure 4. Percentage of Subjects with Heartburn-free 24-hour Days by Diary Day During the Placebo Follow-up Period (Days 1 to 7 Following Completion of the 14-day Double-Blind Treatment Period) (FAS Population)



Source: Reviewer's graphs derived from data in [Table 27](#) and [Table 28](#).

Reviewer comments: *Not unexpectedly, the treatment difference favoring esomeprazole decreases steadily over the course of the 7-day follow-up period. In both studies it appears that the treatment difference approaches zero on day 4 of the 7-day follow-up period.*

6.1.10 Additional Efficacy Issues/Analyses

FAS population versus MITT population

As previously discussed in section 5.3 [Discussion of Individual Studies/Clinical Trials](#) and in section 6.1.3 [Subject Disposition](#), the Sponsor pre-specified the population for the efficacy analyses as all randomized subjects who had one dose of randomized treatment and had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment (i.e., the FAS population). However, the statistical reviewer noted that the “valid” requirement may not be assessed impartially. As such, the FAS population may be a biased representation of the target population. Accordingly, the statistical reviewer requested the Sponsor perform analyses of the primary and secondary endpoints using a modified ITT (MITT) population, defined as all randomized subjects who took at least one dose of randomized treatment.

In Study 1 the MITT and FAS populations are exactly the same (i.e., there were no randomized subjects who took drug and did not have post-baseline data). In Study 2, there were 6 subjects in total (3 subjects in each treatment arm) who were randomized and treated, but did not have post-baseline data (FAS=320 subjects, MITT=326 subjects). See [Figure 1](#) for a summary of population flow in Study 1 and Study 2.

[Table 21](#) shows results of the primary efficacy analysis for Study 1 and Study 2 using the MITT population.

Table 21. Percentage of Heartburn-Free 24-Hour Days During 14 Days of Treatment (MITT Population)

| Study | Esomeprazole | | Placebo | | Treatment Difference ¹ | | |
|-------|--------------|--------------|---------|--------------|-----------------------------------|---------------|----------------------|
| | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean (SE) | 95% CI | P-value ² |
| 1 | 168 | 46.13 (2.24) | 163 | 33.07 (2.26) | 13.06 (2.86) | (7.44, 18.68) | <0.0001 |
| 2 | 165 | 47.62 (1.95) | 161 | 32.76 (1.98) | 14.86 (2.70) | (9.53, 20.18) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square; SE, standard error

¹ Obtained from ANCOVA with centers and treatment as fixed effects and heartburn frequency during the run-in phase as covariate.

² Because the MITT population was not pre-specified in the SAP, **p-values are presented for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 1, page 24, Response to information request in 74-day letter.

Reviewer comments: *As mentioned previously, the MITT and FAS populations were identical in Study 1; therefore, primary analysis results are identical for Study 1 in both the MITT and the FAS population. Further, because the difference in numbers between the MITT and the FAS population in Study 2 were balanced across the treatment arms (i.e., 3 fewer subjects in each treatment arm of the FAS population than the MITT population), this reviewer would not expect a substantial change in primary analysis results using the MITT population instead of the FAS population. Indeed, the results in the MITT population are nearly identical with those previously reported in the pre-specified FAS population (Table 8). These findings support the findings of the primary efficacy analysis.*

Percentage of days with no heartburn over Days 1-4 of treatment period

In an Information Request to the Sponsor, the statistical reviewer, Dr. Wen Jen Chen, asked the Sponsor to perform efficacy analysis on percentage of days with no heartburn over Days 1 to 4 of the treatment period. Results are summarized in Table 22.

Table 22. Percentage of Heartburn-Free 24-Hour Days During Days 1 to 4 of Treatment (FAS Population)

| Study | Esomeprazole | | Placebo | | Treatment Difference ¹ | | |
|-------|--------------|--------------|---------|--------------|-----------------------------------|---------------|----------------------|
| | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean (SE) | 95% CI | P-value ² |
| 1 | 168 | 40.77 (2.51) | 163 | 32.57 (2.54) | 8.20 (3.21) | (1.89, 14.52) | 0.0110 |
| 2 | 162 | 43.28 (2.22) | 158 | 28.43 (2.25) | 14.85 (3.09) | (8.78, 20.92) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square; SE, standard error

¹ Obtained from ANCOVA with centers and treatment as fixed effects and heartburn frequency during the run-in phase as covariate.

² Because this endpoint was not pre-specified in the SAP, **p-values are presented for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 1, page 7, Response to information request in 74-day letter.

Reviewer comments: *The percentage of heartburn-free 24-hour days during Days 1 to 4 of treatment was higher in the esomeprazole arm than the placebo arm in both Study 1 and 2. These findings are congruent with results of the pre-specified secondary endpoint that compared the proportion of subjects with 0, 1, 2, 3, or 4 days with no heartburn over Days 1 to 4 in both studies (see Table 11). The magnitude of the treatment difference favoring esomeprazole during the first 4 days of treatment is*

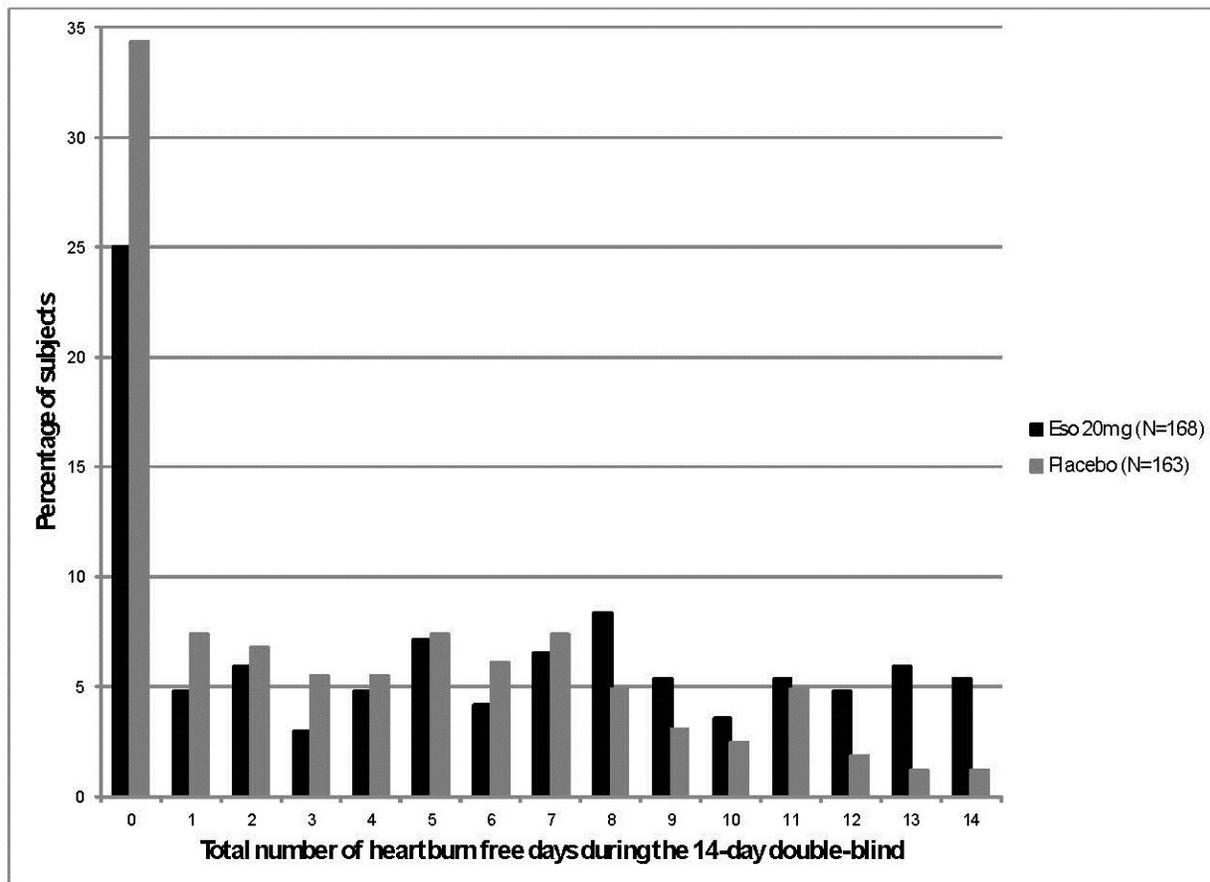
smaller than the magnitude of the treatment difference favoring esomeprazole during the entire 14 days of treatment in Study 1 (8.2% vs. 13.1%) and in Study 2 (14.9% vs. 15.3%). This finding supports qualitatively the proposed labeling claim that states “it may take 1 to 4 days for full effect.”

Total number (cumulative) of heartburn-free 24-hour days during the 14-day double-blind treatment period

This medical officer requested that for each of the two studies, the Sponsor provide a distribution bar graph that plots the percentage of subjects (by treatment arm) against the total number (cumulative) of heartburn-free 24-hour days during the 14-day double-blind treatment period.

[Figure 5](#) shows the data for Study 1 and [Figure 6](#) shows the data for Study 2. See [Table 29](#) in the Appendix for the tabular summary of the number and percentage of subjects (by treatment arm) with heartburn-free 24-hour days (from 0 to 14) during the 14-day double-blind treatment period in both studies.

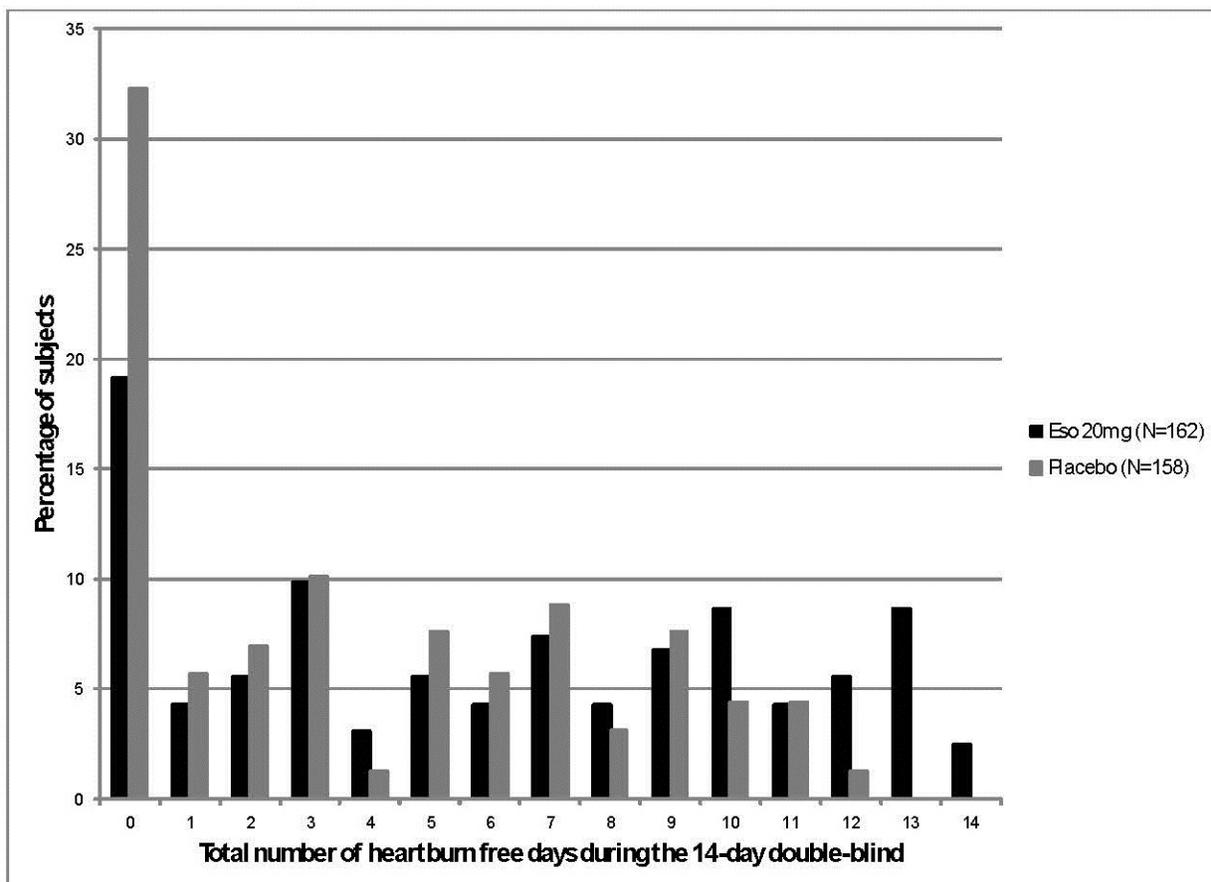
Figure 5. Study 1 Percentage of Subjects Versus Total Number of 24-Hour Heartburn-free Days During the 14-Day Double-blind Period (FAS Population)



Source: Figure 1, page 10 of Sponsor's Response to November 18, 2013 information request.

Reviewer comments: *In Study 1, approximately 25% of esomeprazole subjects reported no heartburn-free days during the 14-day treatment period, as compared with 34% of placebo subjects. Approximately 39% of esomeprazole subjects had more than 7 total heartburn-free days over the 14-day treatment period, as compared with 20% of placebo subjects. Moreover, the overall trend in the distribution curve (i.e., higher percentage of placebo subjects than esomeprazole subjects with 1, 2, 3, 4, 5, 6, or 7 total heartburn-free days and higher percentage of esomeprazole subjects than placebo subjects with 8, 9, 10, 11, 12, 13, or 14 total heartburn-free days) supports the primary efficacy finding that the esomeprazole arm had a significantly higher proportion of heartburn-free 24-hour days than the placebo arm.*

Figure 6. Study 2 Percentage of Subjects Versus Total Number of 24-Hour Heartburn-free Days During the 14-Day Double-blind Period (FAS Population)



Source: Figure 2, page 11 of Sponsor's Response to November 18, 2013 information request.

Reviewer comments: *The distribution curve for Study 2 demonstrates somewhat more variability than that for Study 1. Nonetheless, the findings are generally consistent across the two studies. In Study 2, approximately 32% of esomeprazole subjects reported no heartburn-free days during the 14-day treatment period, as compared with 19% of placebo subjects. Approximately 41% of esomeprazole subjects had more than 7 total heartburn-free days over the 14-day treatment period, as compared with 21% of placebo subjects.*

Handling of inconsistencies in the raw study database

In the SDTM Data Reviewer's Guide, the Sponsor discussed inconsistencies in the raw study database dataset DIARYNM (which was based on the daily IVRS questions presented to study subjects; see [Appendix 3: IVRS Daily Self-Assessment Diary](#) for the diary questions). Specifically, the Sponsor indicated that in some cases, a subject could have reported having heartburn during the day and/or night, but the overall heartburn variable could contain a "No". Additionally, some subjects called in several times a day

and therefore have multiple values on the same assessment date in the DIARYNM dataset. Regarding these inconsistencies, the Sponsor noted the following:

“These inconsistencies happened because of how the IVRS recorded the data in such situations. The inconsistencies became apparent at the analysis phase of the studies, and thus were handled at that stage.

To handle this, following rules were used for these two cases:

Multiple rows: If there are multiple values on the same assessment date use the last record (row).

The reason for choosing the last row is that it in most cases contained the most complete set of data.

Heartburn inconsistency:

These rules were applied to ensure that a patient with either daytime or night time heartburn would be counted as having overall heartburn.

* If Day Heartburn or Night Heartburn = yes, then Overall Heartburn = yes and Overall Severity = max (Day Severity, Night Severity)

* If Overall Heartburn = missing and Day Heartburn = missing and Night Heartburn = no, then Overall Heartburn = missing

* If Overall Heartburn = missing and Day Heartburn = no and Night Heartburn = missing, then Overall Heartburn = missing

* If Overall Heartburn = no and Day Heartburn = no and Night Heartburn = missing, then Overall Heartburn = no

* If Overall Heartburn = no and Day Heartburn = missing and Night Heartburn = no, then Overall Heartburn = no

* If Overall Heartburn = yes then it is not overruled by Day = no or Night = no answers

To handle both of the inconsistencies described above adjustments were made when data was converted into the SDTM database from the RAW study database.”

This medical officer sought to assess if the inconsistencies in the raw study database were balanced across study arms (in which case any inconsistencies would not be expected to change substantially the magnitude of the treatment difference in the

esomeprazole or placebo arms). Thus, in an Information Request, the Sponsor was asked to perform an exploratory analysis on the primary endpoint, using the following modification to the rules discussed in section 2.1:

If either Day Heartburn or Night Heartburn = yes AND Overall Heartburn = no, then Overall Heartburn = no.

Table 23 presents results of this exploratory analysis.

Table 23. Exploratory Analysis¹: Percentage of Heartburn-Free 24-Hour Days During Days 1 to 14 of Treatment (FAS Population)

| Study | Esomeprazole | | Placebo | | Treatment Difference ² | | |
|-------|--------------|--------------|---------|--------------|-----------------------------------|---------------|----------------------|
| | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean (SE) | 95% CI | P-value ³ |
| 1 | 168 | 50.00 (2.12) | 163 | 37.50 (2.14) | 12.51 (2.71) | (7.17, 17.85) | <0.0001 |
| 2 | 162 | 51.90 (1.91) | 158 | 36.86 (1.93) | 15.04 (2.65) | (9.83, 20.26) | <0.0001 |

Abbreviations: CI, confidence interval; LS, least square; SE, standard error

¹ This exploratory analysis examines the scenario in which either Day Heartburn or Night Heartburn = yes AND Overall Heartburn = no, then Overall Heartburn = no.

² Obtained from ANCOVA with centers and treatment as fixed effects and heartburn frequency during the run-in phase as covariate.

³ Because this endpoint was not pre-specified in the SAP, **p-values are presented for informational purposes only.**

Source: Reviewer's table, adapted from Sponsor's Table 3, page 11, Response to information request in 74-day letter.

Reviewer comments: *As would be expected, the percentage of heartburn-free days increased for both the treatment groups when the rule devised to eliminate the inconsistency between a subject's response of no heartburn in the last 24 hours, but reporting either daytime or nighttime symptoms for the same period, is ignored. Importantly, when compared with the pre-specified primary efficacy analysis results, the treatment difference in this exploratory analysis remained essentially unchanged for Study 1 (13%) and for Study 2 (15%). This medical officer is reassured by the above exploratory analysis because it demonstrates that the inconsistencies in the raw database were balanced across the treatment groups in both studies.*

Also, for each treatment arm in each of the two studies, the Sponsor was asked to provide the proportion of subjects (% , n/N) who reported the following:

- a) Day Heartburn = yes, Night Heartburn = no, Overall Heartburn = no
- b) Day Heartburn = no, Night Heartburn = yes, Overall Heartburn = no
- c) Day Heartburn = yes, Night Heartburn = yes, Overall Heartburn = no

Table 24 shows the number and percentage of subjects who reported the inconsistencies listed above (a, b, or c) at least one time during either the run-in or randomized treatment period.

Table 24. Subjects in Study 1 and Study 2 that Reported, at Least Once During the Run-in and/or Treatment Phase, Heartburn Either During the Day and/or at Night but Did not Report Any During the Past 24 Hours (FAS Population)

| | Tot Number of Subjects | Esomeprazole 20 mg | | | | Tot Number of Subjects | Placebo | | | |
|-------------------|------------------------|-----------------------|------------------------|------------|--------------------|------------------------|------------|------------|------------|--------------------|
| | | Criteria A | Criteria B | Criteria C | Criteria A, B or C | | Criteria A | Criteria B | Criteria C | Criteria A, B or C |
| | | N (%) | N (%) | N (%) | N (%) | | N (%) | N (%) | N (%) | N (%) |
| Study D961RC00001 | 168 | 23 (13.7%) | 41 (24.4%) | 25 (14.9%) | 66 (39.3%) | 163 | 27 (16.6%) | 36 (22.1%) | 13 (8.0%) | 62 (38.0%) |
| Study D961RC00002 | 162 | 28 (17.3%) | 38 (23.5%) | 18 (11.1%) | 64 (39.5%) | 158 | 19 (12.0%) | 34 (21.5%) | 22 (13.9%) | 59 (37.3%) |
| Criteria A: | Day Heartburn = yes, | Night heartburn = no, | Overall heartburn = no | | | | | | | |
| Criteria B: | Day Heartburn =no, | Night heartburn =yes, | Overall heartburn = no | | | | | | | |
| Criteria C: | Day Heartburn = yes, | Night heartburn =yes, | Overall heartburn = no | | | | | | | |

Source: Sponsor's Table 4, page 12, Response to information request in 74-day letter.

Reviewer comments: *The percentage of esomeprazole and placebo subjects in Study 1 meeting at least one of the conditions was 39% and 38%, respectively. Similarly, the percentage of esomeprazole and placebo subjects in Study 2 meeting at least one of the conditions was 40% and 37%, respectively. Importantly, the percentage of subjects who reported the inconsistencies listed above (a, b, or c) was balanced across treatment arms in both studies and comparable across Study 1 and Study 2.*

While the percentage of subjects who reported the inconsistencies listed above (a, b, or c) was approximately 37% to 40%, the total amount of call-in days meeting at least one of the conditions divided by the total number of calls was approximately 4%. [Table 25](#) shows the number and percentages of actual responses meeting any of the three criteria.

Table 25. Days in Study 1 and Study 2 for Which Subjects Reported Different Heartburn Criteria During the Study

| | Total number of call-in days | Esomeprazole 20 mg | | | | Total number of call-in days | Placebo | | | |
|-------------------|------------------------------|-----------------------|--------------|------------------------|--------------------|------------------------------|--------------|--------------|--------------|--------------------|
| | | Criteria A | Criteria B | Criteria C | Criteria A, B or C | | Criteria A | Criteria B | Criteria C | Criteria A, B or C |
| | | N (%) | N (%) | N (%) | N (%) | | N (%) | N (%) | N (%) | N (%) |
| Study D961RC00001 | 3249 | 35 (1.1%) | 75 (2.3%) | 30 (0.9%) | 140 (4.3%) | 3257 | 43 (1.3%) | 51 (1.6%) | 17 (0.5%) | 111 (3.4%) |
| Study D961RC00002 | 3047 | 45 (1.5%) | 67 (2.2%) | 29 (1.0%) | 141 (4.6%) | 3059 | 30 (1.0%) | 54 (1.8%) | 31 (1.0%) | 115 (3.8%) |
| Criteria A: | Day Heartburn = yes, | Night heartburn = no, | | Overall heartburn = no | | | | | | |
| Criteria B: | Day Heartburn =no, | Night heartburn =yes, | | Overall heartburn = no | | | | | | |
| Criteria C: | Day Heartburn = yes, | Night heartburn =yes, | | Overall heartburn = no | | | | | | |

Source: Sponsor's Table 5, page 13, Response to information request in 74-day letter.

Reviewer comments: *In this reviewer's assessment, the percentage of subjects that reported one of the above inconsistencies is high (37% to 40%). Moreover, subjects were supposed to call in once a day, not multiple times. However, as noted by the Sponsor, "some patients called in several times a day and therefore have multiple values on the same assessment date in the DIARYNM dataset." It is unclear why some subjects called in multiple times daily, but this reviewer suspects that some subjects may have called in the afternoon/evening to report daytime heartburn and then again in the morning to report nighttime heartburn. Regardless, it appears that the Sponsor implemented an appropriate strategy to handle inconsistencies in reporting of heartburn symptoms. A conservative approach was taken to ensure that a subject with either daytime or night time heartburn would be counted as having overall heartburn.*

Overall, this medical officer is reassured by the above exploratory analyses because they affirm that inconsistencies in reporting of heartburn symptoms through the IVRS were balanced across both treatment groups in each of the two studies.

7 Review of Safety

Safety Summary

For a full review of safety, please refer to the review performed by Dr. Jane Filie in the Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA (NDA 204-655).

Additional Submissions / Safety Issues

During the first cycle review of NDA 202-342 esomeprazole strontium, which relied on FDA's determination of safety and efficacy for esomeprazole magnesium, the Agency

identified several deficiencies, including inadequate demonstration of esomeprazole strontium use in pregnancy and lactation, insufficient toxicology data for strontium to support administration of esomeprazole strontium to children less than 2 years of age, and the need to demonstrate that strontium, in the presence of esomeprazole, does not have an adverse effect on skeletal development.

To address the deficiencies identified in the CR letter issued after the first review cycle for NDA 202-342 (issued November 15, 2011), the Sponsor for NDA 202-342 (Hanmi USA, Inc.) submitted, on October 29, 2012, reproductive and developmental toxicology studies in rats for review. These studies compared esomeprazole strontium and esomeprazole magnesium, at equimolar concentrations of esomeprazole to a vehicle control. This design permitted comparisons of esomeprazole strontium to esomeprazole magnesium. There was a particular focus on bone effects.

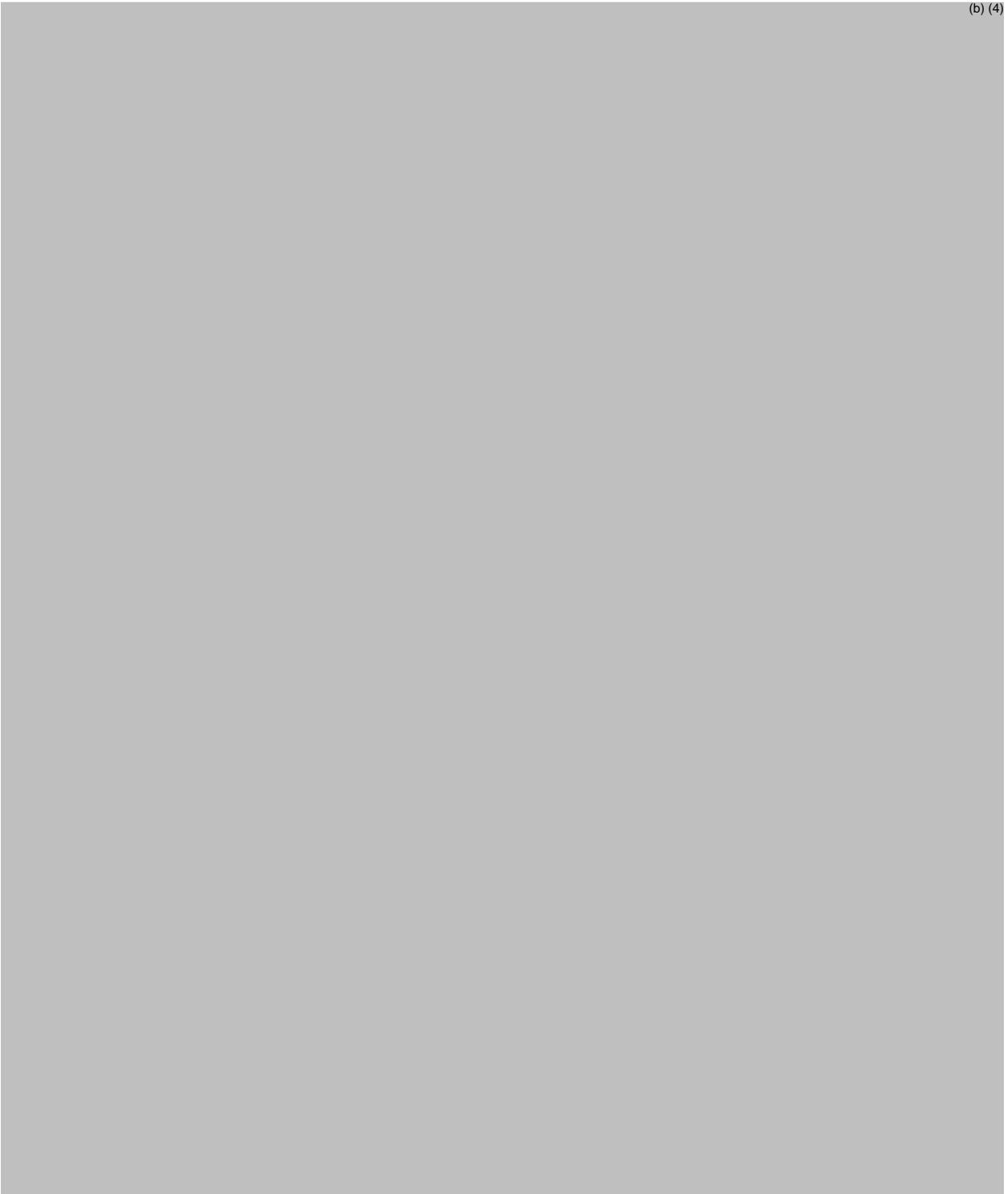
In rat studies, bone changes were observed in dams exposed to both esomeprazole salts, and there was no evidence of a differential impact for the strontium salt vs. the magnesium salt. Maternal exposure, postnatal exposure and exposure during a juvenile study all demonstrated that esomeprazole resulted in bone changes and alterations in growth and development in rats. Again, there was no differential impact for the strontium vs. magnesium salt. These studies were conducted due to concerns regarding the adequacy of characterization of safety of exposure to strontium in young children, including during pregnancy and extending up to 2 years of age. These studies did not reveal a safety signal attributable to strontium. Because the magnesium exposure associated with the esomeprazole magnesium product was only a fraction of the magnesium present in the animal chow, the reviewers concluded that the changes observed relative to vehicle were attributable to the esomeprazole, not to the salts themselves.

The levels of esomeprazole exposure that were associated with the changes were substantively higher than the MRHD (maximum recommended human dose of 40 mg, based on mg/m^2), with the exception of mild bone marrow hypocellularity in offspring at 3.4 times the MRHD. (Maternal and offspring bone effects occurred at 33.6 times the MRHD. Growth and developmental impact was observed at 16.8 times the MRHD.) A calcium and Vitamin D deficient diet did not magnify these effects or lower the exposure level associated with these observations. Ultimately, these animal study findings were incorporated into labeling for esomeprazole strontium, which was approved on August 6, 2013.

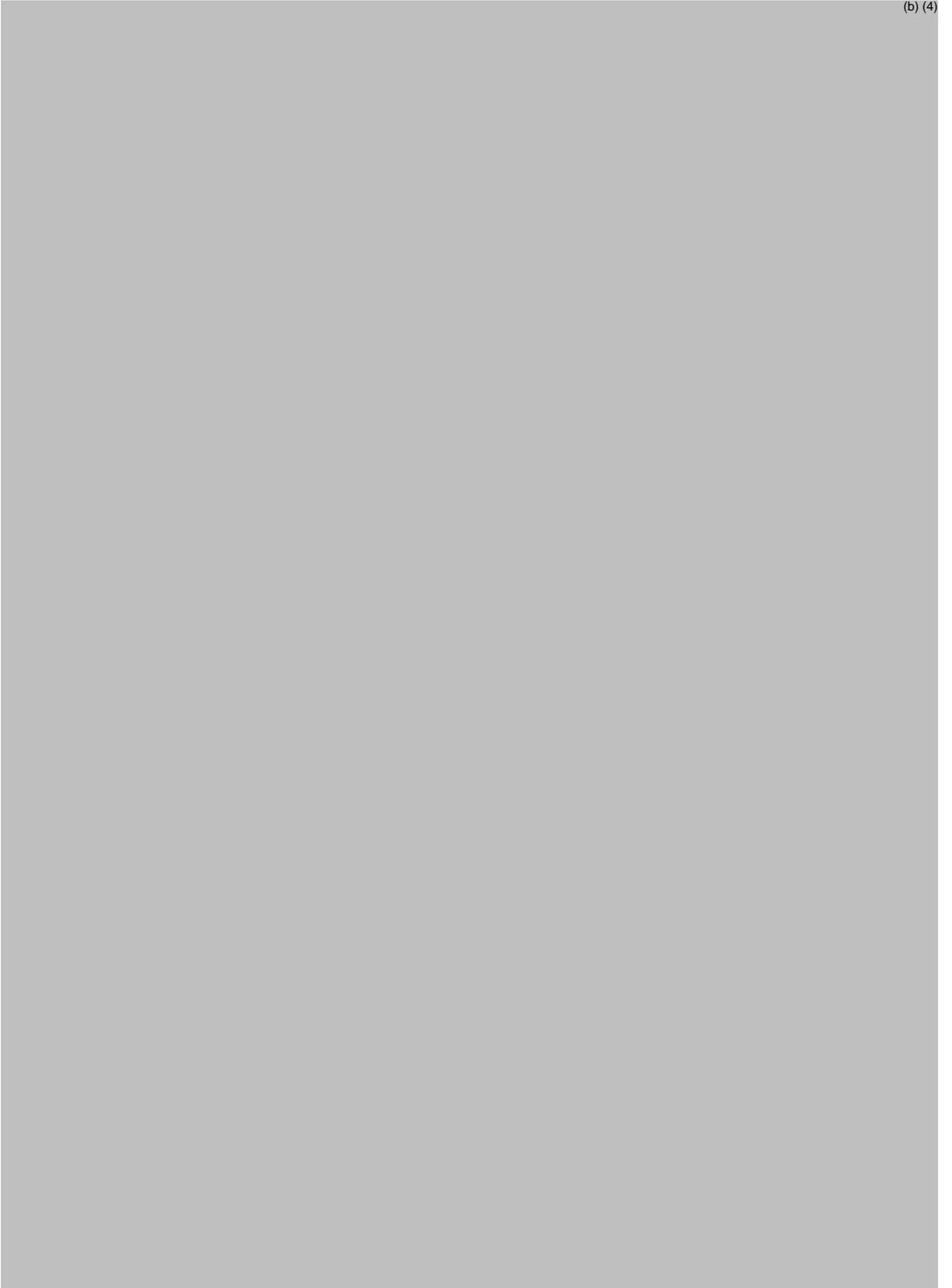
Given the Agency's finding that the aforementioned findings in the animal studies were attributable to the esomeprazole (not to the salts themselves), the Agency issued a Safety Labeling Change (SLC) Notification to AstraZeneca (the Sponsor of esomeprazole magnesium and omeprazole, which is an enantiomer of esomeprazole) on October 10, 2013. In this Notification, the Agency indicated it had become aware of animal data indicating that the use of esomeprazole in pregnancy may cause fetal harm.

Clinical Review
Farrokh Sohrabi, MD
NDA 204-655
Nexium (esomeprazole magnesium) Delayed-Release Capsules OTC 20 mg

In accordance with section 505(o)(4) of the FDCA, based on the new safety information described above; the Agency indicated that the new safety information should be included in the labeling for Nexium (esomeprazole magnesium) products as follows:



(b) (4)





(b) (4)

On November 8, 2013, AstraZeneca responded to the Agency's Notification. Negotiations are currently ongoing between the Agency and AstraZeneca with regard to product labeling in the prescription setting.



(b) (4)

Clinical Review
Farrokh Sohrabi, MD
NDA 204-655
Nexium (esomeprazole magnesium) Delayed-Release Capsules OTC 20 mg

Reviewer comments: *Although the SLC negotiations are ongoing at the time of completion of this review, this medical officer does not anticipate that any changes to labeling of prescription PPIs relating to the current SLC will affect the Sponsor's proposed safety labeling language for OTC esomeprazole magnesium.*

8 Postmarket Experience

For a full review of safety, please refer to the review performed by Dr. Jane Filie in the Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA (NDA 204-655).

9 Appendices

Appendix 1: Discussion of Individual Trials – D961RC00001 and D961RC00002

The two phase 3 trials in this NDA submission were identical in design and protocol.

Title

A Phase III Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial of 14-Day Treatment with Esomeprazole 20 mg Once Daily in Subjects with Frequent Heartburn

Primary Objective

“To determine the efficacy of esomeprazole 20 mg qd over a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with nonprescription medications without consulting a prescriber”

Trial Design

Randomized, placebo-controlled, double-blind, parallel-group phase 3 trial

Duration

The first subject was enrolled on August 11, 2011 and the last subject’s last visit was on October 19, 2011. Database lock occurred on April 19, 2012.

Key Inclusion Criteria

1. Provision of informed consent prior to any study specific procedures
2. Males and non-pregnant, non-lactating females ≥ 18 years old
3. Females must be postmenopausal, surgically sterilized or use a medically acceptable form of birth control. Women of childbearing potential must agree to use or continue to use an acceptable form of birth control throughout the conduct of the study, and have a negative pregnancy test at Visit 2. Acceptable forms of birth control include:
 - a. a vasectomized male partner
 - b. female sterilization (“tubes tied”)
 - c. intrauterine devices (IUDs)
 - d. Depo-Provera
 - e. etonogestrel implants (Implanon)
 - f. Ortho Evra
 - g. normal and low-dose combined oral contraceptives
 - h. norelgestromin/ethinyl estradiol (EE) patch
 - i. intravaginal device (Nuva Ring)
 - j. hysterectomy

4. Subjects should experience heartburn at least 2 days a week over the past 4 weeks
5. If heartburn medications have been used, subjects should have heartburn symptoms that have been responsive to antacids, non-prescription H₂RAs, or short-term non-prescription or prescription PPIs at approved doses
6. Subjects must discontinue antacids, H₂RAs and/or PPI treatment prior to the start of the run-in phase. The washout period is ≥ 1 day for antacids and ≥ 7 days for H₂RAs and/or PPIs.

Key Exclusion Criteria

1. A history (past or present) of erosive esophagitis verified by endoscopy
2. A history (past or present) of pathologic intraesophageal pH monitoring
3. The need for continuous treatment with H₂RAs, PPIs, gastric prokinetic drugs, or antacids for any indication throughout the study (e.g., long-term prescription therapy)
4. Subjects with history of GERD diagnosed by a physician
5. Subjects taking any medication prescribed for GERD (i.e. treatment of erosive reflux esophagitis, long-term management of patients with healed esophagitis to prevent relapse, and symptomatic treatment of gastroesophageal reflux disease [GERD])
6. Subjects that have required more than one 14-day course of PPI treatment within the past 4 months
7. Subjects who have had a 14-day course of PPI treatment for heartburn > 3 times within the past year
8. The need for continuous treatment with antifungals, antiretroviral drugs (atazanavir, nelfinavir and saquinavir), cilostazol, warfarin (Coumadin), clopidogrel, tacrolimus, diazepam, digoxin, or iron salts (multi-vitamins with iron or dietary supplements with iron are allowed) or the use of these agents at any time between Visit 1 and the final evaluation at Visit 5
9. Any medical condition or concomitant therapy, which may interfere with the evaluation of heartburn treatment or constitute a safety concern
10. Known hypersensitivity to omeprazole magnesium, esomeprazole, Gelusil or their excipients.
11. Inability to take study medication or complete the study and all study procedures
12. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
13. Previous enrollment in the present study
14. Participation in another clinical study with an investigational product during the last 30 days or throughout the duration of this study

Randomization Criteria

To be considered eligible to continue participation into the treatment phase, subjects must continue to meet the specific inclusion/exclusion criteria as follows:

1. Subjects must experience and report via IVRS at least 1 episode of heartburn during 2 separate 24-hour periods (2 episodes of heartburn in total) during the run-in period
2. Subjects must be compliant in reporting heartburn symptoms via IVRS 5 of 7 days during the run-in period

Trial Conduct

Screening and washout: Day -23 to -9

- Discontinue antacids, H₂RAs, and /or PPI treatment.
- Washout period for antacids: ≥1 day
- Washout period for H₂RAs and/or PPIs: ≥7 days

7-day single-blind placebo run-in: Day -8 to -1

- Aimed to ensure that subjects had sufficient frequent heartburn and could comply with daily reporting of symptoms
- Complete a daily diary via IVRS to document heartburn symptoms during the previous 24-hour period
- Subjects began taking the placebo run-in medication on Day -7 and began reporting heartburn symptoms on Day -6 and at each subsequent 24-hour period through Day 0

Randomization: Day 0

- Subjects randomized if they reported ≥2 days with heartburn during the run-in period (i.e., heartburn during 2 separate 24-hour periods), and were compliant in reporting symptoms via IVRS on at least 5 of 7 days

14-day double-blind randomized treatment period: Day 1 to Day 14

- Continue recording daily heartburn symptoms in IVRS for the previous 24-hour period during the 14-day treatment regimen
- Return to investigation center for assessments on Day 15
- On Day 15, answer Global Assessment Questions (GASTQ) in order to measure satisfaction with the study treatment over the previous 14-days

7-day single-blind placebo follow-up: Day 15 to Day 22

- Continue recording heartburn symptoms beginning Day 17 via IVRS during the follow-up period through Day 23
- Return to investigational center for final assessments (Study Completion) on Day 23

The schedule of visits for the trial is summarized in [Table 26](#).

Table 26. Schedule of Visits – Trial D961RC00001 and Trial D961RC00002

| Study Stage | Screening | Placebo Run-In | Randomization | Placebo Follow-Up | Study Completion |
|--|-----------|----------------|---------------|-------------------|------------------|
| Study Day | -23 to -9 | -8 to -1 | 0 | 15 | 23 |
| Visit Number | 1 | 2 | 3 | 4 | 5 |
| Informed Consent | X | | | | |
| Inclusion/Exclusion Criteria | X | X | | | |
| Demographics | X | | | | |
| Medical/Surgical History | X | X | | | |
| Vital Signs/Physical Examination | X | | | | X |
| Electrocardiogram | X | | | | |
| Laboratory Assessment ^a | X | | | X | |
| Urine Pregnancy Test ^b | | X | | | |
| Washout of antacids, H2RAs, and/or PPIs ^c | X | | | | |
| Provide IVRS Instructions ^d | | X | | | |
| Review Dosing Instructions ^e | | X | X | X | |
| Diary Initiated in IVRS ^d | | X | | | |
| Diary Collected in IVRS ^d | | | X | X | X |
| Determine Eligibility for Randomization ^f | | | X | | |
| Dispense Study Medication and Gelusil Rescue Medication ^g | | X | X | X | |
| Collect Study Medication and Gelusil Rescue Medication | | | X | X | X |
| Global Assessment in IVRS | | | | X | |
| Adverse Events ^h | | X | X | X | X |
| Serious Adverse Events ⁱ | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X |

a. Labs are non-fasting; includes hematology, clinical chemistry and urinalysis

b. Urine pregnancy test required at Visit 2; however, post-menopausal women (no menstruation for > 12 months), women that have had a hysterectomy, and women that have had tubal ligations do NOT need to have a urine pregnancy test.

c. Washout period is ≥ 1 day for antacids and ≥ 7 days for H2RAs and/ or PPIs.

d. Subjects will report responses and rescue medication usage by calling into an interactive voice response system (IVRS) on a daily basis between 6:00 am and 12:00 pm (noon). Subjects will respond to the same prompts every day. Subjects will record daily diary data through the run-in, treatment, and follow-up periods as well as at study completion.

e. Subjects will self-medicate with study medication each morning prior to eating. Each 24-hour time period begins when the subject takes the first dose of the study medication and ends prior to the subject taking the next dose on the following day.

f. Visit 3 should be scheduled in the afternoon so that the subject has time to make the last placebo run-in IVRS call and the investigator has the reported heartburn data from the placebo run-in period needed to determine the subject's eligibility for randomization.

g. Rescue medication will be dispensed at Visit 2, Visit 3, and Visit 4 as needed (1 box at V2, 2 boxes at V3, and 1 box at V4). Boxes dispensed will be recorded at each visit and accountability for dispensed rescue medication will be done at each subsequent visit with final accountability done at study follow-up.

h. AEs are collected from time of initiation of study drug (placebo run-in) until follow up period. AEs will be assessed since the previous visit.

i. Collection of SAEs will begin the time the Informed Consent is obtained until the follow up period. SAEs will be assessed since the previous visit.

Source: Reviewer's table, adapted from Sponsor's Table 1, page 17 of 49, Protocol D961RC00001, edition no. 2.

Removal of Subjects from Therapy or Assessment

Subjects could be discontinued from investigational product in the following situations:

- Subject decision; the subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event
- Severe non-compliance to study protocol
- Development of any study specific criteria for discontinuation

Withdrawn subjects were not replaced.

Prior and Concurrent Therapy

Subjects were not allowed any new prescriptions, OTC medications, or herbal/nutritional therapies during the study. Subjects were not to receive antifungals, antiretroviral drugs (atazanavir, nelfinavir and saquinavir), cilostazol, warfarin (Coumadin), clopidogrel, tacrolimus, diazepam, digoxin, or iron salts (multi-vitamins with iron or dietary supplements with iron were allowed) at any time between Visit 1 and the final evaluation at Visit 5.

Study Medication

For all phases of the two studies, study drug was taken once daily. The capsules were swallowed whole (not chewed or crushed) with a glass of water once a day before eating in the morning. Subjects were instructed to eat breakfast daily.

Rescue Medications

The sole permitted rescue medication was Gelusil. Subjects were to chew one tablet of Gelusil for heartburn symptoms as needed and allowed to repeat hourly if symptoms returned. The protocol specified that subjects should be encouraged to minimize rescue medication use to allow the effects of the study medication to be fully assessed.

Subjects were not to receive treatment with any antacids, H₂RAs, gastric prokinetic drugs, or PPIs during the study, no matter what the indication for use, other than Gelusil, which was provided by the site.

Compliance

Study personnel were to account for all study drugs, as well as the rescue medication, dispensed to and returned from the subject. The Principal Investigator was responsible for establishing routines for correct handling of the study drug. The administration of all study drugs (including rescue medication) was to be recorded in the appropriate sections of the eCRF. Treatment compliance was also to be captured in the IVRS system.

Outcome Measures

Efficacy

Measures of efficacy were assessed by data recorded by subjects in an IVRS daily self-assessment diary. The Rave Web Based Data Capture (WBDC) system was used for data collection and query handling. See [Table 26](#) for specific procedures performed and subject data collected.

Primary Efficacy Endpoint

The primary endpoint was percentage of heartburn-free 24-hour days during 14 days of double-blind treatment.

Secondary Efficacy Endpoints

Secondary efficacy endpoints for this trial included:

- Proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both weeks 1 and 2 between V3 and V4)
- Proportion of days with no heartburn over Days 1-4; (the first 4 consecutive days subjects are on randomized treatment, between V3 and V4)
- Proportion of subjects with heartburn 1 day or less during the final week of treatment; the final week of treatment is defined as the last 7 consecutive days subjects are on randomized study drug (between V3 and V4)
- Proportion of subjects with heartburn 1 day or less during the second week of treatment; The second week of treatment is defined as the second 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 8 through 14)
- Proportion of subjects with heartburn 1 day or less during the first week of treatment; the first week of treatment is defined as the first 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 1 through 7)

Study Design and Statistical Analysis

These phase 3 trials were intended to assess the efficacy and safety of a 14-day course of treatment with esomeprazole 20 mg once daily in subjects with frequent heartburn who are likely to self-treat with non-prescription medications without consulting a prescriber and without a confirmed GERD diagnosis. Subjects were to be recruited from sites recommended by an independent Contract Research Organization (CRO). Approximately 500 subjects were to be enrolled in each trial and 300 subjects, 150 to each arm, were to be randomized into each trial. The number of subjects was estimated based on the primary efficacy results of two trials conducted to support the partial OTC switch of lansoprazole 15 mg. In those trials, there was a 14% difference between treatments (active – placebo) in heartburn-free days over the 14-day treatment period with a standard deviation of approximately 30%. Assuming a similar effect, the Sponsor estimated that 120 evaluable subjects per treatment arm would provide 95% power at an alpha level = 0.05 (2-sided). In order to account for the combined effect of early discontinuation and missing data, the Sponsor estimated that 150 subjects per group would need to be randomized into each of the two esomeprazole trials.

Three datasets were used for analyses: safety, full analysis set, and per-protocol. The definition of these datasets was as follows:

- Safety analysis set: all randomized subjects who took at least one dose of study medication. Erroneously treated subjects (e.g., those randomized to treatment A but actually given treatment B) were accounted for in the actual treatment group.
- Full analysis set (FAS): all randomized subjects who took at least one dose of randomized treatment and had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment. Subjects were classified according to randomized treatment. This analysis set was used for all efficacy analyses.
- Per-protocol (PP) analysis: a subset of the FAS excluding data from subjects with certain protocol deviations (determined by study team prior to unblinding of the data). Subjects were classified according to actual treatment received. This analysis set was used in sensitivity analyses to examine the robustness of FAS results for the primary variable and secondary efficacy endpoints

All statistical tests were 2-sided with a significance level of 5%, i.e., $\alpha=0.05$ unless otherwise specified. Calculation of percentages was to exclude missing data as a category.

Sponsor's Plan for Handling of Missing Data

For the primary endpoint, proportion of days with no heartburn over the 14-day treatment, missing data were handled as follows:

$$y = [(number\ of\ 24\text{-hour\ days\ with\ no\ heartburn}) + m * (proportion\ of\ 24\text{-hour\ days\ with\ no\ heartburn\ during\ the\ run-in\ phase)]]/14$$

Where m = the number of days with missing data

When calculating the proportion of 24-hours days or nighttimes with no heartburn during the run-in phase, the denominator was the number of days the subject actually was in run-in. The calculation was based on only non-missing values [e.g., if a subject had only 5 days in the run-in phase and of those 2 days with heartburn then the proportion of 24-hour days or nighttimes with no heartburn during the run-in phase for this subject is : $(5-2)/5 = 3/5$].

For the secondary endpoints when calculating number of subjects who were heartburn-free for a given day and for the secondary endpoint when calculating number of subjects with resolution of heartburn, or number of subjects who were heartburn-free for 0, 1, 2, 3 or 4 days, missing data were assumed to be days with heartburn.

Primary and Secondary Analyses

A hierarchical testing procedure was used to control the type I error. The primary and secondary efficacy endpoints were analyzed sequentially in the following order:

1. The percentage of 24-hour days with no heartburn during 14 days of treatment (primary endpoint)
2. The resolution of frequent heartburn, defined as heartburn 2 days or less during the 14-day randomized period (both weeks 1 and 2)
3. The percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase
4. The percentage of subjects with heartburn 1 day or less during the final week of treatment
5. The percentage of subjects with heartburn 1 day or less during the second week of treatment
6. The percentage of subjects with heartburn 1 day or less during the first week of treatment

When a test resulted in a statistically insignificant result, the next test in the sequence was not carried out.

The primary analysis was percentage of heartburn-free 24-hour days during 14 treatment days and was analyzed based on the FAS for the FAS analysis and PP Analysis Set for PP analysis.

A sensitivity analysis was performed where subject missing data were assumed to be days with heartburn. When calculating the proportion of subjects who were heartburn-free for a given day, subjects without data for that day were assumed to have had heartburn.

The percentage of 24-hour days with no heartburn over 14 days of treatment, expressed as percentages and analyzed as a continuous variable, was analyzed using analysis of covariance (ANCOVA) model including treatment and center as factors and frequency of heartburn during the run-in phase as a covariate. Model-based point estimates, 95% confidence intervals, and two-sided p-value were reported.

For secondary analysis, a hierarchy of evaluation was pre-specified to control type I error. If the heartburn data were missing for any day during the given week of the double-blind treatment phase, then it was assumed that the subject had heartburn, irrespective of actual treatment being esomeprazole or placebo.

The count of 24-hour days with no heartburn over Days 1-4 was analyzed using a proportional odds model (i.e., cumulative logit model) for ordinal outcomes with treatment as factor and the baseline results as a covariate. The results were expressed in terms of an odds ratio and its associated confidence interval. If the assumption of proportional odds model was not met, then the same model with few response categories was performed (i.e., merging categories). Proportion of days with no heartburn over Days 1-4 was summarized using descriptive statistics.

For all other secondary variables relating to resolution of frequent heartburn within a specified period, the proportion of subjects with resolution of frequent heartburn by treatment was compared by using a chi-square test.

Protocol Amendments

There were two protocol amendments to the original protocol dated May 23, 2011. Database lock occurred April 19, 2012.

Amendment #1 occurred on July 28, 2011 before the start of subject recruitment and included the following changes:

- Updated the secondary objective to clarify how resolution of frequent heartburn would be assessed. Secondary objective modified as follows:
 - May 23, 2011 (original): “determine the proportion of subjects with resolution of frequent heartburn (as defined as reporting heartburn one day or less during the final week of the treatment phase of the study. The final week is defined as the subject’s last seven days while taking study medication). When calculating the proportion of subjects who are heartburn-free for a given day, subjects without data for that day will be assumed to have had heartburn.”
 - July 28, 2011 (revised): “determine the proportion of subjects with resolution of frequent heartburn; (defined as reporting heartburn 1 day or less during the week) for the final week, first week, and second week of the treatment phase of the study.”
- Amended the secondary endpoints to correspond with the amended secondary objective

- May 23, 2011 (original)
 - Proportion of subjects with heartburn one day or less during the final week of treatment (Days 8-14)
 - Proportion of days with no heartburn over Days 1-4
- July 28, 2011 (revised)
 - Proportion of subjects with heartburn 1 day or less during the final week of treatment; the final week of treatment is defined as the subject's last 7 days while taking study medication
 - Proportion of subjects with heartburn 1 day or less during the first week of treatment; the first week of treatment is defined as the first 7 calendar days on treatment
 - Proportion of subjects with heartburn 1 day or less during the final week of treatment; the second week of treatment is defined as the second 7 calendar days on treatment
 - Proportion of days with no heartburn over Days 1-4
- Modified Section 12.2.6 Adjusting for multiplicity to reflect the amended secondary endpoints
 - May 23, 2011 (original): The primary and secondary efficacy variables will be analyzed sequentially in the following order:
 1. The percentage of 24-hour days with no heartburn during 14 days of treatment (primary efficacy variable)
 2. The resolution of frequent heartburn
 3. The percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase
 - July 28, 2011 (revised): The primary and secondary efficacy variables will be analyzed sequentially in the following order:
 1. The percentage of 24-hour days with no heartburn during 14 days of treatment (primary efficacy variable)
 2. The resolution of frequent heartburn during the final week of treatment
 3. The resolution of frequent heartburn during the second week of treatment
 4. The percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase
 5. The resolution of frequent heartburn during the first week of treatment
- Modified inclusion criteria as follows:
 - Inclusion criterion 3 amended, based on FDA advice, to include details of the acceptable forms of birth control
 - Inclusion criterion 4 modified to include "over the past 4 weeks" to confirm the presence of heartburn:
 - May 23, 2011 (original): "Subjects should experience heartburn at least 2 days a week"

- July 28, 2011 (revised): “Subjects should experience heartburn at least 2 days a week **over the past 4 weeks**”
- Modified exclusion criteria as follows:
 - Exclusion criterion 6 modified, based on FDA advice, to clarify number of 14-day courses of PPI treatment:
 - May 23, 2011 (original): “Subjects requiring 14-day course of PPI treatment more often than every 4 months”
 - July 28, 2011 (revised): “Subjects that have required more than one 14-day course of PPI treatment within the past 4 months”
 - Exclusion criterion 7 added, based on FDA advice, to restrict the number of 14-day courses of PPI treatment in the past year: “Subjects who have had a 14-day course of PPI treatment for heartburn >3 times within the past year”
 - Original exclusion criterion 7 (“Subjects currently taking greater than the standard approved PPI doses for any GERD indication (e.g., BID [Twice daily] dosing)” deleted, based on FDA advice, due to its redundancy with exclusion criterion 5 (“Subjects taking any medications prescribed for GERD (i.e., treatment of erosive reflux esophagitis, long-term management of patients with healed esophagitis to prevent relapse, and symptomatic treatment of GERD)”)
 - Exclusion criterion 8 modified, based on FDA advice, to include additional concomitant medications:
 - May 23, 2011 (original): “The need for continuous treatment with antifungals, antiretroviral drugs (atazanavir, nelfinavir and saquinavir), cilostazol, warfarin (Coumadin), clopidogrel, tacrolimus, cilostazol, or diazepam or the use of these agents at any time between Visit 1 and the final evaluation at Visit 5”
 - July 28, 2011 (revised): “The need for continuous treatment with antifungals, antiretroviral drugs (atazanavir, nelfinavir and saquinavir), cilostazol, warfarin (Coumadin), clopidogrel, tacrolimus, diazepam, **digoxin, or iron salts (multi-vitamins with iron or dietary supplements with iron are allowed)** or the use of these agents at any time between Visit 1 and the final evaluation at Visit 5”
 - Exclusion criterion 10 (“Clinically significant and/or unstable renal or hepatic disease”) deleted based on FDA advice. Rationale for deletion was based on the fact that prescription labeling states that the PK of esomeprazole in patients with renal impairment is not expected to be altered relative to healthy volunteers and in subjects with severe hepatic insufficiency, a dose not exceeding 20 mg once daily is recommended.
- Modified Section 5.1 Restrictions during the study and Section 5.6 Concomitant and post-study treatment(s) as follows:
 - May 23, 2011 (original):

- Subjects should be cautioned that any new prescription, OTC or herbal/nutritional therapies should be discussed thoroughly with the Investigator prior to initiation.
- Subjects will receive Gelusil tablets (WellSpring Pharmaceutical Corporation) from the sites as a rescue medication which should be administered according to label directions.
- July 28, 2011 (revised):
 - Subjects will not be allowed any new prescriptions, OTC medications, or herbal/nutritional therapies during the study. The Principal Investigator should review all prescriptions, OTC medications, or herbal/nutritional therapies currently being used by study participants.
 - Subjects will receive Gelusil tablets (WellSpring Pharmaceutical Corporation) from the sites as a rescue medication.
- Daytime heartburn was additionally defined, in the IVRS daily self-assessment diary, based on FDA advice, to assist subjects when evaluating their heartburn for the daily diary (subjects had to qualify both daytime and nighttime heartburn severity)
 - May 23, 2011 (original): “Nighttime heartburn is defined as the time from going to bed until the following morning’s daily dose of study drug.”
 - July 28, 2011 (revised): “Daytime heartburn is defined as the time from self-administration of the daily dose of study drug until going to bed. Nighttime heartburn is defined as the time from going to bed until the following morning’s daily dose of study drug. Subjects will receive instructions on the definition of daytime and nighttime heartburn to facilitate their answers in the IVRS self-assessment diary.”

Amendment #2 occurred on November 10, 2011 following completion of subject recruitment and prior to unblinding, and included the following changes:

- Added a secondary objective to clarify the parameters of the treatment periods being evaluated and analyzed for the study and to include an additional secondary endpoint for overall evaluation of heartburn resolution during the 14-day randomized treatment period (both Weeks 1 and 2). The added secondary objective is “**determine the proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both Weeks 1 and 2 between V3 and V4).**” The final week, first, week, and second week of treatment were defined as follows: “**For the purposes of this study, the final week of treatment is defined as the last 7 consecutive days subjects are on randomized study drug (between V3 and V4). The first week of treatment is defined as the first 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 1 through 7). The second week of treatment is defined as the second 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 8 through 14).**”

- Added a secondary efficacy endpoint to support the updated secondary objective: **“proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both Weeks 1 and 2).”**
- Amended the secondary endpoints to reflect the added secondary objective and the updated definitions of treatment periods being evaluated (e.g., the final week, the first week, and the second week):
 - July 28, 2011 (previous):
 - Proportion of subjects with heartburn 1 day or less during the final week of treatment; the final week of treatment is defined as the subject’s last 7 days while taking study medication
 - Proportion of subjects with heartburn 1 day or less during the first week of treatment; the first week of treatment is defined as the first 7 calendar days on treatment
 - Proportion of subjects with heartburn 1 day or less during the final week of treatment; the second week of treatment is defined as the second 7 calendar days on treatment
 - Proportion of days with no heartburn over Days 1-4
 - November 10, 2011 (revised):
 - **Proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both weeks 1 and 2 between V3 and V4)**
 - Proportion of days with no heartburn over Days 1-4; **(the first 4 consecutive days subjects are on randomized treatment, between V3 and V4)**
 - Proportion of subjects with heartburn 1 day or less during the final week of treatment; **the final week of treatment is defined as the last 7 consecutive days subjects are on randomized study drug (between V3 and V4)**
 - Proportion of subjects with heartburn 1 day or less during the second week of treatment; **the second week of treatment is defined as the second 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 8 through 14)**
 - Proportion of subjects with heartburn 1 day or less during the first week of treatment; **the first week of treatment is defined as the first 7 consecutive days subjects are on randomized study drug (between V3 and V4; Days 1 through7)**
- Modified Section 12.2.6 Adjusting for multiplicity to reflect the amended secondary endpoints
 - July 28, 2011 (previous): The primary and secondary efficacy variables will be analyzed sequentially in the following order:
 1. The percentage of 24-hour days with no heartburn during 14 days of treatment (primary efficacy variable)

2. The resolution of frequent heartburn during the final week of treatment
 3. The resolution of frequent heartburn during the second week of treatment
 4. The percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase
 5. The resolution of frequent heartburn during the first week of treatment
- November 10, 2011 (revised): The primary and secondary efficacy variables will be analyzed sequentially in the following order:
 1. The percentage of 24-hour days with no heartburn during 14 days of treatment (primary efficacy variable)
 2. The resolution of frequent heartburn, defined as heartburn 2 days or less during the 14-day randomized period (both weeks 1 and 2)
 3. The percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase
 4. The resolution of frequent heartburn during the final week of treatment
 5. The resolution of frequent heartburn during the second week of treatment
 6. The resolution of frequent heartburn during the first week of treatment

Statistical Analysis Plan Amendments

There were two amendments to the original SAP dated September 9, 2011. Database lock occurred April 19, 2012.

Amendment #1 occurred on December 16, 2011 following completion of subject recruitment and prior to unblinding. The changes to the SAP were pursuant to Amendment #2 to the protocol that occurred on November 10, 2011. Changes to the SAP included the following:

- Section 3.2 The secondary efficacy variables
 - Amended secondary endpoints listed
 - Change to analysis plan for days with no heartburn:
 - September 9, 2011: “For the analysis perspective the count of days with no heartburn will be analyzed instead of proportion of days. Proportion of days will be summarized using descriptive statistics.”
 - December 16, 2011: “For the analysis of proportion of days with no heartburn over Days 1-4, the count of days with no heartburn for each patient will be analyzed. Proportion of days with no heartburn over Days 1-4 will be summarized using descriptive statistics.”
- Section 4.1 General principles:
 - Handling of missing values: New text added for calculating the proportion of 24-hour days or nighttime with no heartburn during the run-in phase:

- “When calculating the proportion of 24-hours days or nighttimes with no heartburn during the run-in phase, the denominator will be the number of days the subject actually was in run-in. The calculation should be based on only nonmissing values, e.g. if a patient has only 5 days in the run-in phase and of those 2 days with heartburn then the proportion of 24-hour days or nighttimes with no heartburn during the run-in phase for this patient is: $(5-2)/5 = 3/5$.”
- Adjusting for multiplicity: Amended hierarchical testing procedure listed to reflect Amendment #2 to the protocol that occurred on November 10, 2011.
- Section 4.2.2.1 Resolution of frequent heartburn: In light of the addition of a new secondary endpoint assessing proportion of subjects reporting heartburn 2 days or less during the 14-day treatment period, new text was added for handling of missing heartburn data, along with an example:
 - “If the heartburn data is missing for any day during the given week of the double-blind treatment phase, then the worst-case scenario will be assumed, i.e. it will be assumed that the subject had heartburn, irrespective of actual treatment being esomeprazole or placebo, in the above derivation.”

Amendment #2 occurred on April 5, 2012 following completion of subject recruitment and prior to unblinding. The changes to the SAP involved an update to Appendix A, which defined the per-protocol population, following blind data review. The update expanded on protocol deviations, and these protocol violations are listed below.

Protocol Deviations and Violations

Subjects were excluded from the per-protocol population if they met any of the following criteria:

1. Not in the FAS population
2. Violated any of the following inclusion criteria: 1, 2, 4, 5 or 6
3. Violated any of the exclusion criteria: 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13 or 14
4. Not compliant with study drug during the randomized double-blind study period (intake of study drug outside the range of 75-125%)
5. Visit 4 window outside of range (<12 days)
6. Received any new prescriptions, OTC medications, or herbal/nutritional therapies during the study, which could affect, or interfere with the subject’s ability to evaluate, the efficacy of the drugs during the double-blind treatment period
7. Received treatment with any H2RAs, PPIs (except for study medication), gastric prokinetic drugs or drugs that may affect symptoms/pathophysiology during the trial
8. Failed to meet either of the two specific randomization criteria during the run-in phase:

Clinical Review

Farrokh Sohrabi, MD

NDA 204-655

Nexium (esomeprazole magnesium) Delayed-Release Capsules OTC 20 mg

- Subjects must experience and report via IVRS at least 1 episode of heartburn during 2 separate 24-hour periods (2 episodes of heartburn in total) during the run-in period. If a subject was in the run-in phase for longer than 7 days, at least 2 of their heartburn episodes must have occurred during the first 7 days.
- Subjects must be compliant in reporting heartburn symptoms via IVRS during the run-in period. Compliance is defined as reporting in at least 5 of first 7 days during their run-in period.

Appendix 2: Number and Percentage of Subjects with Heartburn-Free 24-Hours Days Throughout Study 1 and Study 2

Table 27. Study D961RC00001 (Study 1) Number (%) of Subjects with Heartburn-Free 24-Hour Days (FAS Population)

| | Diary Day ^a | Esomeprazole 20 mg, N=168 | | Placebo, N=163 | | |
|-------------------------|-------------------------------------|-------------------------------|--------------------------------------|-------------------------------|--------------------------------------|------------|
| | | Number of subjects calling in | Heartburn free subjects ^b | Number of subjects calling in | Heartburn free subjects ^b | |
| Run-in period | -12 | 2 | 0 (0.00) | 0 | 0 (0.00) | |
| | -11 | 2 | 0 (0.00) | 1 | 0 (0.00) | |
| | -10 | 2 | 1 (50.00) | 7 | 0 (0.00) | |
| | -9 | 16 | 0 (0.00) | 15 | 0 (0.00) | |
| | -8 | 32 | 6 (18.75) | 38 | 5 (13.16) | |
| | -7 | 88 | 6 (6.82) | 85 | 14 (16.47) | |
| | -6 | 150 | 23 (15.33) | 152 | 15 (9.87) | |
| | -5 | 158 | 27 (17.09) | 153 | 27 (17.65) | |
| | -4 | 153 | 26 (16.99) | 153 | 33 (21.57) | |
| | -3 | 156 | 35 (22.44) | 155 | 35 (22.58) | |
| | -2 | 154 | 34 (22.08) | 154 | 37 (24.03) | |
| Randomization | -1 | 161 | 27 (16.77) | 156 | 29 (18.59) | |
| | 0 | 133 | 34 (25.56) | 131 | 35 (26.72) | |
| | During treatment^c | 1 | | 61 (36.31) | | 49 (30.06) |
| | | 2 | | 60 (35.71) | | 47 (28.83) |
| | | 3 | | 61 (36.31) | | 46 (28.22) |
| | | 4 | | 62 (36.90) | | 41 (25.15) |
| | | 5 | | 57 (33.93) | | 40 (24.54) |
| | | 6 | | 72 (42.86) | | 41 (25.15) |
| | | 7 | | 74 (44.05) | | 34 (20.86) |
| | | 8 | | 71 (42.26) | | 46 (28.22) |
| | | 9 | | 61 (36.31) | | 41 (25.15) |
| | | 10 | | 76 (45.24) | | 47 (28.83) |
| | | 11 | | 74 (44.05) | | 46 (28.22) |
| | | 12 | | 72 (42.86) | | 49 (30.06) |
| | | 13 | | 81 (48.21) | | 50 (30.67) |
| 14 ^d | | | 76 (45.24) | | 51 (31.29) | |
| Follow-up period | 1 | 136 | 63 (46.32) | 133 | 47 (35.34) | |
| | 2 | 138 | 66 (47.83) | 138 | 42 (30.43) | |
| | 3 | 134 | 54 (40.30) | 135 | 48 (35.56) | |
| | 4 | 134 | 53 (39.55) | 124 | 47 (37.90) | |
| | 5 | 126 | 49 (38.89) | 122 | 41 (33.61) | |
| | 6 | 120 | 53 (44.17) | 111 | 44 (39.64) | |
| | 7 | 32 | 11 (34.38) | 39 | 15 (38.46) | |

^a Day 1 of follow-up period is the day following visit 4 and corresponds to day 15 in the request.

^b The percentage is calculated using the number of subjects calling in as the denominator.

^c For the treatment period missing values are handled as stated in the Protocol (i.e., assumed be days with heartburn) and N was used as the divisor.

^d The figures for the number of heartburn free subjects on day 14 is correct in this table but differs slightly from what is shown in table 55 of the CSR. This correction should have been included in the CSR errata list.

Source: Table 1 of Appendix 1, Response to November 18, 2013 information request.

Table 28. Study D961RC00002 (Study 2) Number (%) of Subjects with Heartburn-free 24-Hour Days (FAS Population)

| | Diary Day ^a | Esomeprazole 20 mg, N=162 | | Placebo, N=158 | |
|-------------------------------------|------------------------|-------------------------------|--------------------------------------|-------------------------------|--------------------------------------|
| | | Number of subjects calling in | Heartburn free subjects ^b | Number of subjects calling in | Heartburn free subjects ^b |
| Run-in period | -10 | 0 | 0 (0.00) | 1 | 0 (0.00) |
| | -9 | 5 | 0 (0.00) | 2 | 0 (0.00) |
| | -8 | 18 | 0 (0.00) | 8 | 1 (12.50) |
| | -7 | 89 | 8 (8.99) | 91 | 8 (8.79) |
| | -6 | 140 | 26 (18.57) | 143 | 22 (15.38) |
| | -5 | 154 | 30 (19.48) | 143 | 29 (20.28) |
| | -4 | 146 | 33 (22.60) | 148 | 38 (25.68) |
| | -3 | 154 | 42 (27.27) | 150 | 37 (24.67) |
| | -2 | 157 | 39 (24.84) | 153 | 38 (24.84) |
| | -1 | 153 | 42 (27.45) | 153 | 36 (23.53) |
| Randomization | 0 | 130 | 33 (25.38) | 124 | 30 (24.19) |
| During treatment^c | 1 | | 48 (29.63) | | 34 (21.52) |
| | 2 | | 65 (40.12) | | 44 (27.85) |
| | 3 | | 68 (41.98) | | 34 (21.52) |
| | 4 | | 70 (43.21) | | 36 (22.78) |
| | 5 | | 73 (45.06) | | 45 (28.48) |
| | 6 | | 68 (41.98) | | 47 (29.75) |
| | 7 | | 70 (43.21) | | 44 (27.85) |
| | 8 | | 82 (50.62) | | 44 (27.85) |
| | 9 | | 71 (43.83) | | 40 (25.32) |
| | 10 | | 66 (40.74) | | 51 (32.28) |
| | 11 | | 75 (46.30) | | 50 (31.65) |
| | 12 | | 69 (42.59) | | 51 (32.28) |
| | 13 | | 83 (51.23) | | 57 (36.08) |
| | 14 ^d | | 74 (45.68) | | 47 (29.75) |
| Follow-up period | 1 | 123 | 65 (52.85) | 133 | 60 (45.11) |
| | 2 | 121 | 57 (47.11) | 133 | 52 (39.10) |
| | 3 | 128 | 58 (45.31) | 126 | 41 (32.54) |
| | 4 | 127 | 51 (40.16) | 120 | 48 (40.00) |
| | 5 | 122 | 53 (43.44) | 122 | 46 (37.70) |
| | 6 | 114 | 45 (39.47) | 115 | 48 (41.74) |
| | 7 | 50 | 17 (34.00) | 47 | 19 (40.43) |

^aDay 1 of follow-up period is the day following visit 4 and corresponds to day 15 in the request.

^bThe percentage is calculated using the number of subjects calling in as the denominator.

^cFor the treatment period missing values are handled as stated in the Protocol (i.e., assumed be days with heartburn) and N was used as the divisor.

^dThe figures for the number of heartburn free subjects on day 14 is correct in this table but differs slightly from what is shown in table 55 of the CSR. This correction should have been included in the CSR errata list.

Source: Table 2 of Appendix 1, Response to November 18, 2013 information request.

Table 29. Study D961RC00001 (Study 1) and Study D961RC00002 (Study 2) Number (%) of Subjects with Heartburn-Free 24-Hour Days (from 0 to 14) During the 14-Day Double-blind Treatment Period (FAS Population)

| Number of Heartburn-free Days | Study 1 | | Study 2 | |
|-------------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | Esomeprazole (N=168) n (%) | Placebo (N=163) n (%) | Esomeprazole (N=162) n (%) | Placebo (N=158) n (%) |
| 0 | 42 (25.0) | 56 (34.4) | 31 (19.1) | 51 (32.3) |
| 1 | 8 (4.8) | 12 (7.4) | 7 (4.3) | 9 (5.7) |
| 2 | 10 (6.0) | 11 (6.8) | 9 (5.6) | 11 (7.0) |
| 3 | 5 (3.0) | 9 (5.5) | 16 (9.9) | 14 (8.9) |
| 4 | 8 (4.8) | 9 (5.5) | 5 (3.1) | 5 (3.2) |
| 5 | 12 (7.1) | 12 (7.4) | 9 (5.6) | 12 (7.6) |
| 6 | 7 (4.2) | 10 (6.1) | 7 (4.3) | 9 (5.7) |
| 7 | 11 (6.6) | 12 (7.4) | 12 (7.4) | 14 (8.9) |
| 8 | 14 (8.3) | 8 (4.9) | 7 (4.3) | 5 (3.2) |
| 9 | 9 (5.4) | 5 (3.1) | 11 (6.8) | 12 (7.6) |
| 10 | 6 (3.6) | 4 (2.5) | 14 (8.6) | 7 (4.4) |
| 11 | 9 (5.4) | 8 (4.9) | 7 (4.3) | 7 (4.4) |
| 12 | 8 (4.8) | 3 (1.8) | 9 (5.6) | 2 (1.3) |
| 13 | 10 (6.0) | 2 (1.2) | 14 (8.6) | 0 |
| 14 | 9 (5.4) | 2 (1.2) | 4 (2.5) | 0 |

Note: Days with missing values are handled as days with heartburn.

Source: Reviewer's table, adapted from Sponsor's Table 7 and Table 8, pages 8-10 of Response to November 18, 2013 information request.

Appendix 3: IVRS Daily Self-Assessment Diary

The following questions were collected via the IVRS system:

1. Rate your overall heartburn severity over the past 24-hours (0=none; 1=mild; heartburn present but easily tolerated; 2=moderate; heartburn sufficient to cause interference with normal daily activity or sleep; and 3=severe; incapacitating heartburn, with subject unable to perform normal daily activities or sleep)
2. Rate your nighttime heartburn severity (0 to 3)
3. Rate your daytime heartburn severity (0 to 3)
4. How many Gelusil tablets have you taken over the previous 24-hours (0 to 12 tablets)?

Appendix 4: Clinical Investigator Financial Disclosure

Covered Clinical Study (Name and/or Number): D961RC00001

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: <u>55</u> | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

The Sponsor provided a signed copy of FDA Form 3454 certifying that it has not entered into any financial arrangements with its clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts.

Clinical Review
 Farrokh Sohrabi, MD
 NDA 204-655
 Nexium (esomeprazole magnesium) Delayed-Release Capsules OTC 20 mg

Covered Clinical Study (Name and/or Number): D961RC00002

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: <u>66</u> | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

The Sponsor provided a signed copy of FDA Form 3454 certifying that it has not entered into any financial arrangements with its clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts.

9.1 Literature Review/References

Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol*. 2009;104(5):1278-1295.

Vandeplass Y, Rudolph CD, Di Lorenzo C, et al. G Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2009;49(4):498-547.

9.2 Labeling Recommendations

Labeling discussions are ongoing at the time of this review. See final label.

It appears that the Sponsor has modeled proposed labeling for esomeprazole OTC on current approved labeling for lansoprazole OTC (i.e., Prevacid 24HR) under NDA 22-327. This medical officer reviewed the Sponsor's proposed annotated draft labeling text.

Reviewer comments: *Proposed labeling for esomeprazole OTC states that "it may take 1 to 4 days for full effect,*

(b) (4)

"
(b) (4)
In this medical officer's assessment, for esomeprazole OTC, the first part of the statement (i.e., "it may take 1 to 4 days for full effect") is supported by the data from a pre-specified secondary endpoint analysis (see Table 11 in section 6.1.5 Analysis of Secondary Endpoints(s) for detailed discussion). Moreover, although exploratory, additional analyses, presented in Table 20 and Figure 2 of section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects, and in Table 22 of section 6.1.10 Additional Efficacy Issues/Analyses, also support qualitatively the statement that "it may take 1 to 4 days for full effect."

In this reviewer's assessment, however, the second part of the proposed labeling statement (i.e., "(b) (4)") is not supported by data from any of the pre-specified analyses. None of the pre-specified secondary endpoints in Study 1 or Study 2 directly assessed "relief of symptoms" (i.e., heartburn-free status) (b) (4). An exploratory analysis of the percentage of subjects with heartburn-free 24-hour days by diary day during the 14-day treatment period (missing days assumed to be days with heartburn), presented in (b) (4)

(b) (4)

The reader is referred to section 6.1.5 Analysis of Secondary

Clinical Review
Farrokh Sohrabi, MD
NDA 204-655
Nexium (esomeprazole magnesium) Delayed-Release Capsules OTC 20 mg

Endpoints(s) and to section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects for a more detailed discussion of these data.

9.3 Advisory Committee Meeting

No advisory committee (AC) meeting was held.

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

/s/

FARROKH SOHRABI
02/21/2014

ROBERT FIORENTINO
02/21/2014

CLINICAL REVIEW

Application Type NDA
Application Number 204-655
Priority or Standard Standard

Submit Date May 30, 2013
Received Date May 30, 2013
PDUFA Goal Date March 30, 2014
Division / Office DNCE/ ODE IV

Reviewer Jane Filie, MD
Team Leader Lesley-Anne Furlong, MD
Completion Date February 20, 2014

Established Name Esomeprazole magnesium
Proposed Trade Name Nexium 24HR
Therapeutic Class Proton-pump Inhibitor
Applicant AstraZeneca

Formulation Delayed-Release Capsules
Dosing Regimen Once daily for 14 days
Indication Treatment of frequent heartburn
Intended Population Adults ≥ 18 y/o

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the standpoint of clinical safety, this reviewer recommends an approval action for NDA 204,655 Nexium 24HR® Delayed-Release Capsules for the relief of frequent heartburn, at the dose of 20 mg once daily for 14 days. This product has an acceptable safety profile and final approvability is contingent upon approval from the clinical efficacy and CMC standpoints, and incorporation of the FDA's labeling recommendations for this product.

1.2 Risk Benefit Assessment

According to Katz et al. (Am J Gastroenterol 2013; 108: 912-914), 10 to 20 % of individuals in the Western world have gastroesophageal reflux disease (GERD) and approximately 38% of the general population complains of dyspepsia. Although the condition is not life threatening, heartburn may be associated with pain, dietary restrictions, disruptions in sleep and decreased work productivity.

The benefit of the treatment with esomeprazole with non-prescription status has been weighed against safety experience in clinical trials, as well as post-marketing safety experience. Consumers have been safely self-treating heartburn with proton pump inhibitors (PPIs) beginning in 2003 in the US when omeprazole (Prilosec OTC) was approved to treat frequent heartburn. Since then, two additional PPI products were approved for OTC use in 2009, lansoprazole (Prevacid 24HR) and a combination of omeprazole and sodium bicarbonate (Zegerid OTC).

The general toxicity of esomeprazole is low. Nonclinical studies have not shown any relevant reproductive toxic or genotoxic effects. Clinical long-term use esomeprazole therapy has not lead to any evidence of carcinogenic potential, which gives more reassurance especially considering the limited duration of treatment of 14 days, including repeating of treatment courses after 4 months in the OTC setting.

Esomeprazole is not known to have any psychotropic or narcotic characteristics, or to be addictive. The incidence of severe or serious adverse events (AEs) following daily administration of esomeprazole 20 mg is low.

The results from the two Phase III studies included in this submission show that esomeprazole 20 mg daily, during a 2-week treatment period, was superior to placebo for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription (Rx) medications. The safety data from these trials did not raise any new concerns as the adverse events (AE) noted were mild to moderate and reversible.

The safety and tolerability of esomeprazole are also supported by extensive post-marketing experience since the drug's international launch in 2000. The majority of adverse reactions reported were mild and transient in nature, the most frequent being headache and gastrointestinal disorders, such as, abdominal pain, diarrhea, flatulence, nausea/vomiting and constipation. The approved oral formulation for Rx use has never been recalled from the international or US market for safety reasons. At the time of this NDA submission of this application esomeprazole was not available OTC, but was approved in the fall 2013 in Europe (Nexium Control®.)

Dose adjustments with the OTC product are not necessary in subjects with concomitant diseases but use of the drug with certain medications may require consulting with a healthcare provider and this is addressed in the proposed OTC label. The risk of concealing a serious condition as a result of self-medication is low, when esomeprazole is taken at the proposed dose of 20 mg per day for 14 days. Warnings in the Drug Facts will alert consumers regarding the use of esomeprazole with known risk factors (hypersensitivity to PPIs, pregnancy, and drug interactions). Information about use and advice when to talk to a doctor or pharmacist are present on the carton.

In summary, this reviewer concludes that the risk-benefit assessment is favorable to support the approval of esomeprazole 20 mg delayed-release capsules for OTC use as directed in proposed labeling: dosed once daily for 14 days for the treatment of frequent heartburn, which may be repeated no sooner than every 4 months.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None at this time.

1.4 Recommendations for Postmarketing Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Esomeprazole belongs to the drug class of PPIs. It inhibits specifically the gastric H⁺/K⁺-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. Esomeprazole is acid labile and is formulated as gastro-resistant capsules containing enteric-coated pellets of esomeprazole magnesium trihydrate. Nexium 24 HR

is proposed to treat frequent heartburn (occurs 2 or more days a week) and is not intended for immediate relief of heartburn in adults (≥ 18 years old).

Esomeprazole was first approved as Rx-only for oral use in Sweden in 2000, and later in the US in 2001 (Nexium[®], referred to as Nexium Rx in the remainder of this review.) It is currently approved in more than 125 countries for various acid-related disorders. Nexium Control[®] was approved for OTC use in Europe in August, 2013. Safety and tolerability of esomeprazole are supported by post-marketing experience exceeding 78 million patient-years of esomeprazole treatment. In addition, more than 90,000 subjects have been exposed to esomeprazole in clinical trials. Since its launch, this drug has never been withdrawn from the international market due to safety reasons.

Nexium Rx is approved for use in adults and children as young as one month of age. The adult indications of Nexium Rx are:

- treatment of GERD
- risk reduction of NSAID-associated gastric ulcer
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence
- pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

The pediatric indications of Nexium Rx are:

- 12 to 17 year old: treatment of symptomatic GERD, healing of erosive esophagitis
- 1 to 11 year old: short-term treatment of symptomatic GERD, healing of erosive esophagitis
- 1 month to < 1 year old: erosive esophagitis

The intended indication for OTC marketing is “*Treatment of frequent heartburn (occurs 2 or more days a week).*” The proposed dosing regimen is a daily oral dose of 20 mg esomeprazole for 14 days, with an option for a repeat 14-day course no sooner than 4 months. The use of this product is to be limited to adults only. The Sponsor does not seek any pediatric indications for OTC marketing. A pediatric waiver has been granted as with all other OTC PPIs because the current position of the Agency is that heartburn in children needs to be evaluated and treated by a physician.

2.2 Currently Available Treatments for Proposed Indications

Available OTC heartburn treatments include:

- antacids to neutralize stomach acid (aluminum and/or magnesium hydroxide, calcium bicarbonate, sodium bicarbonate)
- histamine 2 receptor antagonists (H₂RAs) to reduce acid production (ranitidine, cimetidine, famotidine, and nizatidine)
- PPIs to block acid production: PPIs became available OTC in the US in 2003 when omeprazole (Prilosec OTC) was approved to treat frequent heartburn. Two additional PPI products were approved for OTC use in 2009, lansoprazole (Prevacid 24HR) and a combination of omeprazole and sodium bicarbonate (Zegerid OTC).

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient esomeprazole is currently marketed as an Rx product only, and is available under the following brand names:

- Nexium® Delayed-Release Capsules (esomeprazole magnesium), 20 mg and 40 mg capsules
- Nexium® Delayed-Release Oral Suspension (esomeprazole magnesium), 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg packets
- Nexium I.V. ® (esomeprazole sodium) for Injection, 20 mg and 40 mg freeze-dried powder for single-use.
- Vimovo® (naproxen and esomeprazole magnesium) Delayed-Release Tablets, 367 mg naproxen/20 mg esomeprazole tablets, indicated for the relief of signs and symptoms of osteoarthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing non-steroidal anti-inflammatory drugs associated gastric ulcers

2.4 Important Safety Issues with Consideration to Related Drugs

The following safety concerns associated with the class of PPI drugs are addressed in the Rx labels under Warnings and Precautions:

- Clostridium difficile associated diarrhea (CDAD): After reviewing reports from FDA's Adverse Event Reporting System (AERS) and the medical literature, FDA issued a Drug Safety Communication (DSC) on February 8, 2012 alerting healthcare professionals and consumers of the positive association of *C.difficile* associated diarrhea with the use of PPIs. Predisposing factors to developing CDAD include hospitalization, advanced age, chronic medical conditions, and taking broad spectrum antibiotics. The issue is addressed in labeling for OTC PPIs with the text "stop use and ask a doctor if you get diarrhea."
- Interaction with clopidogrel: The metabolism of clopidogrel to its active metabolite can be impaired by use with drugs that inhibit CYP2C19 activity. Patients on PPIs should consider use of alternative anti-platelet therapy. The interaction is addressed in labeling for omeprazole and proposed labeling for esomeprazole with the text "ask a doctor or pharmacist before use if you are taking clopidogrel," which is further described as a blood thinning medicine.
- Osteoporosis and bone fractures: FDA issued a DSC on March 23, 2011 alerting healthcare providers and consumers of an increased risk of fractures of the hip, wrist, or spine associated with the use of PPIs at high doses and /or for one year or more. The conclusion was drawn based on published epidemiological studies and not on clinical trial since most of these are of 6-months duration. FDA concluded that the OTC doses of PPI do not incur in increased fracture risk, therefore changes to the OTC label were not recommended.
- Hypomagnesemia: FDA issued a DSC on March 2, 2011 alerting healthcare professionals and consumers of the risk of hypomagnesemia when taking PPIs for more than one year. The mechanism responsible for hypomagnesemia associated

with long term PPI use is unknown; however, long term use of PPIs may be associated with changes in intestinal absorption of magnesium. These findings were based on the review of reports from AERS, medical literature and periodic safety update reports. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia, healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically thereafter. FDA concluded that there is very little risk of hypomagnesemia when OTC PPIs are used according to the directions on the label.

- Atrophic gastritis: Has been noted with long-term omeprazole (precursor) therapy. OTC PPIs are not labeled for long-term use.
- Interference with diagnostic investigations for neuroendocrine tumors: May occur due to hypergastrinemia as the result of increases in intragastric pH, enterochromaffin-like cell hyperplasia and increased chromogranin A. This information is targeted to the healthcare provider and is not necessary on consumer labeling.
- Increased level of methotrexate (MTX): Literature suggests that concomitant use of PPIs with MTX, primarily high dose MTX, may elevate and prolong serum levels of MTX, possibly leading to MTX toxicity (see also 7.2.6 and 7.5.5).
- Decreased levels of PPI: St. John's Wort and rifampin decrease the levels of PPIs

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor engaged in several exchanges during the development program for this product under IND 111,185. The following are the main points of discussion during the interactions with the Sponsor:

- PIND Meeting (05/16/2011):
 - FDA agreed to their study design, definition of heartburn (Montreal), secondary endpoints.
 - FDA advised that the directions for use in the label (for OTC marketing) should reflect the way the product was taken in the clinical efficacy trials.
 - If the proposed OTC label had similar elements (e.g., indications, warnings, directions for use) compared with approved OTC PPI labels, then a Label Comprehension (LC) study was not needed.
 - The detailed manufacturing process (b) (4) would need to be included in the application.
 - Agreement was reached regarding the extent of the safety data. In addition to the safety data generated from the OTC efficacy trials, the following safety information for esomeprazole should be included at the time of the NDA submission: a review of safety information from the Sponsor's postmarketing database, US AE data, Worldwide AE data, FDA Adverse Event Reporting System (AERS) database, World Health Organization (WHO) International Drug Monitoring program, Drug Abuse and Overdose Data- National Poison Data System (NPDS) from the American Association of Poison Control

Centers (AAPCC) and Drug Abuse Warning Network (DAWN), and literature review for esomeprazole active ingredient.

- The Sponsor was to provide the following:
 - Information regarding potential interaction(s) between esomeprazole and other drugs which include information from postmarketing adverse event reporting and the literature.
 - List of countries where esomeprazole is marketed as a nonprescription product. Include English translations of foreign nonprescription labels.
 - Information on whether esomeprazole has been withdrawn from any foreign markets due to safety or regulatory reasons.
- Agreement was reached regarding the cut-off dates of the safety data.
- Original IND 111,185 submission in 06/2011
- Pre-NDA Interaction (01/15/2013): The Sponsor did not come for a face-to-face meeting but was satisfied with responses and advice provided:
 - FDA noted that a pediatric waiver request would be evaluated during the review of the NDA.
 - FDA also agreed with the Sponsor's approach to include draft labeling based on currently approved OTC PPIs, with product specific information.
 - FDA concurred with the Sponsor's approach to cross-reference previously approved NDAs for the nonclinical data.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

From the clinical safety perspective, the submission is complete and well organized to allow easy navigation, with fully functional hyperlinks throughout the entire submission. At this time, this reviewer is unaware of any irregularities with respect to the conduct of the studies. Inspections of the study sites were not deemed necessary according to the clinical reviewers from DGIEP.

3.2 Compliance with Good Clinical Practices

The Sponsor states that procedures, internal quality control measures and audit programs provides reassurance that the clinical study program was carried out in accordance with Good Clinical Practice (GCP), as documented by the International Conference on Harmonization (ICH). Quality of study data was assured through monitoring of investigational centers, provision of appropriate training of study personnel, and use of data management procedure.

3.3 Financial Disclosures

Pursuant to the requirements outlined in 21 CFR 54.2 (a) and (b), the Sponsor states that:

- AstraZeneca has not entered into any financial arrangement with any clinical investigators responsible for conducting the submitted clinical trials.
- The clinical investigators, who are required to disclose any proprietary interest in this product or a significant equity in the Sponsor company, did not disclose any such interests to the Sponsor.
- No clinical investigator listed in the application was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Esomeprazole, the S-isomer of omeprazole, is acid labile and is therefore formulated as gastro-resistant capsules containing enteric coated pellets of esomeprazole magnesium trihydrate. *In vivo* conversion to the R-isomer is negligible.

The esomeprazole 20 mg delayed-release capsule for OTC (esomeprazole magnesium trihydrate 22.3 mg) is a sealed hard gelatin capsule with opaque, amethyst body and cap. Apart from the colored gelatin banding, (b) (4)

The seal consists of a yellow gelatin band in radial format that covers the joined portion of the body and cap. The colored gelatin banding has been added to achieve tamper-evident capsules and also to differentiate the OTC from the Rx product. According to the Sponsor, the presence of the gelatin band (regarded as a non-release controlling excipient) is not expected to have any impact on product performance. (b) (4)

The Sponsor cross-references the original NDA 21,153 Nexium Capsules for the chemistry information.

Medical Officer Comment: The effect of the gelatin band on the product's performance is being addressed by FDA's Chemistry, Manufacturing and Controls (CMC) team's review, which had not been finalized at the time this clinical review was completed.

4.2 Clinical Microbiology

No new information is provided.

4.3 Preclinical Pharmacology/Toxicology

The non-clinical data available on esomeprazole, in combination with the non-clinical documentation on omeprazole, plus the extensive experience of the clinical use of esomeprazole and omeprazole, are referred to in support of the nonprescription status of esomeprazole 20 mg, once daily for 14 days, in adults. No additional non-clinical studies were conducted. Results from the non-clinical bridging studies between esomeprazole and the racemate omeprazole showed that these two compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Therefore, the non-clinical database on omeprazole is also relevant to the safety assessment of esomeprazole, enabling the long-term repeat-dose and carcinogenicity studies and most reproductive studies to be bridged to the previous omeprazole studies.

Non-clinical bridging studies reveal no particular hazard for humans based on conventional studies of repeat dose toxicity, genotoxicity, and toxicity to reproduction. Carcinogenicity studies in the rat with the racemate have shown gastric enterochromaffin-like (ECL) cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

All the non-clinical studies on the active substance esomeprazole and omeprazole were submitted and reviewed in NDA 21,153. The non-clinical data supporting the clinical oral use of esomeprazole is described in the Nexium Rx Package Insert.

Medical Officer Comment: Esomeprazole magnesium is characterized as Pregnancy Category (b) (4). The proposed labeling addressing the use in pregnant women is acceptable. For further detail regarding the non-clinical data, please refer to the pharmacology/toxicology review by Dr. Robert Dorsam, which had not been finalized at the time this clinical review was completed.

4.4 Clinical Pharmacology

No new clinical pharmacology data were generated from the two Phase III studies. A summary of available data on esomeprazole 20 mg and 40 mg was provided.

4.4.1 Mechanism of Action

Esomeprazole reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell, where it inhibits the enzyme H⁺K⁺-ATPase, which is the “proton pump”, and inhibits both basal and stimulated acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a racemic mixture of S- and R- isomers. 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 mg to 40 mg and leads to inhibition of gastric acid secretion.

4.4.2 Pharmacodynamics

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell.

According to the Nexium Rx label, the effect of esomeprazole magnesium on intragastric pH was assessed in one study after daily administration of 20 mg and 40 mg capsules for 5 days. The percentage of time that the gastric pH remained above 4 was 53% (12.7 h) for the 20 mg capsule (median 24-hour pH 4.1) and 70% (16.8 h) for the 40 mg capsule (median 24-hour pH 4.9). In a second study, the effect of esomeprazole magnesium 40 mg administered once daily for five days was similar to the first study: the intragastric pH remained above 4 68% (16.3 h) of a 24-hour period.

The effect of esomeprazole magnesium on serum gastrin concentration was evaluated in trials up to 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 (ECL) cell hyperplasia and increased Chromogranin A levels. The latter may cause false positive results in diagnostic investigations from neuroendocrine tumors.

Human gastric biopsy specimens were obtained from more than 3,000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no cases of ECL cell carcinoids, dysplasia, or neoplasia were found in these patients. In addition none of these effects were found in another group of 1,000 patients treated with esomeprazole 10, 20 or 40 mg daily up to 6 to 12 months.

4.4.3 Pharmacokinetics

Esomeprazole, is acid labile and is administered orally as enteric-coated granules. The absorption of esomeprazole is rapid, with peak plasma levels (C_{max}) occurring approximately 1 to 2 hours after dose. The absolute bioavailability is 50% after a single dose of 20 mg and increases to 68% after repeated once-daily administration. For 40 mg esomeprazole the corresponding values are 64% and 89%, respectively. The apparent volume of distribution at steady state in healthy subjects is approximately 16 L. Esomeprazole is 97% plasma protein bound in humans. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Esomeprazole is completely metabolized by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, i.e., extensive metabolizers. Total plasma clearance is approximately 22 L/h after a single dose and 16 L/h after repeated administration of 20 mg. After a 40 mg single dose, total plasma clearance is approximately 17 L/h and approximately 9 L/h after repeated administration. The plasma elimination half-life is approximately 1.2 and 1.3 hours after repeated once daily dosing of 20 mg and 40 mg, respectively.

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg twice daily. The area under the plasma concentration-time (AUC) curve increases with repeated administration to steady state of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time - and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, and the remainder in the feces. Less than 1% of the parent drug is found in the urine.

Special Populations

Poor metabolizers

Approximately 3% of the population in the western world lack a functional CYP2C19 enzyme and are called poor metabolizers. In these individuals the metabolism of esomeprazole is probably mainly catalyzed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean AUC is approximately double in poor metabolizers compared with subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean C_{max} is about 60% higher than in extensive metabolizers. This higher exposure however has not raised safety concerns and no specific changes to dosing have been made.

Gender

Pharmacokinetic studies have shown that the AUC and C_{max} values were slightly higher (13%) in females than in males at steady state but dose adjustment based on gender have not been recommended.

Impaired hepatic function

The metabolism of esomeprazole in subjects with mild to moderate liver insufficiency may be impaired, but no dose adjustment is required. The metabolic rate is decreased in subjects with severe liver insufficiency resulting in a doubling of the area under the plasma concentration time curve of esomeprazole. Therefore, a dose of 20 mg should not be exceeded in subjects with severe hepatic insufficiency.

Impaired renal function

No studies have been performed in subjects with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the pharmacokinetics of esomeprazole is not expected to be altered in subjects with impaired renal function. Therefore, the label for Nexium Rx does not make recommendations for dosing adjustments in this population.

Geriatric

The AUC and C_{max} values were slightly higher (28% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric

Nexium 24HR is not intended for use in subjects under the age of 18 years. Nexium Rx is approved for children as young as 1 month of age through adolescence. The pharmacokinetic parameters of children 12 to 17 years of age are comparable to adults but vary in younger children and these differences resulted in specific dosing recommendation by age groups for the Rx product.

5 Sources of Clinical Data

The clinical data reviewed for this application include the following:

- Two clinical trials conducted by the Sponsor for the OTC clinical development program
- Safety data from postmarketing pharmacovigilance databases
- Relevant literature

Because the Sponsor proposes an OTC label that is essentially identical to the currently available PPIs in the market and is not requesting any additional claims, OTC consumer studies were not required.

5.1 Tables of Clinical Trials

The clinical trials conducted to support the OTC marketing of Nexium 24 HR are listed in Table 1 below.

Table 1. Table of Clinical Trials

| Type of study | Study identifier | Location of study report in Module 5 | Objective(s) of the study | Study design and type of control | Test products, Dosage regimen, Route of administration | No. of subjects rand/ treated | Healthy subjects or diagnosis of patients | Duration of treatment | Study status; type of report |
|------------------------------------|------------------|--------------------------------------|---|--|--|-------------------------------|--|--|------------------------------|
| Controlled Clinical Studies | | | | | | | | | |
| Efficacy | D961RC00001 | 5.3.5.1 | To determine the efficacy of esomeprazole 20 mg qd over a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription medications without consulting a prescriber | Double-blind, randomized, placebo, parallel group, multicenter | Esomeprazole (magnesium trihydrate) capsules 20 mg Placebo Oral qd | 340/331 | Adults with frequent heartburn occurring ≥ 2 days per week, but without a confirmed GERD diagnosis. | 14-day screening/wash-out 7-day single blind placebo run-in 14-day randomized double-blind treatment 7-day single blind placebo follow-up | Complete Full |
| Efficacy | D961RC00002 | 5.3.5.1 | To determine the efficacy of esomeprazole 20 mg qd over a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription medications without consulting a prescriber | Double-blind, randomized, placebo, parallel group, multicenter | Esomeprazole (magnesium trihydrate) capsules 20 mg Placebo Oral qd | 341/326 | Adults with frequent heartburn occurring ≥ 2 days per week, but without a confirmed GERD diagnosis. | 14-day screening/wash-out 7-day single blind placebo run-in 14-day randomized double-blind treatment 7-day single blind placebo follow-up | Complete Full |
| Qd once daily | | | | | | | | | |

(Source: Summary of Clinical Efficacy, Table 2, p. 10)

5.2 Review Strategy

This clinical review focuses on the clinical safety aspect of this application, primarily the safety information from the clinical trials conducted for the OTC program and postmarketing safety information. Reviewers in the Division of Gastrointestinal and Inborn Errors Products (DGIEP) will assess the application from the clinical efficacy perspective. Reviewers in chemistry, pharmacology/toxicology, and clinical pharmacology will evaluate data pertinent to their respective discipline. Labeling will be reviewed by interdisciplinary scientists (IDS) from the Division of Nonprescription Clinical Evaluation (DNCE). Lastly, acceptability of the proposed proprietary name is reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE.)

5.3 Discussion of Individual Clinical Trials

The Sponsor conducted two clinical trials of identical design in the US—D961RC00001 and D961R00001- to support the indication “treatment of frequent heartburn.”

Synopsis of Trials D961RC00001 and D961RC00002

The clinical trials were multi-center, randomized, double-blind, parallel-group, and placebo-controlled. The trial population consisted of male and female subjects, ≥ 18 years of age with frequent heartburn occurring ≥ 2 days per week, but without a confirmed GERD diagnosis.

After completing screening assessments and a washout period, subjects entered a single blind, one-week placebo run-in period (Day -8 to Day -1) where they completed a daily diary via Interactive Voice Response System (IVRS) to document heartburn symptoms during the previous 24-hour period. At the end of the placebo run-in period, subjects returned to the investigational site for review of the daily diary and possible randomization into the study.

Subjects who reported at least one episode of heartburn during 2 separate 24-hour periods (2 episodes of heartburn in total) during the run-in period, and who were compliant in reporting at least 5 of 7 days via IVRS, were eligible to be randomized into one of the trials for a 14-day regimen of double-blind once daily dosing of esomeprazole 20 mg capsule or matching placebo.

Randomized subjects continued to record heartburn symptoms daily via IVRS for the previous 24-hour period during the 14-day treatment regimen. At the end of the 14-day treatment period, subjects returned to the investigational site for assessments on Day 15. Safety assessments performed during the two clinical trials are discussed in Section 7 Review of Safety.

After the randomized treatment period, subjects entered a single blind, one-week placebo follow-up period. Subjects continued to record heartburn symptoms via IVRS. Rescue medication, (Gelusil®), was distributed by the sites and was available to the subjects during the run-in, double-blind treatment, and follow-up periods.

The primary endpoint for the trials was the percentage of heartburn-free 24-hour days during 14 days of double-blind treatment. Each 24-hour time period began when the subject took a dose of the study drug and ended just prior to the subject taking the next dose on the following day. The secondary endpoints were as follows:

- proportion of subjects with resolution of heartburn, i.e., reporting heartburn 2 days or less during the 14-day randomized treatment period
- proportion of subjects who experienced heartburn-free days during each of the first 4 days of treatment
- proportion of subjects with heartburn 1 day or less during:
 - the final week of treatment (defined as the last 7 consecutive days subjects are on randomized study drug)
 - the second week of treatment (defined as the second 7 calendar days subjects are on randomized study drug, Days 8 through 14)

- first week of treatment (defined as the first 7 calendar days subjects are on randomized study drug, Days 1 through 7)

The results are discussed in detail in the clinical efficacy review by the DGIEP.

6 Review of Efficacy

The clinical efficacy review of this NDA will be addressed by the reviewers of DGIEP. Over-the-counter consumer use studies were not conducted because the proposed labeling is essentially identical to other approved PPIs.

At the time of this review, DGIEP has not indicated any issues regarding the efficacy assessment that would preclude the approval of this product. Please refer to the clinical review by Dr. Farrohk Sohrabi and Dr. Robert Fiorentino for the assessment of efficacy.

7 Review of Safety

Summary

Esomeprazole was approved as an Rx drug in the US in 2001. The safety profile of esomeprazole is well characterized. Other PPIs have been available in the US market since 1989 with the approval of omeprazole (Prilosec). The PPIs are usually well tolerated and the AEs are generally mild and reversible. The most common AEs of Nexium Rx are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth. The label for Nexium Rx has the following warnings:

- Symptomatic response to Nexium does not preclude the presence of **gastric malignancy**.
- **Atrophic gastritis** has been noted in biopsies of patients treated long-term with omeprazole
- Published studies suggest that PPI therapy like Nexium may be associated with an increased risk of ***Clostridium difficile* associated diarrhea**, especially in hospitalized patients.
- Published observational studies suggest that PPI therapy may be associated with an increased risk for **osteoporosis-related fractures** of the hip, wrist, or spine in patients receiving high-dose and long-term treatment.
- **Hypomagnesemia** has been reported in patients treated with PPIs for at least three months. Patients on digoxin or other drugs that may cause hypomagnesemia such as diuretics may need monitoring of magnesium levels.

- Concomitant use of PPIs with high dose **methotrexate** may elevate and prolong serum levels of MTX possibly leading to MTX toxicity.
- Avoid concomitant use with **clopidogrel** because it reduces its inhibition of platelet aggregation.
- **St. John's Wort** and **rifampin** decrease the concentration of esomeprazole.

As of December 2012, more than 91,000 subjects have been exposed to esomeprazole in clinical trials, and the worldwide postmarketing prescription exposure exceeds 80 million patient-years. For this application the Sponsor pooled the safety data from the two esomeprazole clinical trials in support of the treatment of adults with frequent heartburn in the OTC setting. The Sponsor also provided a summary of safety data of esomeprazole from five databases:

- Data from the Sponsor- maintained global post-marketing safety database
- FDA Adverse Events Reporting System (AERS)
- World Health Organization (WHO)/ Vigibase
- American Association of Poison Control Centers/ National Poison Data System (AAPCC/NPDS)
- Drug Abuse Warning Network (DAWN)

In addition, the Sponsor provided a literature review of esomeprazole and additional information regarding potential interactions between esomeprazole and other drugs.

The safety data from the clinical trials show that esomeprazole 20 mg has a good safety profile when used for a limited period of time, as it did not incur SAEs and the AEs noted were generally mild. This profile is supported by the post-marketing safety data and the other safety databases. No new safety signals have been identified. The SAEs found in the databases are all listed in the Nexium Rx label.

7.1 Methods

The Integrated Summary of Safety (ISS) submitted to support the approval of this product for the treatment of adults with frequent heartburn in the OTC setting includes the following:

- Pooled safety data from clinical trials conducted in support of the OTC development program:
 - D961RC00001
 - D961RC00002
- Data from the Sponsor's "Sapphire" post-marketing safety database
- FDA AERS database
- WHO- Vigibase International Drug Monitoring Program
- Drug Abuse and Overdose Data
 - AAPCC/NPDS
 - DAWN
- Review of the published literature for the active ingredient esomeprazole

- Information regarding potential interactions between esomeprazole and other drugs which include information from post-marketing AE reporting and published literature.

Medical Officer Comment: According to advice from FDA the Sponsor was to summarize and analyze the safety data by dose and duration of use, gender, race, and age subgroups and the Sponsor did provide such analyses. The Sponsor also provided the safety data agreed upon.

7.1.1 Clinical Trials Used to Evaluate Safety

Safety data from two identical clinical trials to support OTC use of esomeprazole were evaluated. The trials, D961RC00001 and D961RC00002, were designed to evaluate the efficacy of esomeprazole 20 mg dosed once daily for the short-term treatment of frequent heartburn, measured by the percentage of heartburn-free 24-hour days during the 14 days of treatment. Both were Phase III, multicenter, randomized, double-blind, placebo-controlled, and parallel-group trials. The population consisted of adults, with frequent heartburn (occurring ≥ 2 days per week), without a confirmed diagnosis of GERD, who were likely to self-treat with non-prescription medications without consulting a prescriber. To be eligible for randomization, subjects were required to be compliant in reporting heartburn symptoms via IVRS for at least 5 of 7 days during the placebo run-in period.

A total of 333 subjects from the two trials were exposed to the study drug. The duration of exposure was similar across both treatment groups for the combined studies. Assessments included physical examinations with vital signs, clinical laboratory tests [hematology and chemistry (Na, K, glucose, creatinine, ALT, AST, alkaline phosphatase)], and urinalysis at baseline and follow-up. Electrocardiogram and pregnancy urine test were performed at baseline only. Adverse events were collected throughout the trial from baseline until the end of the trial.

7.1.2 Categorization of Adverse Events

The two studies, D961RC00001 and D961RC00002, were pooled for AE summaries and safety data were presented by preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) vocabulary version 14.1. The number of subjects who had any AEs, AEs with outcome death, SAEs, AEs that led to discontinuation of study drug, and other significant AEs were summarized. Adverse events were also summarized by PT presented by maximum reported intensity and by PT presented by the investigator's causality assessment.

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

Because the two trials had the same design, the safety data were pooled by treatment. The safety analysis set in both trials included all randomized subjects who took at least one dose of the study drug.

Medical Officer Comment: The data pooling strategy and categorization of AEs are acceptable.

7.2 Adequacy of Safety Assessments

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

Overall exposure

Approximately 91,000 received esomeprazole in the clinical development program for esomeprazole. Of the 657 subjects in the safety analysis set of the OTC clinical program, 333 subjects received at least 1 dose of esomeprazole 20 mg and 324 subjects received placebo. The median duration of exposure was 14 days for both esomeprazole and placebo groups (mean 14.6 in both groups). The range of exposure was 5 to 26 days in the esomeprazole group and 7 to 26 days in the placebo group.

Besides the safety data derived from the two clinical trials, the post-marketing database shows that esomeprazole has an accumulated population exposure of 80 million patient-years since this drug's launch in the worldwide market in 2000. This exposure includes exposure to doses of esomeprazole higher than what is being proposed for OTC marketing, as well as longer duration of treatment. This extent of exposure provides reassurance when we are considering the approval of the lowest effective dose of esomeprazole for short duration of treatment in the OTC setting.

The exposure data shows that the subjects were exposed to esomeprazole ranging from 5 to 26 days when the treatment phase was 14 days. This reflects a total dose exposure of 100 mg to 520 mg of esomeprazole. Table 2 below shows the duration of exposure during the treatment period of the two efficacy trials combined.

Table 2. Combined Data (D961RC00001 and D961RC00002) - Duration of Exposure During Treatment Period (Safety Analysis Set)

| Duration of exposure (days) | | Esomeprazole 20 mg (N=333) | Placebo (N=324) |
|-----------------------------|----------------------|----------------------------|-----------------|
| Randomized treatment | n | 330 | 322 |
| | Mean | 14.60 | 14.62 |
| | SD | 1.76 | 1.57 |
| | Median | 14 | 14 |
| | Min | 5 | 7 |
| | Max | 26 | 26 |
| | Total treatment days | 4818 | 4709 |

[Source: Integrated Summary of Safety (ISS), Table 4, p. 20 (109)]

Medical Officer Comment: The overall exposure to esomeprazole is adequate to support safety in the OTC setting. It is noteworthy that in both groups there were subjects who medicated themselves longer than the recommended 14-day use. The Sponsor clarified that the subjects were dispensed bottles containing 30 capsules and were instructed to take only one capsule a day for 14 days. Despite the instructions, some continued to take their medication after 14 days. Because the trial was not designed to provide information as an actual use study, we cannot draw any conclusions about how the drug will be used in the OTC market from the manner in which the drug was used in the trial. The Sponsor intends to market this product in bottles of 14 capsules, packaged in one-bottle, two-bottle, and three-bottle cartons, which may to an extent help consumers limit each treatment to 14 days.

Demographics of Target Populations

The pooled demographics in the OTC clinical program, comprising the major safety populations are summarized in Table 3 below.

The treatment groups were balanced for demographic characteristics with respect to age, gender, race and ethnicity.

- Overall, the trials included more females (57.3% in the esomeprazole group and 55.2 % in the placebo group) than males (42.6% in the esomeprazole group and 55.25% in the placebo group).
- Age: The ages spanned from 18 years of age up to 95 years of age. The mean age was 42.6 in the esomeprazole group and 44.3 in the placebo group. The median ages were 42 in the esomeprazole group and 45 in the placebo group.
- With respect to race, the majority of participants were White (63% in the esomeprazole group and 67.9 % in the placebo group) followed by African-American

(33.9% in the esomeprazole group and 31.1% in the placebo group). Other races (Asian, Native Hawaiian/ Pacific Islander, American Indian/Alaska Native and others not specified) were represented by a small number of individuals, 3% (10/333) in the esomeprazole group and 0.9% (3/ 324) in the placebo group.

- In terms of ethnicity, the subjects were categorized as Hispanic or Latino and Non-Hispanics; there were more non-Hispanics (82.58% in the esomeprazole group and 85.8 % in the placebo group) than Hispanics or Latinos.

Table 3. Demographic Characteristics-Combined Data D961RC00001 and D961RC00002 (Safety Analysis Set)

| Demographic characteristic | | Esomeprazole 20 mg (N=333) | Placebo (N=324) |
|----------------------------|----------------------------------|----------------------------|-----------------|
| Age(years) | n | 333 | 324 |
| | Mean | 42.6 | 44.3 |
| | SD | 13.1 | 13.0 |
| | Median | 42.0 | 45.0 |
| | Min | 19.0 | 18.0 |
| | Max | 90.0 | 85.0 |
| Sex n (%) | F | 191 (57.36) | 179 (55.25) |
| | M | 142 (42.64) | 145 (44.75) |
| | Total | 333 (100.0) | 324 (100.0) |
| Race n (%) | WHITE | 210 (63.06) | 220 (67.90) |
| | BLACK OR AFRICAN AMERICAN | 113 (33.93) | 101 (31.17) |
| | ASIAN | 0 (0.00) | 1 (0.31) |
| | NATIVE HAWAIIAN/PACIFIC ISLANDER | 1 (0.30) | 0 (0.00) |
| | AMERICAN INDIAN/ALASKA NATIVE | 4 (1.20) | 0 (0.00) |
| | OTHER | 5 (1.50) | 2 (0.62) |
| | Total | 333 (100.0) | 324 (100.0) |
| Ethnic Group n (%) | HISPANIC OR LATINO | 58 (17.42) | 46 (14.20) |
| | ALL OTHER | 275 (82.58) | 278 (85.80) |
| | Total | 333 (100.0) | 324 (100.0) |

All other reflects documented as not Hispanics or Latino and those not applicable

[Source: ISS, Table 5, page 21 (109)]

Medical Officer Comment: The treatment arms were well balanced for the demographic characteristics. The age distribution was appropriate for the intended population and the population was diverse to a certain extent because races other than White and African American had a small representation which historically has occurred with other NDA applications.

7.2.2 Explorations for Dose Response

No dose-response finding studies were undertaken with Nexium 24HR. The dose proposed for the OTC indication was based on the lowest currently approved dose of Nexium Rx.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted as part of the OTC development program.

7.2.4 Routine Clinical Testing

Clinical laboratory tests included hematology, chemistry (Na, K, glucose, creatinine, ALT, AST, alkaline phosphatase)], and urinalysis at baseline and follow-up. Electrocardiogram and pregnancy urine test were performed at baseline only.

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

The low pH in the stomach prevents bacterial contamination. Bacterial overgrowth in the small intestine, usually by the normal gut flora, can be seen if gastric acid secretion is reduced (hypochlorhydria) such as in atrophic gastritis. A similar increase in bacterial growth has also been reported in some patients on high doses of acid suppressing drugs. In September 2012, the prescription labels for omeprazole, esomeprazole and lansoprazole received class labeling changes warning of cases of *Clostridium difficile* associated diarrhea. The proposed label for Nexium 24HR does include language to address this safety issue: "Stop use and ask a doctor if ...you get diarrhea.

Other warnings for this class is the association with bone fractures and hypomagnesemia with long-term use (>1 year) but these were not addressed in the OTC label because of the short-term use with the OTC indication.

Another class labeling change for Rx PPIs occurred in May 2012, which warns of the increase and prolongation of MTX levels with the use of PPIs. This warning is not reflected on the OTC labels of PPIs or in the proposed label for Nexium 24HR.

No particular actions were taken in the two trials to monitor for adverse effects that are characteristic for the pharmacological class besides what is generally acceptable for patient safety monitoring.

Medical Officer Comment: The safety monitoring was acceptable considering the low dose and limited duration of use of the study drug. I recommend the inclusion of a warning regarding concomitant use of this drug with MTX because of the potential risk of MTX toxicity and for consistency with the Rx label. If this change is instituted for

esomeprazole, the same change should be implemented for OTC omeprazole and lansoprazole products.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the randomized treatment phase and follow-up phase in either trial.

At the start of the placebo run-in period in trial D961RC00002, prior to receiving any treatment, 1 subject (E7808221) had an AE with outcome of death. The cause of death was reported as acute cardiac arrest; the subject was never exposed to esomeprazole 20 mg or placebo. The following is a narrative of this fatal case (verbatim):

Subject D961RC00002/E7808221: “A 45-year-old White male with frequent heartburn, with no past medical history, surgical history or prior medications was enrolled into the study on 12 August 2011. The baseline physical exam, including vital signs, was normal. The baseline laboratory parameters (chemistry, hematology and urine analysis), were normal. The baseline ECG was reported as non-specific ST-T wave changes in ECG evaluation (abnormal). Subject returned for Visit 2 on [REDACTED] (b) (6) to start the placebo run-in period. During the visit, he was dispensed IP (placebo) with instructions to start the medication the following morning. After returning home from the study visit, the subject was reported with an acute cardiac arrest (verbatim) [REDACTED] (b) (6) which resulted in death on [REDACTED] (b) (6). The event was considered serious due to a life-threatening event, an important medical event, and resulted in death. An autopsy was not performed.”

Medical Officer Comment: It is concerning that this subject was not clinically followed when his baseline ECG was interpreted as abnormal and was randomized to begin the treatment phase of the trial. Although his death was not related to any drug received, it reinforces the notion that in clinical practice myocardial infarction may be misdiagnosed as heartburn. The proposed OTC label does include language to ask a doctor if other symptoms accompany the heartburn that might suggest the occurrence of myocardial ischemia.

7.3.2 Non-Fatal Serious Adverse Events

In trial D961RC00001, one subject (E7808144) experienced 2 SAEs (hypertension exacerbation and worsening migraines) during the placebo run-in period, and discontinued the study before randomization. In study D961RC00002, one subject (E7802279) experienced an SAE of myocardial infarction during the placebo run-in period, before receiving any study medication, and discontinued the study before randomization. Below is the narrative for this case (verbatim):

“Subject D961RC00002/E7802279: A 60-year-old African-American male with frequent heartburn was enrolled into the study on 26 August 2011. His medical history included coronary artery disease, gout and peripheral artery disease, all of which were ongoing at the time of the study. He had a past medical history of cardiac chest pain, shortness of breath, dyspnea on exertion, and myocardial infarction. Surgical history included cardiac stent placement (1998) and amputation of right great toe. His medications at the time of enrollment included Oral Tums® (calcium carbonate) for heartburn. At baseline (Visit 1), physical examination was normal. Laboratory parameters (chemistry, hematology, and urinalysis) were unremarkable. The baseline ECG on 26 August 2011 was reported as normal. On [REDACTED] (b) (6) the subject reported a myocardial infarction (verbatim: heart attack) during the wash-out period. Vitals signs were assessed, labs were drawn, ECG, an echocardiogram (ECHO), and a chest X-ray were performed. The ECG showed sinus tachycardia, ST elevation, acute infarct. The subject was admitted to the hospital, and underwent a cardiac catheterization, resulting in stent placement. The SAE resolved on [REDACTED] (b) (6) and the subject was discharged. The subject came in for Visit 2 on 6 September 2011 and was immediately terminated from the study. No other assessments were done and placebo run-in study medication was not dispensed.”

Medical Officer Comment: No treatment associated SAEs occurred during the treatment phase of the clinical trials. Unlike the fatal case described in Section 7.3.1., this subject had a known history of cardiac disease, but had normal baseline evaluation. It is difficult to make a determination whether the heartburn symptoms he was experiencing at enrollment were indeed symptoms of heartburn or discomfort associated with cardiac ischemia without an assessment of cardiac enzymes, especially with the normal baseline ECG. Although the SAE reported was not associated with any treatment because it occurred before randomization, again this case illustrates that cardiac ischemia and GERD symptoms can overlap; thus, consumers need to be aware of the possibility of serious cardiac underlying conditions manifesting with heartburn. The Drug Facts does provide language in the Warnings section alerting consumers of other signs and symptoms of cardiac ischemia in the section “Ask a doctor before use if you have...”. This reviewer proposes elevating the cautionary language regarding ischemic cardiac events to a higher level “Do not use if:...”. See discussion in section 9.2 Labeling Recommendations. .

7.3.3 Dropouts and/or Discontinuations

In study D961RC00001, 2 subjects in the placebo group discontinued treatment due to cholelithiasis and nasopharyngitis, respectively. In study D961RC00002, 1 subject in the esomeprazole 20 mg group (subject E7808221) reported an AE (sinusitis) leading to discontinuation of the treatment.

Medical Officer Comment: It is plausible that this SAE (sinusitis) may be associated with the study drug given the pattern of the post-marketing reports which show a number of AE reports describing infections.

7.3.4 Significant Adverse Events

There were no other significant AEs identified in either of the clinical trials conducted.

7.3.5 Submission Specific Primary Safety Concerns

No other serious or clinically significant AEs were identified in the trials.

7.4 Supportive Safety Results

Supportive safety results from the two clinical trials comprising the OTC clinical program are summarized in the sections below. Overall the events reported were isolated incidents spread across different SOCs and no specific pattern was identified.

7.4.1 Common Adverse Events

Overall, the percentage of patients with at least one treatment-emergent adverse event (TEAE) was similar in the esomeprazole group: 12% (40/333) in the esomeprazole group and 10% (31/324) in the placebo group. The most commonly reported TEAEs reported among the esomeprazole-treated group were: constipation, bronchitis, hemoglobin decreased, blood glucose decreased, cough, sinusitis, upper respiratory infection.

The System Organ Classes (SOC) that presented the most TEAEs in the esomeprazole-treated group which were higher than the placebo group, and more than 1% are: Infections and infestations (3%), Investigations (3%), Nervous System Disorders (1.5%), Injury, Poisoning and Procedural Complications (1.2%). Below is Table 4 showing TEAEs by SOC that were more frequently associated with TEAEs in the esomeprazole-treated group and in $\geq 0.5\%$ of the subjects. The events were spread across different SOCs and no specific pattern was identified.

Table 4. SOCs with more TAES in the Esomeprazole-Treated Group and in $\geq 0.5\%$ of Subjects- Combined data (D961RC00001 and D961RC00002)

| System Organ Class | Esomeprazole Mg 20 mg N= 333 (%) | Placebo N= 324 (%) |
|--|-------------------------------------|-----------------------|
| Infections and Infestations | 10 (3) | 5 (1.54) |
| Investigations | 10 (3) | 5 (1.54) |
| Nervous System Disorders | 5 (1.5) | 1 (0.31) |
| Respiratory, Thoracic and Mediastinal Disorders | 5 (1.5) | 1 (0.31) |
| Injury, Poisoning and Procedural Complications | 4 (1.2) | 3 (0.93) |
| Musculoskeletal and Connective Tissue Disorders | 3 (0.9) | 2 (0.62) |
| Psychiatric Disorders | 3 (0.9) | 0 (0) |
| Reproductive System and Breast Disorders | 2 (0.6) | 0 (0) |

(Reviewer's table based on Sponsor's ISS, Appendix 1, Table 2, p.5- see Sponsor's full table is this review's Appendix 9.4 Table 23)

In the clinical trials, the most frequently reported TEAEs were constipation in the esomeprazole 20 mg treatment group (0.9%) and nausea in the placebo treatment group (1.2%). TEAEs experienced by at least 0.5% of subjects in the esomeprazole-treated group that were higher than the placebo group and $\geq 0.5\%$ of the patients are presented by preferred term (PT) Table 5 below.

Table 5. PTs more frequent in the Esomeprazole-Treated Group and $\geq 0.5\%$ of subjects During the Treatment Period (Safety analysis set)- Combined data (D961RC00001 and D961RC00002)

| Preferred Term | Esomeprazole Mg 20 mg N= 333 (%) | Placebo N= 324 (%) |
|--------------------------------------|-------------------------------------|--------------------|
| Constipation | 3 (0.9) | 2 (0.6) |
| Bronchitis | 2 (0.9) | 2 (0.6) |
| Hemoglobin Decreased | 2 (0.6) | 0 (0) |
| Blood Glucose Decreased | 2 (0.6) | 1 (0.3) |
| Cough | 2 (0.6) | 1 (0.3) |
| Sinusitis | 2 (0.6) | 1 (0.3) |
| Upper Respiratory Tract Infection | 2 (0.6) | 1 (0.3) |

[Reviewer's table based on Sponsor's ISS, Table 7, p. 24 (109)-see Sponsor's full table in this review's Appendix 9.4 Table 24]

Medical Officer Comment: The most commonly reported AEs during esomeprazole

20 mg treatment were in the SOCs of Infections and Infestations (n=10, 3% subjects) and Investigations (n=10, 3% subjects). The number of each TEAEs was small and the events were mostly mild to moderate in intensity.

It is noteworthy that these AEs differ from the most frequently reported AEs according to the label for Nexium Rx. The most frequently reported AEs in the safety data of the clinical trials assessing Nexium 20 mg and 40 mg for erosive esophagitis were headache and diarrhea. These TEAS occurred in less than 0.5% of the subjects in the OTC trials and there does not seem to be an explanation for these results.

7.4.2 Laboratory Findings

There were isolated changes in laboratory tests conducted during the two OTC clinical trials but the data did not suggest any clinically significant effect of the study drug on hematology and chemistry tests obtained (Na, K, glucose, creatinine, ALT, AST, alkaline phosphatase), as well as on urinalysis.

Medical Officer Comment: The assessment of the level of magnesium was not part of the clinical laboratory monitoring.

7.4.3 Vital Signs

A complete physical examination including vital signs was performed at baseline and at the end of the randomized treatment period. BMI, height and weight were only obtained at baseline. There were isolated changes in blood pressure and heart rate, none however that raises concerns of the proposed dose and duration for OTC use.

7.4.4 Electrocardiograms (ECGs)

ECGs were conducted only at baseline to assess eligibility for participation in the trial.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this OTC indication.

7.4.6 Immunogenicity

This is not applicable to this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No assessments of dose-dependency for AEs were conducted as part of the OTC development program. The label of Nexium Rx however, indicates that the incidence of AEs is similar between the 20 mg and the 40 mg strengths.

7.5.2 Time Dependency for Adverse Events

No assessments of time-dependency for AEs were conducted as part of the OTC development program. The label of Nexium Rx however, indicates that the occurrence of AEs is increased with longer treatment duration.

7.5.3 Drug-Demographic Interactions

The treatment groups were well balanced for demographic characteristics with respect to the gender, age, race and ethnicity. The subjects were categorized based on: age (<65 years, ≥65 years), gender (male, female), race (White, Black/African American, and Other), and ethnicity (Hispanic or Latino, and All others) as shown on Table 6 below. Effects of age, gender, race and ethnicity were analyzed. There was no prevalence of any particular AEs in any category that would indicate a trend of medical importance.

Table 6. Number (%) of subjects with AEs by age, gender, race, and ethnicity (safety analysis set)

| | Esomeprazole 20 mg | | Placebo | |
|------------------------|--------------------|-----------|---------|-----------|
| | N | n (%) | N | n (%) |
| Total population | 333 | 40 (12.0) | 324 | 31 (9.6) |
| Age | | | | |
| <65 years | 317 | 37 (11.7) | 307 | 29 (9.5) |
| ≥65 years | 16 | 3 (18.8) | 17 | 2 (11.8) |
| Gender | | | | |
| Male | 142 | 13 (9.2) | 145 | 13 (9.0) |
| Female | 191 | 27 (14.1) | 179 | 18 (10.1) |
| Race | | | | |
| White | 210 | 23 (11.0) | 220 | 20 (9.1) |
| Black/African American | 113 | 15 (13.3) | 101 | 10 (9.9) |
| Other | 10 | 2 (20.0) | 3 | 1 (33.3) |
| Ethnicity | | | | |
| All Others | 275 | 32 (11.6) | 278 | 24 (8.6) |
| Hispanic or Latino | 58 | 8 (13.8) | 46 | 7 (15.2) |

AE Adverse event; N Total number of subjects in treatment group and subgroup;
 n Number of subjects with AEs

(Source: Sponsor's ISS, Table 9, p. 28 (109))

Medical Officer Comments: It should be noted that the number of subjects ≥ 65 years of age, and the number of subjects of 'Other' race was small, therefore the data is not conducive for drawing conclusions in these particular population subsets based on the OTC trials.

7.5.4 Drug-Disease Interactions

Hepatic Impairment

Based on PK studies in subjects with hepatic impairment, Rx labeling indicates that a dose of 20 mg daily should not be exceeded in patients with severe hepatic insufficiency and dose adjustment is unnecessary in patients with lesser hepatic insufficiency. The OTC dose is 20 mg daily, which is acceptable for subjects with hepatic impairment.

Renal Impairment

Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in subjects with impaired renal function. Rx labeling indicates that dose adjustment is not required in subjects with impaired renal function.

7.5.5 Drug-Drug Interactions

There were no reports of drug-drug interactions in the OTC trials. However, the studies were designed to restrict the use of certain concomitant medications in order to avoid known drug interactions. These medications included antifungals, antiretroviral drugs (atazanavir, nelfinavir and saquinavir), warfarin (coumadin), clopidogrel, tacrolimus, diazepam, cilostazol, digoxin, or the use of these agents at any time between enrollment and trial completion. In addition, use of iron salt (multivitamins with iron or dietary supplements with iron were allowed) was also an exclusion criterion.

Medical Officer Comments: Drug interactions may occur when esomeprazole is taken concomitantly with several drugs. The following is the list of drugs that should not be taken with esomeprazole, from the Nexium Rx Medication Guide: warfarin, ketoconazole, voriconazole, atazanavir, nelfinavir, saquinavir, products that contain iron, digoxin, St. John's Wort, rifampin, cilostazol, diazepam, tacrolimus, erlotinib, methotrexate, and clopidogrel.

*The proposed Drug Facts has a warning regarding concomitant use of drugs:
"Ask a doctor or pharmacist before use if you are taking:*

- *warfarin, clopidogrel or cilostazol (blood-thinning medicines)*
- *prescription antifungal or anti-yeast medicines*
- *digoxin (heart medicine)*

- *diazepam (anxiety medicine)*
- *tacrolimus (immune system medicine)*
- *prescription antiretrovirals (medicines for HIV infection)*

The warning regarding the use of MTX was recently a class labeling change for the prescription PPIs. This reviewer recommends the addition of MTX to the warnings on the OTC label because of the risk of MTX toxicity with concomitant use, as well for consistency with the Rx label.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new carcinogenicity and teratogenicity studies have been conducted as part of the development program of this OTC product. According to the Sponsor, there is no new human carcinogenicity issues currently related to the use of esomeprazole magnesium in humans.

Medical Officer Comments: Carcinogenicity risk is not expected with the limited proposed use of esomeprazole magnesium 20 mg in the OTC setting. No new carcinogenicity studies were conducted but the Nexium prescription label has the following information:

- *“The carcinogenic potential of Nexium was assessed using studies of omeprazole, of which esomeprazole is an enantiomer.”*
- *“A 78-week mouse carcinogenicity study 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.”*

7.6.2 Human Reproduction and Pregnancy Data

There were no reports of pregnancy or lactation in the OTC trials.

Esomeprazole 20 mg OTC is not intended for use in pregnant and lactating women. Nexium Rx is classified as Pregnancy Category (b) (4). Based on non-clinical data, in house data and data from the literature, no clinically significant increased risk for severe complications or malformations have been confirmed when PPIs are used during pregnancy or lactation. The excretion of esomeprazole in the milk has not been measured, thus it is not known whether esomeprazole is excreted in human milk.

Since the drug launch in 2000 up to December 31, 2012, AstraZeneca has received 605 case reports of pregnancy (including paternal exposure and child case reports with placental exposure) of which 223 pregnancy outcomes have been reported as follows:

- 10 intrauterine deaths/stillbirths
- 1 ectopic pregnancy
- 4 terminations due to fetal defects (trisomy 18, alobar haloprosencephaly, congenital hand malformation, limb reduction defect)
- 5 babies born with congenital malformations: hypospadias, syndactily, cleft palate/lip, anotia, mild hemangiomas
- 29 spontaneous abortions
- 21 elective termination (fetal defects unknown)
- 4 transplacentally exposed children with AEs and 11 non-healthy babies. In 1 report oligohydramnios was reported, but pregnancy outcome was unknown
- 138 healthy babies born.

According to the Sponsor, the number of known pregnancy outcomes in AstraZeneca's safety data base was limited; however, the reports did not indicate any causal relationship between esomeprazole and complications during pregnancy, particularly considering the congenital malformation background rate of 2.8% in the general population (Jensen et al, 2004). As for most case reports received from market use, detailed information is often scarce and confounding factors such as concurrent disease and/or other concomitant medication might exist.

Medical Officer Comment: It is difficult to draw any definitive conclusions with respect to pregnancy outcomes for the reason pointed by the Sponsor and also without knowing the denominator for the use of the drug in this population for any type of safety assessment. I concur that no pattern can be identified with the available data.

The risks associated with esomeprazole use in pregnant women and nursing mothers has not been formally investigated clinically, therefore this drug should only be used if clearly necessary and under the oversight of a physician. The proposed Drug Facts label includes language that addresses the use of the drug during pregnancy and lactation: "If pregnant or breastfeeding: ask a health professional before use." This is the current language for drugs of Pregnancy Category (b) (4) in the OTC setting. Should esomeprazole ever become a drug of Pregnancy Category C the same language may still apply.

7.6.3 Pediatrics and Assessment of Effects on Growth

This is not applicable to this application.

Medical Officer Comment: The Sponsor has requested a waiver for pediatric studies which was granted as the OTC indication is deemed inappropriate for the pediatric population. Pediatric gastroenterologists recommend that children with symptoms of

heartburn should be under the direction of a physician. The Agency's current position is that treatment of heartburn in the pediatric population is not appropriate in the OTC setting and a physician should be consulted before use in children under 18 years of age. This is consistent with the OTC PPI products currently approved and marketed in the US (e.g., omeprazole and lansoprazole.)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of overdose, drug abuse or dependency in the studies D961RC00001 or D961RC00002.

AstraZeneca's post-marketing database contained 229 case reports of overdose involving 545 AEs until December 31, 2012: 35 were serious and 194 were non-serious. Out of the 194 non-serious reports, 121 were overdose reports without any associated AEs.

Of the 35 serious AE reports, three had fatal outcomes:

- In one report, the patient suffered from cancer and was treated with multiple drugs; the contribution of esomeprazole to the fatal outcome was considered unlikely by the reporting physician.
- The remaining 2 reports contained very limited information that did not allow a causality assessment for the role of esomeprazole in relation to the fatal outcomes.

The most commonly reported event terms associated with overdose were: accidental overdose (n=115), overdose (n=94), intentional overdose (n=18). For reports of overdose, both intentional and unintentional, the most commonly reported concurrent AEs were: medication error (n=15), headache (n=11), diarrhea (n=10), drug ineffective (n=10), nausea (n=19), GERD (n=8), malaise (n=7) and vomiting (n=7). Ingestions exceeding the recommended doses did not seem to be associated with any safety concerns. The Sponsor concluded that the overdose experience from clinical trials and post-market safety reports indicated that the risk of organ toxicity is low.

Safety data from other post-marketing databases such as AAPCC and DAWN indicate that esomeprazole does not have psychotropic or narcotic characteristics, and is not addictive.

Medical Officer Comment: According to the Nexium Rx label, there was limited experience of doses exceeding 240 mg. The label provides information related to the overdose experience with omeprazole up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen with normal use of the drug. This is somewhat reassuring given there were no fatalities or severe organ injury with such high doses of omeprazole.

7.6.5 Information Regarding Potential Drug Interactions

The Sponsor provided a summary of the known drug interactions that occur with esomeprazole and which are already addressed in the Nexium Rx label. There are no new drug interactions with esomeprazole that require additional labeling. The OTC product does contain cautionary language alerting consumers to not use esomeprazole with certain drugs.

7.7 Additional Submissions / Safety Issues

The Sponsor submitted a 4-month safety update (4MSU) on September 27, 2013 and based on the information reviewed, no new safety concerns were identified. The 4MSU summarized new safety information from all post-marketing AEs regarding oral esomeprazole use received by AstraZeneca from January 1, 2013 through April 30, 2013, and a summary of the literature search conducted to identify any relevant safety information with the use of orally-administered esomeprazole covering this time period. FDA agreed at the pre-NDA meeting that external database searches for the 4MSU would not be required, as the magnitude of the additional data, relative to the data included in the original searches was expected to be small, with no significant impact on the overall safety profile of esomeprazole.

The safety data included in the 4MSU did not identify any new safety concerns and mirrored what was already known with the previous post-marketing data submitted in the NDA. During the 4 MSU reporting period, AstraZeneca received 2,129 case reports associated with 6,140 AE terms. Of these case reports, 59% case reports (1,257/ 2,129) with 4,408 associated events were reported from the US. A majority of the case reports were non-serious: 80% (1,702/ 2,129) overall, of which 62% (1,062 /1,702) were from the US. Overall, there were 399 serious non-fatal case reports, of which 45% (179/ 399) originated from the US. There were 28 case reports with fatal outcome and 16 (57%) of these were reported from the US.

During the period of 01 January 2013 through 30 April 2013 there was no new information from clinical trials. A search of the scientific literature also did not identify any new safety information regarding the general safety of treatment with esomeprazole use per oral. This 4MSU supplements the postmarketing data reviewed in section 8.

8 Postmarketing Experience

As of December 2012, more than 91,000 subjects have been exposed to esomeprazole in clinical trials, and the worldwide postmarketing prescription exposure exceeds 80 million patient years. The corresponding US exposure was approximately 36 million

patient-years. The exposure was calculated from the number of tablets/sachets delivered to wholesalers worldwide, and a daily dose of 1 tablet/sachet was assumed.

The Sponsor provided a summary of esomeprazole safety information from five databases (Sponsor's post-marketing database, AERS, WHO Vigibase, AAPCC/NPDS, and DAWN), a literature review of esomeprazole and information regarding potential interactions between esomeprazole and other drugs.

Esomeprazole has a well-established safety profile and has been marketed for prescription use for more than twelve years. Esomeprazole was first approved on 10 March 10, 2000 and in the US in February, 2001. It is currently approved in more than 125 countries and substantial post-marketing safety information is available.

8.1 AstraZeneca's Global Postmarketing Database

8.1.1 Overall analysis

AstraZeneca's (AZ) database contains all worldwide safety information derived from various post-marketing sources such as consumers, health professionals, pharmaceutical manufacturers, regulatory authorities and case reports from published literature, including both serious and non-serious reports. A large portion of the case reports originated from consumers: 77% and 88% of the case reports for global and US cases, whereas 23% and 12% were cases from medically confirmed sources in the global and US databases, respectively.

The search for all post-marketing AE reports received by AstraZeneca and entered onto their database from March 10, 2000 to December 31, 2012 resulted in a total of 69,032 case reports including 163,030 AE terms. Of the total case reports, 52,161 (76%) were reported from the US with 129,657 (80%) associated events. Most of the commonly reported AE terms were either considered to reflect the underlying disease, or represented terms which are listed for esomeprazole in the core product labeling and are included in the Nexium Rx label. Overall, for the case reports received from the US, the pattern of reported AE terms was similar as for the case reports received globally. The demographic characteristics with respect to age, gender, and ethnicity were also comparable between the global case reports and the US case reports.

8.1.2 Deaths

There were 1,352 cases with fatal outcome which accounted for 1.9% of the total number of cases (1,352/69,032) and 1,186 of the fatal cases were from the US). The fatal cases were associated with 1,999 AE terms. Of all the fatal cases, 315 were medically confirmed. The SOCs associated with the AEs were comparable between the global and US reported cases. The most common SOCs associated with fatal cases were: General Disorders and Administration Site Conditions, Neoplasms Benign,

Malignant and Unspecified, Cardiac Disorders, Respiratory Disorders, Infections and Infestations. The five SOCs accounted for 66.5% and 73.1% of the SOCs in the global and US databases respectively. Table 7 below shows the SOCs most frequently associated with the cases of fatal outcome that occurred >1% (for the entire tables see Appendix 9.4 Tables 25 and 26)

Table 7. AZ SOC most frequently associated with fatal cases (>1%)- Global and US

| Global | | | US | | |
|-----------------------------|-----|------|-------------------------------|-----|------|
| SOC | N | % | SOC | N | % |
| Gen. Dis. & Adm. Site Cond. | 869 | 43.5 | Gen. Dis. and Adm. Site Cond. | 821 | 49.3 |
| Neoplasms | 192 | 9.6 | Neoplasms | 176 | 10.6 |
| Cardiac Disorders | 179 | 9 | Cardiac Disorders | 151 | 9.1 |
| Respiratory Disorders | | | Respiratory Disorders | | |
| Infections and Infestations | 88 | 4.4 | Infections and Infestations | 69 | 4.1 |

[Reviewer's table based on ISS, Tables 13 and 14, p.48-49 (109)]

The AE PTs associated with the fatal cases were comparable between the global and US reported cases. Below is Table 8 showing the most frequently reported AEs by PT that occurred more than 1%. The complete tables with the globally and US reported fatal AEs by PT, at a frequency as low as 0.5%, can be found in Appendix 9.4 Tables 27 and 28.

Table 8. AZ PT most frequently reported with fatal cases >1%- Global and US

| Global | | | US | | |
|----------------------------|-----|-------|----------------------------|-----|-------|
| AE PT | N | % | AE PT | N | % |
| Death | 789 | 39.47 | Death | 766 | 32.82 |
| Myocardial infarction | 56 | 2.8 | Myocardial infarction | 47 | 2.82 |
| Neoplasm malignant | 39 | 1.95 | Neoplasm malignant | 39 | 2.34 |
| Pneumonia | 30 | 1.5 | Lung neoplasm malignant | 29 | 1.74 |
| Lung neoplasm malignant | 29 | 1.45 | Pneumonia | 26 | 1.56 |
| Cardiac disorder | 25 | 1.25 | COPD ¹ | 25 | 1.5 |
| COPD ¹ | 25 | 1.25 | Cardiac disorder | 23 | 1.38 |
| Cardiac failure congestive | 23 | 1.15 | Cardiac failure congestive | 22 | 1.32 |
| Cardiac arrest | 21 | 1.05 | Cerebrovascular accident | 18 | 1.08 |
| Cerebrovascular accident | 19 | 0.95 | Cardiac arrest | 17 | 1.02 |

¹Chronic obstructive pulmonary disease

[Reviewer's table based on ISS, Tables 18 and 19, p. 55-56 (109)]

Death, myocardial infarction and neoplasm malignant were the most commonly reported fatal AEs for the global and US case reports:

- Death: Most of the case reports with AE of "Death" derive from patients participating in data collection programs that do not actively obtain AE data. This information reflects change in their status in the program and there are no details about the circumstances of the event "Death". The Sponsor states that attempts to obtain details on the death circumstances have been unsuccessful. A review of a sample of MedWatch forms by this reviewer showed that many patients were very ill prior to treatment with esomeprazole, and treated with other drugs that could possibly be related to the fatal outcome making it difficult to make any determinations regarding the role of esomeprazole in the fatal outcome.
- "Neoplasm malignant": The Sponsor notes that the most common term associated with "neoplasm malignant" was cancer (unspecified). Many patients were elderly, and the location of the neoplasm was not reported in most cases. Within the case reports in which the site of the neoplasm was reported, no specific pattern was identified. The association of cancers of the stomach, colon and pancreas with PPIs has been suggested in the literature but at this time no definitive conclusion can be made based on the available information.

- Myocardial infarction: Some reports with events of myocardial infarction as well as other cardiovascular events including cerebrovascular events indicate that the patients have underlying conditions that put them at risk for myocardial infarction and stroke, such as cardiovascular disease, smoking, obesity, advanced age, use of medications such as antihypertensives, anticoagulants, statins, and antidiabetics. Therefore any definitive conclusions regarding an association between esomeprazole and cardiac outcomes cannot be made with the available data.

8.1.3 Serious Adverse Events- Non-Fatal

There were 12,059 non-fatal serious cases in the post-marketing database. These cases accounted for 17.4% (12,059/69,032) of the total number of cases, of which 71% (8,564/12,059) were from the US. The SOCs associated with the non-fatal SAEs cases were similar between the global and US reports. The five SOCs most frequently associated with the non-fatal serious cases were Gastrointestinal Disorders, General Disorders and Administration Site Disorders, Injury, Poisoning and Procedural Complications, Nervous System Disorders and Musculoskeletal Disorders. Table 9 below shows the five most common SOCs that were associated with the serious non-fatal cases (For the Sponsor’s full tables see Appendix 9.4 Table 25 and 26.)

Table 9. AZ SOC most frequently associated with serious non-fatal cases - Global and US

| Global | | | US | | |
|--|-------|------|--|-------|------|
| SOC | N | % | SOC | N | % |
| Gastrointestinal Disorders | 7,711 | 18 | Gastrointestinal Disorders | 6,638 | 18.9 |
| General Disorders and Administration Site Conditions | 4,618 | 10.8 | Injury, Poisoning and Procedural Complications | 4,351 | 12.4 |
| Injury, Poisoning and Procedural Complications | 4,548 | 10.6 | General Disorders and Administration Site Conditions | 3,921 | 11.2 |
| Nervous System Disorders | 3,482 | 8.1 | Nervous System Disorders | 2,837 | 8.1 |
| Musculoskeletal and Connective Tissue Disorders | 2,333 | 5.4 | Musculoskeletal and Connective Tissue Disorders | 1,986 | 5.7 |
| Respiratory, Thoracic and Mediastinal Disorders | 2,155 | 5 | Respiratory, Thoracic and Mediastinal Disorders | 1,850 | 5.3 |

[Reviewer’s table based on ISS, Tables 13 and 14, p.48-49 (109)]

The most frequently reported SAEs by PT in the global database that occurred > 1% were: drug dose omission, GERD, malaise, cerebrovascular accident, dyspepsia, myocardial infarction, vomiting, fall, and neoplasm malignant. For the full tables of the

most frequently reported non-fatal SAEs by PT see the Sponsor’s tables in Appendix 9.4 Tables 29 and 30.

8.1.4 Common Adverse Events

Of the 69,032 case reports, the majority 80%, (55,621/69,032) were non-serious adverse events, of which 76% (42,411/55,621) were in the US. Table 10 below shows the most commonly reported AEs by PT for both the global and US databases that occurred in a frequency >1%. They are distributed among the SOCs described above and are described in the Rx label with the exception of drug dose omission, drug ineffective, and intentional drug misuse.

Table 10. AZ Most frequently reported common AEs by PT: Global and US (cut-off 1%)

| Preferred Term | Global | | US | |
|----------------------------------|---------------|--------------|---------------|--------------|
| | n | % | n | % |
| Drug dose omission | 8 533 | 5.2 | 8 381 | 6.4 |
| Gastrooesophageal reflux disease | 6 148 | 3.8 | 5 696 | 4.4 |
| Drug ineffective | 5 195 | 3.2 | 4 499 | 3.5 |
| Diarrhoea | 4 459 | 2.7 | 3 258 | 2.5 |
| Malaise | 4 233 | 2.6 | 3 942 | 3.0 |
| Dyspepsia | 4 174 | 2.5 | 3 706 | 2.8 |
| Headache | 3 964 | 2.4 | 2 696 | 2.1 |
| Abdominal pain upper | 3 671 | 2.2 | 2 745 | 2.1 |
| Nausea | 3 519 | 2.1 | 2 337 | 1.8 |
| Vomiting | 2 439 | 1.5 | 1 983 | 1.5 |
| Abdominal pain | 2 284 | 1.4 | 1 615 | 1.2 |
| Abdominal discomfort | 2 057 | 1.3 | 1 802 | 1.4 |
| Dizziness | 2 013 | 1.2 | 1 162 | 0.9 |
| Pain | 1 864 | 1.1 | 1 705 | 1.3 |
| Osteoporosis | 1 661 | 1.0 | 1 628 | 1.2 |
| Intentional drug misuse | 1 650 | 1.0 | 1 532 | 1.2 |
| Flatulence | 1 615 | 1.0 | 1 223 | 0.9 |
| Total: | 163691 | 100.0 | 130347 | 100.0 |

The data are sorted by decreasing frequency in the Global column.

AEs with a frequency of at least 1% in the Global column are included in this table.

The totals are those for the entire dataset, not just the data in the table.

[Source: ISS. Table 15, p. 50 (109)]

8.1.5 Analyses by age, gender and race

Below is Table 11 showing the distribution of the types of AEs with respect to age, gender and races in the global postmarketing database, which includes the US cases.

Table 11. AZ AE by Age, Gender, and Race

| | | Fatal outcome | Serious Non-Fatal ^a | Non-serious | Overall | |
|---|---|----------------------|--------------------------------|--------------|--------------|--------------|
| Total number of case reports | | 1352 | 12059 | 55621 | 69032 | |
| Total number of adverse event preferred terms | | 1999 | 42955 | 118076 | 163030 | |
| Age, years | N | 1032 | 9521 | 34659 | 45212 | |
| | Mean | 68 | 61 | 58 | 59 | |
| | Range | 0-103 | 0-109 | 0-106 | 0-109 | |
| Age group, years (yrs) n (%) | <12 yrs | 5 (0.4) | 66 (0.5) | 333 (0.6) | 404 (0.6) | |
| | ≥12 to 17 yrs | 0 (0.0) | 39 (0.3) | 196 (0.4) | 235 (0.3) | |
| | ≥18 to 64 yrs | 407 (30.1) | 5553 (46.0) | 21534 (38.7) | 27494 (39.8) | |
| | ≥65 to 74 yrs | 224 (16.6) | 1909 (15.9) | 6732 (12.1) | 8865 (12.8) | |
| | ≥75 yrs | 396 (29.3) | 1954 (16.2) | 5864 (10.5) | 8214 (11.9) | |
| | Unknown | 320 (23.6) | 2538 (21.1) | 20962 (37.7) | 23820 (34.6) | |
| Gender n (%) | Female | 671 (49.6) | 7786 (64.6) | 35894 (64.5) | 44351 (64.2) | |
| | Male | 639 (47.3) | 4050 (33.6) | 16153 (29.0) | 20842 (30.2) | |
| | Unknown | 42 (3.1) | 223 (1.8) | 3574 (6.5) | 3839 (5.6) | |
| Ethnic origin n (%) | African /Black /African-American /African-Caribbean | 4 (0.3) | 95 (0.8) | 674 (1.2) | 773 (1.1) | |
| | Asian /Chinese | 7 (0.5) | 36 (0.3) | 338 (0.6) | 381 (0.6) | |
| | Caucasian | 48 (3.6) | 1532 (12.7) | 10845 (19.5) | 12425 (18.0) | |
| | Native Alaskan - Inuit /Native American /Other | 4 (0.3) | 58 (0.5) | 289 (0.5) | 351 (0.5) | |
| | Hispanic | 3 (0.2) | 45 (0.4) | 513 (0.9) | 561 (0.8) | |
| | Unknown | 1286 (95.1) | 10293 (85.3) | 42962 (77.3) | 54541 (79.0) | |
| | Report type n (%) | Literature | 10 (0.7) | 76 (0.6) | 120 (0.2) | 206 (0.3) |
| | | Other spontaneous | 1342 (99.3) | 11983 (99.4) | 55501 (99.8) | 68826 (99.7) |
| Case outcome n (%) | Died | 1343 (99.3) | 0 (0.0) | 0 (0.0) | 1343 (1.9) | |
| | Not recovered | 0 (0.0) | 1023 (8.5) | 5048 (9.1) | 6071 (8.8) | |
| | Recovering | 0 (0.0) | 694 (5.8) | 1480 (2.7) | 2174 (3.1) | |
| | Recovered w sequelae | 0 (0.0) | 53 (0.4) | 50 (0.1) | 103 (0.1) | |
| | Recovered | 0 (0.0) | 2031 (16.8) | 5171 (9.3) | 7202 (10.4) | |
| | Unknown/Not entered | 9 (0.7) ^b | 8258 (68.5) | 43872 (78.8) | 52139 (75.6) | |
| Medically confirmed report n (%) | Yes | 315 (23.3) | 4087 (33.9) | 11187 (20.1) | 15589 (22.6) | |
| | No | 1037 (76.7) | 7972 (66.1) | 44434 (79.9) | 53443 (77.4) | |

^a Serious cases excluding fatal outcome. May include both serious and non-serious AE terms.

^b Case outcome unknown but AE outcome indicates that the patient died.

Source: ISS, Table 11, p. 45 (109)]

Age

Age was available in 45,212 (65.4%) case reports and was unknown in approximately one third (23,820/69,032, 34.5%) of the total global reports. The age range spanned from 0 (this drug is approved down to 1 month of age, so less than 1 year of age) to 109 years-old. The mean age was 59 years of age.

Pediatric cases (<18 years of age) accounted for 1.4% (639/45,212) of the cases with reported age. Five pediatric fatal reports (0.01%, 5/45,212) were associated with the following SOCs (ISS Appendix 2, Table 13, p. 350):

- Cardiac Disorders
- Respiratory, Thoracic and Mediastinal Disorders
- Infections and Infestations
- Gastrointestinal Disorders
- Investigations
- Surgical and Medical Procedure,
- Congenital, Familial and Genetic Disorders

The number of non-fatal SAEs was also small (0.2%, 105/45,212) in the pediatric population compared to the other age groups.

With respect to the elderly population (>65 years of age), there were 17,079 (37.7%, 17,079/45,212) reports in global database: 19.6% (8,865/45,212) were ≥ 65 to 74 years of age and 18.16% (8,214/45,212) ≥ 75 years of age. There were 620 (1.3%, 620/45,212) fatal reports in the population ≥ 65 years of age and the following are the most frequently associated SOCs:

- General Disorders and Administration Site Conditions
- Neoplasms Benign, Malignant and Unspecified
- Cardiac Disorders
- Respiratory, Thoracic and Mediastinal Disorders
- Infections and Infestations

With respect to non-fatal SAEs there were 3,863 reports (8.5%, 3,863/45,212) in individuals ≥ 65 years of age.

Lastly, there were 407 fatal reports (0.9%, 407/45,212) in the adult population ≥ 18 - 65 years of age and 5553 (12.2%, 5553/45,212) non-fatal SAE reports. The number and proportion of reports did not differ much from the elderly population and the SOCs associated with these SAES are comparable between these two adult populations.

In terms of AEs, an increased incidence of accidental exposures is noted in the pediatric population. As expected, association with neoplasms is more expected in the adult population compared with the pediatric population. The cardiac AEs noted in the pediatric population seem to be associated with cardiac defects rather than other

cardiac conditions which are expected to be more prevalent in the adult population. When comparing the two adult subpopulations, 18 to 64 years of age and 65 years of age and above, the incidence of cardiac SAEs and AEs seem to be comparable. Other patterns or clusters of other AEs were not noted among the adult subpopulations.

Gender

Information regarding gender was available in 94.4% in the case reports (65,193). There were overall more reports received from females (44,351/65,193) than males (20,842/65,193), 68 % and 31.9 % respectively. With regard to reported event terms, GERD, diarrhea, malaise, dyspepsia, abdominal pain, nausea and vomiting were among the most commonly reported event terms for both men and women.

Medical Officer Comment: Of note the percentage of case reports of osteoporosis was similar between females and males in the global database. One would expect a higher percentage of cases in the female subgroup due to the fact that osteoporosis is more prevalent in women.

Race

Overall, only 20.2% of the case reports contained information with regard to race thus making it difficult to draw any firm conclusions of AE pattern. Adverse events were similarly distributed across the different groups of ethnic origin, with gastrointestinal terms being the most commonly reported, together with malaise, headache and pain.

8.1.6 Dose and Time to Onset

The information regarding dose and time to onset was available in a limited number of the case reports. Information regarding dose was available in 5.3% of the global reports. There were no relevant differences in AE patterns between dose groups (defined as 20 mg, 40 mg and other/unknown). The most commonly occurring symptoms were gastrointestinal such as diarrhea, nausea, abdominal pain, vomiting and dyspepsia, together with other terms also known to be associated with esomeprazole such as headache, rash, pruritus and dizziness. No dose response pattern was identified from the available data which is concordant with the data on the Nexium Rx label.

With respect to time to onset, information was available in 15.2% of the global reports. The majority of cases were non-medically confirmed consumer reports. Time to onset categories were defined as 0-14 days, 15-120 days, \geq 120 days, and Unknown. The most commonly occurring symptoms in all time to onset categories were gastrointestinal (diarrhea, nausea, abdominal pain and flatulence) together with other terms previously known to be AEs for esomeprazole such as headache, dizziness, rash and pruritus.

8.1.7 Other Adverse Events of Interest

Cardiovascular Disorders

Medical Officer Comment: It is noteworthy that the cardiac adverse events are frequently associated with fatal and non-fatal SAEs not only in the post-marketing database but also in other safety databases. There may be some plausible explanation as for such association. One is the use of PPIs by patients with underlying cardiovascular conditions that concomitantly have GERD or simply dyspepsia. The other plausible explanation is that patients may mistakenly attribute epigastric discomfort to gastrointestinal cause where in fact the symptoms are due to cardiac etiology. The signs and symptoms of dyspepsia and GERD overlap significantly.

In 2007, the Division of Drug Risk Evaluation-OSE reviewed a submission from AZ containing two trial reports which suggested an increased frequency of serious cardiac events in patients treated with omeprazole and esomeprazole. The objective of the trials was to determine the long-term efficacy of medical or surgical treatment of severe GERD. OSE determined that because of faulty randomization in one of the trials and insufficient follow-up of patients in the other trial, the association between cardiac events and PPI use was inconclusive based on these trials (OSE RCM# 2007-1315.)

A review of a sample of narratives proved it was not possible to make an association between the use of esomeprazole and cardiac events based on the reports. The quality of the reports was suboptimal, and the patients in general had predisposing factors for serious cardiac events such as previous history of cardiac disease or conditions that predispose to cardiac disease. In order to draw any conclusions regarding such association perhaps an adequately designed epidemiological study could serve to answer this question.

Stevens Johnsons Syndrome

Medical Officer Comment: Although this adverse event was not reported frequently to the Sponsor's database, it was one of the most frequently reported SAEs in the WHO Vigibase. One difference noted about the WHO database is that the majority of the reports come from physicians, thus reporting bias is possible because physicians may be more inclined to report such a serious AE. This reviewer assessed a sample of the narratives of cases of Stevens Johnson syndrome, toxic epidermal necrolysis (TEN) and Lyell syndrome. None of the cases occurred in the pediatric population. All the case reports were confounded by multidrug use and in none of the cases reviewed esomeprazole was the only drug use. Therefore, an association of esomeprazole and any of these serious drug eruptions cannot be made with the available data. Stevens Johnson syndrome and TEN are listed on the Nexium Rx label under section 6.2

Postmarketing experience. The reactions listed in section 6.2 are preceded by the qualifying statement, "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."

Osteoporosis

Medical Officer Comment: Osteoporosis was reported with a frequency of 1.0 and 1.2 % in the AZ database for global and US reports. An increase in reports was noted after 2007 subsequently to published articles regarding osteoporosis and fractures in 2006. In 2011, FDA issued a DSC alerting the public about the increased risk of fractures associated with use of PPIs at high doses and/or for more than one year. The exact mechanisms for an increased risk of fractures with proton pump inhibitor use are not known. Epidemiologic studies reviewed by FDA at that time found no consistent association between chronic proton pump inhibitor use and bone mineral density.

In summary, the available data, including findings from several epidemiological studies, suggest a possible increased risk of fractures of the hip, wrist, and spine in patients using proton pump inhibitors. The data suggest that the increased risk may be dependent upon dose, duration of use, or both. At the present time, there is uncertainty about the magnitude of this risk. In light of this uncertainty, when prescribing proton pump inhibitors, healthcare professionals should consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition.

Of note is that the SOC "Musculoskeletal disorders" occurred more in the category ≥ 120 days (9.2%) compared with the 15-120 days category (4.5%) and in the category 0-14 days (4.8%), under which the PT Fracture would be reported. This information supports the notion that the effects on bone are associated with long-term treatment.

8.2 FDA DRUG SAFETY DATABASE -ADVERSE EVENTS REPORTING SYSTEM

The summary of the safety data from FDA's AERS includes cases reported to FDA up to June 30, 2012. The AERS database used is the FDA public release that is cleansed and de-duplicated. The data contain case reports where esomeprazole was recorded as a suspect or interacting agent. The AE terms were presented by PT according to the MedDRA version 15.1.

A total of 27,263 case reports were identified with 86,698 associated AE terms. Of the 27,263 cases, 60.4% were non-serious cases; 36.6% were non-fatal serious case reports and 3.0% of the case reports included fatal outcome. The case reports

originated mostly from consumers, 66% of the case reports, whereas 14% were from medically confirmed reporters. For the remaining case reports, a few were received from lawyers; the majority of the other reports did not provide the reporter's occupation. Table 12 below shows a gradual increase in reports since its launch and the distribution of the cases by seriousness.

Table 12. AERS Number of Case Reports Received by FDA by Year and Seriousness

| Initial FDA year | Not serious | | Non-fatal serious | | Fatal serious | | All cases | |
|----------------------------|--------------|--------------|-------------------|--------------|---------------|--------------|--------------|--------------|
| | N | % | N | % | N | % | N | % |
| 2001 | 10 | 0.1 | 710 | 7.1 | 11 | 1.3 | 731 | 2.7 |
| 2002 | 9 | 0.1 | 226 | 2.3 | 12 | 1.5 | 247 | 0.9 |
| 2003 | 7 | 0.0 | 218 | 2.2 | 10 | 1.2 | 235 | 0.9 |
| 2004 | 6 | 0.0 | 273 | 2.7 | 16 | 2.0 | 295 | 1.1 |
| 2005 | 10 | 0.1 | 312 | 3.1 | 23 | 2.8 | 345 | 1.3 |
| 2006 | 17 | 0.1 | 311 | 3.1 | 35 | 4.3 | 363 | 1.3 |
| 2007 | 779 | 4.7 | 460 | 4.6 | 35 | 4.3 | 1274 | 4.7 |
| 2008 | 863 | 5.2 | 558 | 5.6 | 95 | 11.6 | 1516 | 5.6 |
| 2009 | 1069 | 6.5 | 909 | 9.1 | 94 | 11.5 | 2072 | 7.6 |
| 2010 | 1516 | 9.2 | 870 | 8.7 | 76 | 9.3 | 2462 | 9.0 |
| 2011 | 4101 | 24.9 | 3323 | 33.3 | 275 | 33.6 | 7699 | 28.2 |
| 2012 | 8085 | 49.1 | 1803 | 18.1 | 136 | 16.6 | 10024 | 36.8 |
| Total cases (col %) | 16472 | 100.0 | 9973 | 100.0 | 818 | 100.0 | 27263 | 100.0 |
| Total cases (row %) | 16472 | 60.4 | 9973 | 36.6 | 818 | 3.0 | 27263 | 100.0 |

(Source: ISS. Appendix 3, Table 2, p. 63)

8.2.1 Deaths

There were 818 (3.0%) reports of deaths with 2,383 associated AE terms which were distributed across a broad range of SOCs. The five SOCs with the highest reports were:

- General Disorders and Administration Site Conditions (19.5%)
- Cardiac Disorders (8.8%)
- Gastrointestinal Disorders (6.9%)
- Respiratory, Thoracic and Mediastinal Disorders (6.6%)
- Investigations (5.7%)

The most frequently reported PT among the death reports were: death (11.5%), completed suicide (2.2%), myocardial infarction (1.8%), TEN (1.3%), and cardiac arrest (1.3%). Table 13 below shows the PTs associated with cases with fatal outcome distributed by age.

Table 13. AERS PT and age group for fatal cases (cut-off 0.5%)

| SOC | MedDRA Preferred Term | <12 | | 12-17 | | 18-65 | | >65 | | No age data | | All ages | |
|-------|---------------------------------------|-----|-----|-------|-----|-------|-----|-----|-----|-------------|------|----------|------|
| | | N | % | N | % | N | % | N | % | N | % | N | % |
| Genrl | Death | 1 | 3.1 | 0 | 0.0 | 89 | 8.8 | 89 | 8.7 | 96 | 30.1 | 275 | 11.5 |
| Psych | Completed suicide | 0 | 0.0 | 0 | 0.0 | 44 | 4.4 | 4 | 0.4 | 4 | 1.3 | 52 | 2.2 |
| Card | Myocardial infarction | 0 | 0.0 | 0 | 0.0 | 22 | 2.2 | 15 | 1.5 | 7 | 2.2 | 44 | 1.8 |
| Skin | Toxic epidermal necrolysis | 0 | 0.0 | 0 | 0.0 | 13 | 1.3 | 15 | 1.5 | 3 | 0.9 | 31 | 1.3 |
| Card | Cardiac arrest | 1 | 3.1 | 0 | 0.0 | 21 | 2.1 | 6 | 0.6 | 2 | 0.6 | 30 | 1.3 |
| Blood | Thrombocytopenia | 0 | 0.0 | 0 | 0.0 | 13 | 1.3 | 11 | 1.1 | 1 | 0.3 | 25 | 1.0 |
| Renal | Renal failure | 0 | 0.0 | 0 | 0.0 | 8 | 0.8 | 12 | 1.2 | 4 | 1.3 | 24 | 1.0 |
| Infec | Pneumonia | 0 | 0.0 | 0 | 0.0 | 4 | 0.4 | 16 | 1.6 | 1 | 0.3 | 21 | 0.9 |
| Card | Cardiac disorder | 0 | 0.0 | 0 | 0.0 | 4 | 0.4 | 13 | 1.3 | 2 | 0.6 | 19 | 0.8 |
| Genrl | General physical health deterioration | 1 | 3.1 | 0 | 0.0 | 8 | 0.8 | 9 | 0.9 | 1 | 0.3 | 19 | 0.8 |
| Infec | Sepsis | 0 | 0.0 | 0 | 0.0 | 10 | 1.0 | 8 | 0.8 | 1 | 0.3 | 19 | 0.8 |
| Neopl | Neoplasm malignant | 0 | 0.0 | 0 | 0.0 | 9 | 0.9 | 7 | 0.7 | 3 | 0.9 | 19 | 0.8 |
| Card | Cardiac failure congestive | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 9 | 0.9 | 4 | 1.3 | 18 | 0.8 |
| Neopl | Lung neoplasm malignant | 0 | 0.0 | 0 | 0.0 | 6 | 0.6 | 9 | 0.9 | 3 | 0.9 | 18 | 0.8 |
| Renal | Renal failure acute | 0 | 0.0 | 0 | 0.0 | 4 | 0.4 | 12 | 1.2 | 2 | 0.6 | 18 | 0.8 |
| Resp | Chronic obstructive pulmonary disease | 0 | 0.0 | 0 | 0.0 | 3 | 0.3 | 14 | 1.4 | 1 | 0.3 | 18 | 0.8 |
| Card | Cardio-respiratory arrest | 0 | 0.0 | 0 | 0.0 | 9 | 0.9 | 5 | 0.5 | 3 | 0.9 | 17 | 0.7 |
| Genrl | Pyrexia | 0 | 0.0 | 0 | 0.0 | 6 | 0.6 | 9 | 0.9 | 2 | 0.6 | 17 | 0.7 |
| Hepat | Hepatic failure | 0 | 0.0 | 0 | 0.0 | 9 | 0.9 | 6 | 0.6 | 2 | 0.6 | 17 | 0.7 |
| Inj&P | Toxicity to various agents | 0 | 0.0 | 0 | 0.0 | 14 | 1.4 | 2 | 0.2 | 1 | 0.3 | 17 | 0.7 |
| Card | Cardiac failure | 1 | 3.1 | 0 | 0.0 | 6 | 0.6 | 9 | 0.9 | 0 | 0.0 | 16 | 0.7 |
| Skin | Stevens-Johnson syndrome | 0 | 0.0 | 0 | 0.0 | 10 | 1.0 | 5 | 0.5 | 1 | 0.3 | 16 | 0.7 |
| Gastr | Vomiting | 0 | 0.0 | 0 | 0.0 | 7 | 0.7 | 5 | 0.5 | 3 | 0.9 | 15 | 0.6 |
| Infec | Septic shock | 0 | 0.0 | 0 | 0.0 | 6 | 0.6 | 8 | 0.8 | 1 | 0.3 | 15 | 0.6 |
| Resp | Respiratory failure | 1 | 3.1 | 0 | 0.0 | 3 | 0.3 | 8 | 0.8 | 3 | 0.9 | 15 | 0.6 |
| Psych | Confusional state | 0 | 0.0 | 0 | 0.0 | 4 | 0.4 | 6 | 0.6 | 4 | 1.3 | 14 | 0.6 |
| Resp | Dyspnoea | 0 | 0.0 | 0 | 0.0 | 7 | 0.7 | 5 | 0.5 | 2 | 0.6 | 14 | 0.6 |
| Gastr | Nausea | 0 | 0.0 | 0 | 0.0 | 6 | 0.6 | 5 | 0.5 | 2 | 0.6 | 13 | 0.5 |
| Blood | Anaemia | 0 | 0.0 | 0 | 0.0 | 3 | 0.3 | 7 | 0.7 | 2 | 0.6 | 12 | 0.5 |
| Blood | Neutropenia | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 6 | 0.6 | 1 | 0.3 | 12 | 0.5 |
| Genrl | Drug interaction | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 3 | 0.3 | 4 | 1.3 | 12 | 0.5 |
| Genrl | Malaise | 0 | 0.0 | 0 | 0.0 | 6 | 0.6 | 6 | 0.6 | 0 | 0.0 | 12 | 0.5 |
| Genrl | Sudden death | 0 | 0.0 | 0 | 0.0 | 10 | 1.0 | 1 | 0.1 | 1 | 0.3 | 12 | 0.5 |
| Nerv | Cerebrovascular accident | 0 | 0.0 | 0 | 0.0 | 3 | 0.3 | 6 | 0.6 | 3 | 0.9 | 12 | 0.5 |
| Nerv | Coma | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 5 | 0.5 | 2 | 0.6 | 12 | 0.5 |
| Vasc | Hypertension | 0 | 0.0 | 0 | 0.0 | 3 | 0.3 | 7 | 0.7 | 2 | 0.6 | 12 | 0.5 |
| Genrl | Condition aggravated | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 6 | 0.6 | 0 | 0.0 | 11 | 0.5 |
| Genrl | Multi-organ failure | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 6 | 0.6 | 0 | 0.0 | 11 | 0.5 |
| Resp | Respiratory arrest | 0 | 0.0 | 0 | 0.0 | 7 | 0.7 | 3 | 0.3 | 1 | 0.3 | 11 | 0.5 |
| Skin | Rash macular | 0 | 0.0 | 0 | 0.0 | 6 | 0.6 | 5 | 0.5 | 0 | 0.0 | 11 | 0.5 |

[Source: ISS, Table 25, p. 68 (109)]

Medical Officer Comment: The SOCs associated with the fatal outcomes for the most part resemble the ones encountered in the Sponsor's post-market database. I note however that the most frequently reported PT terms in the FDA AERS included "Completed suicide" and "Toxic epidermal necrolysis" which were not among the most reported fatal SAEs in the Sponsor's database. See section 8.1.7 for brief discussion on the adverse event "Toxic epidermal necrolysis".

8.2.2 Serious Adverse Events- Non-Fatal

With regard to non-fatal serious AEs, there were 9,973 (36.6%) reports with 38,054 associated AE terms. Five SOCs accounted for 52% of all the reported terms:

- Gastrointestinal Disorders (17.0%)
- General Disorders and Administration Site Conditions (12.0%)
- Injury, Poisoning and Procedural Complications (9.1%)
- Nervous Systems Disorders (8.4%)
- Musculoskeletal and Connective Tissue Disorders (5.4%)

Of the 38,054 PTs, the most frequently reported were: drug dose omission (2.7%), GERD (2.1%), malaise (1.8%), drug ineffective (1.6%), vomiting (1.1%), dyspepsia (1.1%), cerebrovascular accident (1.1%), myocardial infarction (1.1%) and nausea (1.1%), fall (1%), diarrhea (1%).

The pattern of the reported events is similar to that encountered in the Sponsor-maintained postmarketing database and reflects adverse events listed in the Rx label.

8.2.3 Common Adverse Events

Five SOCs accounted for 63% of all the reported AE terms:

- Gastrointestinal Disorders (22.7%)
- Injury, Poisoning and Procedural Complications (14.5%)
- General Disorders and Administration Site Conditions (14.4 %)
- Nervous System Disorders (6.3%)
- □Musculoskeletal and Connective Tissue Disorders (6.1%)

Of the 86,698 AE terms, the most commonly reported PTs were:

- drug dose omission (7.6%)
- GERD (4.1%)
- malaise (2.7%)
- dyspepsia (2.4%)
- drug ineffective (2.4%)
- osteoporosis (1.8%)
- multiple fractures (1.5%)
- vomiting (1.4%)

- abdominal pain upper (1.4%)
- pain (1.2%)
- abdominal discomfort (1.1%)
- nausea (1.1%)

See Sponsor's table of AERS AEs by PT and seriousness in Appendix 9.4, Table 31

8.2.4 Adverse events by age, gender and ethnicity

Of all fatal case reports (818), 78.7%% (644/ 818) contained information with regard to age. Of the 818 fatal cases, 8 were in the pediatric population (< 18 years of age), mostly in children < 12 years of age and the SOCs most frequently associated with these pediatric fatal SAEs were: General Disorders and Administration Site Conditions, Respiratory, Thoracic and Mediastinal Disorders, Gastrointestinal Disorders, Cardiac Disorders, Investigations. The proportion of fatal case reports was similar between adults 18 to 65 years of age (322/644, 50%) and > 65 years of age (314/644, 48.75%)

Table 14. AERS SOC and age group for fatal cases

| SOC | <12 | | 12-17 | | 18-65 | | >65 | | No age data | | All ages | |
|----------------------------|-----------|--------------|----------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Genrl | 5 | 15.6 | 0 | 0.0 | 182 | 18.1 | 166 | 16.2 | 112 | 35.1 | 465 | 19.5 |
| Card | 3 | 9.4 | 0 | 0.0 | 96 | 9.5 | 82 | 8.0 | 28 | 8.8 | 209 | 8.8 |
| Gastr | 4 | 12.5 | 0 | 0.0 | 54 | 5.4 | 89 | 8.7 | 17 | 5.3 | 164 | 6.9 |
| Resp | 5 | 15.6 | 0 | 0.0 | 52 | 5.2 | 79 | 7.7 | 21 | 6.6 | 157 | 6.6 |
| Inv | 3 | 9.4 | 0 | 0.0 | 64 | 6.4 | 58 | 5.7 | 11 | 3.4 | 136 | 5.7 |
| Nerv | 0 | 0.0 | 0 | 0.0 | 63 | 6.3 | 51 | 5.0 | 19 | 6.0 | 133 | 5.6 |
| Infec | 2 | 6.3 | 0 | 0.0 | 46 | 4.6 | 74 | 7.2 | 7 | 2.2 | 129 | 5.4 |
| Neopl | 0 | 0.0 | 0 | 0.0 | 49 | 4.9 | 56 | 5.5 | 22 | 6.9 | 127 | 5.3 |
| Inj&P | 1 | 3.1 | 0 | 0.0 | 63 | 6.3 | 40 | 3.9 | 16 | 5.0 | 120 | 5.0 |
| Blood | 1 | 3.1 | 1 | 33.3 | 52 | 5.2 | 51 | 5.0 | 8 | 2.5 | 113 | 4.7 |
| Skin | 0 | 0.0 | 1 | 33.3 | 45 | 4.5 | 58 | 5.7 | 6 | 1.9 | 110 | 4.6 |
| Psych | 1 | 3.1 | 0 | 0.0 | 73 | 7.3 | 22 | 2.2 | 9 | 2.8 | 105 | 4.4 |
| Hepat | 0 | 0.0 | 1 | 33.3 | 49 | 4.9 | 38 | 3.7 | 11 | 3.4 | 99 | 4.2 |
| Vasc | 2 | 6.3 | 0 | 0.0 | 19 | 1.9 | 43 | 4.2 | 10 | 3.1 | 74 | 3.1 |
| Renal | 0 | 0.0 | 0 | 0.0 | 25 | 2.5 | 36 | 3.5 | 9 | 2.8 | 70 | 2.9 |
| Metab | 0 | 0.0 | 0 | 0.0 | 23 | 2.3 | 36 | 3.5 | 7 | 2.2 | 66 | 2.8 |
| Musc | 0 | 0.0 | 0 | 0.0 | 15 | 1.5 | 14 | 1.4 | 2 | 0.6 | 31 | 1.3 |
| Surg | 2 | 6.3 | 0 | 0.0 | 15 | 1.5 | 8 | 0.8 | 1 | 0.3 | 26 | 1.1 |
| Eye | 0 | 0.0 | 0 | 0.0 | 9 | 0.9 | 5 | 0.5 | 1 | 0.3 | 15 | 0.6 |
| Immun | 0 | 0.0 | 0 | 0.0 | 4 | 0.4 | 6 | 0.6 | 0 | 0.0 | 10 | 0.4 |
| SocCi | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 2 | 0.2 | 0 | 0.0 | 7 | 0.3 |
| Repro | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 5 | 0.5 | 0 | 0.0 | 5 | 0.2 |
| Cong | 2 | 6.3 | 0 | 0.0 | 2 | 0.2 | 0 | 0.0 | 0 | 0.0 | 4 | 0.2 |
| Endo | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 0.4 | 0 | 0.0 | 4 | 0.2 |
| Preg | 1 | 3.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 0.6 | 3 | 0.1 |
| Ear | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 1 | 0.0 |
| Total Terms (col %) | 32 | 100.0 | 3 | 100.0 | 1006 | 100.0 | 1023 | 100.0 | 319 | 100.0 | 2383 | 100.0 |
| Total Terms (row %) | 32 | 1.3 | 3 | 0.1 | 1006 | 42.2 | 1023 | 42.9 | 319 | 13.4 | 2383 | 100.0 |
| Total Cases (row %) | 7 | 0.9 | 1 | 0.1 | 322 | 39.4 | 314 | 38.4 | 174 | 21.3 | 818 | 100.0 |

(Source: ISS, Appendix 3, Table 14, p. 278)

As for gender, there were more reports received for females (64.7%) than males (28.3%). For both groups, the event terms were similar between men and women with

GERD, malaise, dyspepsia, vomiting, abdominal pain, pain, abdominal discomfort, nausea and diarrhea being among the most commonly reported. No pattern of AEs was identified for either gender.

The information regarding dose and time to onset was available in a limited amount of the case reports. Dose information was available for 7.4% of the reports. There were no major differences between the dose groups (defined as 20 mg, 40 mg and other/unknown). The most common PTs were nausea, diarrhea, thrombocytopenia, pyrexia, hyponatremia, neutropenia, condition aggravated and pruritus. No dose response pattern was identified from the available data.

Information regarding time to onset was available in 15.9% of the reports. The time to onset categories were defined as 0-14 days, 15-120 days, ≥ 120 days and Unknown. The most commonly occurring symptoms in all categories were headache, dizziness, and gastrointestinal events such as abdominal pain, diarrhea and nausea. The AE profile was unaffected by treatment duration.

Medical Officer Comment: There were no new or unexpected safety findings from the reports from the FDA/AERS database except for cases of "Toxic epidermal necrolysis" which was the third most common PT associated with fatal cases. Most of the commonly reported AE terms, either reflected the underlying disease or represented terms which are listed events for esomeprazole in the Nexium Rx label. As for case reports with fatal outcome the AE terms were distributed across a broad range of SOCs. When stratified by age, no consistent age-group dependent pattern was identified from the reports. With respect to gender, there were no apparent differences in the overall distribution of AE between males and females. There were no relevant differences in AE patterns between dose groups and the reported event terms were similar between all "time to onset" categories.

8.3 World Health Organization International Drug Monitoring Program: WHO Vigibase Drug Safety Database

The Sponsor obtained case reports of AEs associated with esomeprazole as a suspect or interacting medication from the WHO drug safety database. The AE terms are presented by PT according to the MedDRA version 15.1. The case reports were segregated by country of origin; those originating outside the US (exUS) were the focus of the Sponsor's review. The first case report identified for esomeprazole in the database was dated November 21, 2000, and the most recent was October 11, 2012. AEs were analyzed by age and gender, as well as by dose and time to onset.

There were a total of 20,407 cases involving 58,723 MedDRA AE terms reported for esomeprazole in the WHO/Vigibase. Of these cases, 75% were reported from US and 25% were exUS cases. Of the 5,117 exUS case reports, 29.1% were categorized as non-serious cases, 22.3% were non-fatal cases, 1.4% were death cases and 47.2%

cases had no outcome data. In contrast to the information captured in the AstraZeneca’s post-marketing database and AERS with regard to reporting sources, a relatively large part of the case reports originated from medically confirmed sources, approximately 75%. Table 15 below shows the SOCs associated with AE reports by seriousness of the foreign cases.

Table 15. WHO Vigibase AEs by SOC and seriousness –exUS (cut-off 1%)

| SOC | Not serious | | Non-fatal serious | | Fatal serious | | No outcome data | | All exUS cases | |
|----------------------------|-------------|--------------|-------------------|--------------|---------------|--------------|-----------------|--------------|----------------|--------------|
| | N | % | N | % | N | % | N | % | N | % |
| Gastr | 596 | 21.0 | 298 | 10.9 | 34 | 11.3 | 950 | 19.3 | 1878 | 17.4 |
| Skin | 571 | 20.2 | 388 | 14.1 | 83 | 27.5 | 815 | 16.5 | 1857 | 17.2 |
| Genrl | 353 | 12.5 | 292 | 10.6 | 38 | 12.6 | 788 | 16.0 | 1471 | 13.6 |
| Nerv | 326 | 11.5 | 232 | 8.5 | 4 | 1.3 | 554 | 11.2 | 1116 | 10.3 |
| Psych | 158 | 5.6 | 172 | 6.3 | 6 | 2.0 | 261 | 5.3 | 597 | 5.5 |
| Musc | 163 | 5.8 | 127 | 4.6 | 6 | 2.0 | 228 | 4.6 | 524 | 4.9 |
| Inv | 95 | 3.4 | 195 | 7.1 | 8 | 2.6 | 220 | 4.5 | 518 | 4.8 |
| Blood | 63 | 2.2 | 217 | 7.9 | 7 | 2.3 | 113 | 2.3 | 400 | 3.7 |
| Resp | 108 | 3.8 | 95 | 3.5 | 10 | 3.3 | 184 | 3.7 | 397 | 3.7 |
| Hepat | 27 | 1.0 | 108 | 3.9 | 16 | 5.3 | 129 | 2.6 | 280 | 2.6 |
| Metab | 55 | 1.9 | 122 | 4.4 | 8 | 2.6 | 84 | 1.7 | 269 | 2.5 |
| Eye | 84 | 3.0 | 55 | 2.0 | 5 | 1.7 | 95 | 1.9 | 239 | 2.2 |
| Renal | 27 | 1.0 | 55 | 2.0 | 11 | 3.6 | 120 | 2.4 | 213 | 2.0 |
| Card | 31 | 1.1 | 50 | 1.8 | 13 | 4.3 | 69 | 1.4 | 163 | 1.5 |
| Vasc | 34 | 1.2 | 49 | 1.8 | 4 | 1.3 | 65 | 1.3 | 152 | 1.4 |
| Infec | 16 | 0.6 | 66 | 2.4 | 28 | 9.3 | 37 | 0.8 | 147 | 1.4 |
| Repro | 68 | 2.4 | 17 | 0.6 | 4 | 1.3 | 56 | 1.1 | 145 | 1.3 |
| Inj&P | 12 | 0.4 | 87 | 3.2 | 4 | 1.3 | 29 | 0.6 | 132 | 1.2 |
| Immun | 6 | 0.2 | 41 | 1.5 | 1 | 0.3 | 57 | 1.2 | 105 | 1.0 |
| Ear | 31 | 1.1 | 16 | 0.6 | 0 | 0.0 | 35 | 0.7 | 82 | 0.8 |
| Surg | 4 | 0.1 | 15 | 0.5 | 6 | 2.0 | 6 | 0.1 | 31 | 0.3 |
| Neopl | 0 | 0.0 | 14 | 0.5 | 4 | 1.3 | 12 | 0.2 | 30 | 0.3 |
| Preg | 0 | 0.0 | 12 | 0.4 | 0 | 0.0 | 9 | 0.2 | 21 | 0.2 |
| Endo | 3 | 0.1 | 9 | 0.3 | 1 | 0.3 | 3 | 0.1 | 16 | 0.1 |
| Cong | 0 | 0.0 | 7 | 0.3 | 1 | 0.3 | 4 | 0.1 | 12 | 0.1 |
| SocCi | 2 | 0.1 | 4 | 0.1 | 0 | 0.0 | 2 | 0.0 | 8 | 0.1 |
| Total terms (col %) | 2833 | 100.0 | 2743 | 100.0 | 302 | 100.0 | 4925 | 100.0 | 10803 | 100.0 |
| Total terms (row %) | 2833 | 26.2 | 2743 | 25.4 | 302 | 2.8 | 4925 | 45.6 | 10803 | 100.0 |
| Total cases (row %) | 1491 | 29.1 | 1139 | 22.3 | 74 | 1.4 | 2413 | 47.2 | 5117 | 100.0 |

(Source: ISS, Appendix 4, Table 9, p. 76)

Table 16 below shows the most frequently reported ex-US cases AEs by PT and seriousness.

Table 16. WHO Vigibase AEs by PT and seriousness- exUS (cut-off 1%)

| SOC | MedDRA Preferred Term | Not serious | | Non-fatal serious | | Fatal serious | | No outcome data | | All exUS cases | |
|-------|----------------------------|-------------|--------------|-------------------|--------------|---------------|--------------|-----------------|--------------|----------------|--------------|
| | | N | % | N | % | N | % | N | % | N | % |
| Genrl | Drug ineffective | 85 | 3.0 | 21 | 0.8 | 1 | 0.3 | 304 | 6.2 | 411 | 3.8 |
| Skin | Pruritus | 113 | 4.0 | 46 | 1.7 | 6 | 2.0 | 156 | 3.2 | 321 | 3.0 |
| Skin | Rash | 74 | 2.6 | 45 | 1.6 | 3 | 1.0 | 165 | 3.4 | 287 | 2.7 |
| Gastr | Nausea | 85 | 3.0 | 46 | 1.7 | 2 | 0.7 | 138 | 2.8 | 271 | 2.5 |
| Nerv | Headache | 92 | 3.2 | 26 | 0.9 | 0 | 0.0 | 146 | 3.0 | 264 | 2.4 |
| Skin | Urticaria | 90 | 3.2 | 45 | 1.6 | 0 | 0.0 | 114 | 2.3 | 249 | 2.3 |
| Gastr | Diarrhoea | 81 | 2.9 | 25 | 0.9 | 1 | 0.3 | 112 | 2.3 | 219 | 2.0 |
| Nerv | Dizziness | 69 | 2.4 | 24 | 0.9 | 0 | 0.0 | 111 | 2.3 | 204 | 1.9 |
| Gastr | Abdominal pain | 39 | 1.4 | 28 | 1.0 | 0 | 0.0 | 129 | 2.6 | 196 | 1.8 |
| Resp | Dyspnoea | 36 | 1.3 | 33 | 1.2 | 5 | 1.7 | 63 | 1.3 | 137 | 1.3 |
| Musc | Myalgia | 52 | 1.8 | 15 | 0.5 | 1 | 0.3 | 64 | 1.3 | 132 | 1.2 |
| Gastr | Vomiting | 40 | 1.4 | 20 | 0.7 | 0 | 0.0 | 62 | 1.3 | 122 | 1.1 |
| Genrl | Fatigue | 27 | 1.0 | 31 | 1.1 | 1 | 0.3 | 47 | 1.0 | 106 | 1.0 |
| Musc | Arthralgia | 39 | 1.4 | 12 | 0.4 | 1 | 0.3 | 54 | 1.1 | 106 | 1.0 |
| Blood | Thrombocytopenia | 21 | 0.7 | 58 | 2.1 | 0 | 0.0 | 24 | 0.5 | 103 | 1.0 |
| | Total terms (col %) | 2833 | 100.0 | 2743 | 100.0 | 302 | 100.0 | 4925 | 100.0 | 10803 | 100.0 |
| | Total terms (row %) | 2833 | 26.2 | 2743 | 25.4 | 302 | 2.8 | 4925 | 45.6 | 10803 | 100.0 |
| | Total cases (row %) | 1491 | 29.1 | 1139 | 22.3 | 74 | 1.4 | 2413 | 47.2 | 5117 | 100.0 |

The data are sorted by decreasing frequency in the All exUS cases column.
 AEs with a frequency of at least 1.0% in the All exUS cases column are included in this table.
 The totals are those for the entire dataset, not just the data in the table.

(Source: ISS, Appendix 4, Table 10, p. 77)

8.3.1 Deaths

There were 74 fatal ex-US case reports, i.e., 1.4% (74/5,117) of all ex-US case reports, with 302 associated AE terms. The three SOCs associated with the most frequently reported terms were:

- Skin and subcutaneous tissue disorders 27.5%,
- General disorders and administration site conditions 12.6%,
- Gastrointestinal disorders 11.3%

The most frequently reported AE terms were:

- TEN (7.6%)
- Stevens-Johnson syndrome (SJS) (4.3%)
- death (3.3%)
- blister (3.3%)
- sepsis (2.6%)
- macule, pruritus, lip erosion and pyrexia (each of them 2.0%)

Table 17 below shows the most frequently reported AEs associated with fatal cases by PT age for foreign reports.

Table 17. WHO Vigibase PT by age for fatal cases- exUS (cut-off 1%)

| SOC | MedDRA Preferred Term | <12 | | 12-17 | | 18-65 | | >65 | | No age data | | All ages | |
|-------|----------------------------|----------|--------------|----------|------------|-----------|--------------|------------|--------------|-------------|--------------|------------|--------------|
| | | N | % | N | % | N | % | N | % | N | % | N | % |
| Skin | Toxic epidermal necrolysis | 0 | 0.0 | 0 | 0.0 | 10 | 11.4 | 13 | 6.4 | 0 | 0.0 | 23 | 7.6 |
| Skin | Stevens-Johnson syndrome | 0 | 0.0 | 0 | 0.0 | 8 | 9.1 | 5 | 2.5 | 0 | 0.0 | 13 | 4.3 |
| Genrl | Death | 0 | 0.0 | 0 | 0.0 | 3 | 3.4 | 6 | 3.0 | 1 | 9.1 | 10 | 3.3 |
| Skin | Blister | 0 | 0.0 | 0 | 0.0 | 4 | 4.5 | 6 | 3.0 | 0 | 0.0 | 10 | 3.3 |
| Infec | Sepsis | 0 | 0.0 | 0 | 0.0 | 3 | 3.4 | 5 | 2.5 | 0 | 0.0 | 8 | 2.6 |
| Skin | Macule | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 5 | 2.5 | 0 | 0.0 | 6 | 2.0 |
| Skin | Pruritus | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 5 | 2.5 | 0 | 0.0 | 6 | 2.0 |
| Gastr | Lip erosion | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 5 | 2.5 | 0 | 0.0 | 6 | 2.0 |
| Genrl | Pyrexia | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 4 | 2.0 | 0 | 0.0 | 6 | 2.0 |
| Resp | Dyspnoea | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 3 | 1.5 | 0 | 0.0 | 5 | 1.7 |
| Skin | Nikolsky's sign | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 4 | 2.0 | 0 | 0.0 | 5 | 1.7 |
| Gastr | Oral mucosa erosion | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 3 | 1.5 | 0 | 0.0 | 5 | 1.7 |
| Renal | Renal failure acute | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 2.0 | 0 | 0.0 | 4 | 1.3 |
| Eye | Ocular hyperaemia | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 2.0 | 0 | 0.0 | 4 | 1.3 |
| Infec | Pneumonia | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.5 | 1 | 9.1 | 4 | 1.3 |
| Repro | Genital erosion | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 2.0 | 0 | 0.0 | 4 | 1.3 |
| Blood | Pancytopenia | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 2 | 1.0 | 0 | 0.0 | 3 | 1.0 |
| Genrl | Drug interaction | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 2 | 1.0 | 0 | 0.0 | 3 | 1.0 |
| Skin | Rash macular | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.5 | 0 | 0.0 | 3 | 1.0 |
| Genrl | Mucosal erosion | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.5 | 0 | 0.0 | 3 | 1.0 |
| Card | Cardiac disorder | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.5 | 0 | 0.0 | 3 | 1.0 |
| Skin | Rash | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 1 | 0.5 | 0 | 0.0 | 3 | 1.0 |
| Genrl | Sudden death | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 1 | 0.5 | 0 | 0.0 | 3 | 1.0 |
| Gastr | Anal erosion | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.5 | 0 | 0.0 | 3 | 1.0 |
| | Total terms (col%) | 1 | 100.0 | 0 | 0.0 | 88 | 100.0 | 202 | 100.0 | 11 | 100.0 | 302 | 100.0 |
| | Total terms (row%) | 1 | 0.3 | 0 | 0.0 | 88 | 29.1 | 202 | 66.9 | 11 | 3.6 | 302 | 100.0 |
| | Total cases (col %) | 1 | 1.4 | 0 | 0.0 | 27 | 36.5 | 43 | 58.1 | 3 | 4.1 | 74 | 100.0 |

The data are sorted by decreasing frequency in the All Fatal cases column.
AEs with a frequency of at least 1.0% in the All Fatal cases column are included in this table.
The totals are those for the entire dataset, not just the data in the table.

Source: ISS, Appendix 4, Table 19, p. 170)

8.3.2 Serious Adverse Events- Non-Fatal

With regard to the 1,139 non-fatal serious reports involving 2,743 AE terms, the following five SOCs were the most frequently associated with these SAE reports:

- Skin and Subcutaneous Tissue Disorders 14.1%
- Gastrointestinal Disorders 10.9%
- General Disorders and Administration Site Conditions 10.6%
- Nervous System Disorders 8.5%
- Blood and Lymphatic System Disorders 7.9%

The most commonly reported PT terms associated with the non-fatal SAEs (ex-US) were:

- thrombocytopenia (2.1%)
- pruritus (1.7%)
- nausea (1.7%)
- hyponatremia (1.7%)

- rash (1.6%)
- urticaria (1.6%)
- agranulocytosis (1.3%)
- dyspnea (1.2%)
- neutropenia (1.2%)
- drug interaction(1.2%)
- fatigue (1.1%)

Medical Officer Comment: It is noteworthy that in this database SAEs involving drug eruptions such as Stevens Johnson syndrome and TEN were encountered more frequently than in the other databases. One plausible explanation is that most of the reports in this database come from physicians who may be more likely to report such serious type of adverse event. More discussion on TEN can be found in section 8.1.7.

8.3.3 Common adverse events

The following five SOCs accounted for 64% of the total AE terms:

- Gastrointestinal Disorders 17.4%
- Skin and Subcutaneous Tissue Disorders 17.2%
- General Disorders and Administration Site Conditions 13.6%
- Nervous System Disorders 10.3%
- Psychiatric Disorders 5.5%

The most frequently reported AE terms for exUS cases were:

- drug ineffective (3.8%)
- pruritus (3.0 %),
- rash (2.7%),
- nausea (2.5%),
- headache (2.4%),
- urticaria (2.3%),
- diarrhea (2.0%),
- dizziness (1.9%),
- abdominal pain (1.8%),
- dyspnea (1.3%),
- myalgia (1.2%)
- vomiting (1.1%)

Table 18 below presents the most frequently reported AE terms in descending order of overall frequency for the foreign (exUS) and US reports.

Table 18. WHO Vigibase common AEs by PT for ex-US and US reports (cut-off 0.5%)

| SOC | MedDRA Preferred Term | exUS | | US | | All cases | |
|-------|--|--------------|--------------|--------------|--------------|--------------|--------------|
| | | N | % | N | % | N | % |
| Inj&P | Drug dose omission | 1 | 0.0 | 3365 | 7.0 | 3366 | 5.7 |
| Gastr | Gastroesophageal reflux disease | 49 | 0.5 | 1758 | 3.7 | 1807 | 3.1 |
| Genrl | Drug ineffective | 411 | 3.8 | 1215 | 2.5 | 1626 | 2.8 |
| Genrl | Malaise | 67 | 0.6 | 1120 | 2.3 | 1187 | 2.0 |
| Gastr | Dyspepsia | 100 | 0.9 | 1053 | 2.2 | 1153 | 2.0 |
| Gastr | Nausea | 271 | 2.5 | 635 | 1.3 | 906 | 1.5 |
| Gastr | Abdominal pain upper | 96 | 0.9 | 726 | 1.5 | 822 | 1.4 |
| Gastr | Vomiting | 122 | 1.1 | 695 | 1.5 | 817 | 1.4 |
| Gastr | Diarrhoea | 219 | 2.0 | 595 | 1.2 | 814 | 1.4 |
| Nerv | Headache | 264 | 2.4 | 490 | 1.0 | 754 | 1.3 |
| Gastr | Abdominal discomfort | 41 | 0.4 | 591 | 1.2 | 632 | 1.1 |
| Genrl | Pain | 44 | 0.4 | 529 | 1.1 | 573 | 1.0 |
| Genrl | Chest pain | 66 | 0.6 | 473 | 1.0 | 539 | 0.9 |
| Gastr | Abdominal pain | 196 | 1.8 | 337 | 0.7 | 533 | 0.9 |
| Nerv | Dizziness | 204 | 1.9 | 315 | 0.7 | 519 | 0.9 |
| Resp | Dyspnoea | 137 | 1.3 | 381 | 0.8 | 518 | 0.9 |
| Skin | Pruritus | 321 | 3.0 | 124 | 0.3 | 445 | 0.8 |
| Skin | Rash | 287 | 2.7 | 143 | 0.3 | 430 | 0.7 |
| Psych | Insomnia | 74 | 0.7 | 324 | 0.7 | 398 | 0.7 |
| Inj&P | Fall | 17 | 0.2 | 377 | 0.8 | 394 | 0.7 |
| Card | Myocardial infarction | 11 | 0.1 | 366 | 0.8 | 377 | 0.6 |
| Genrl | Fatigue | 106 | 1.0 | 254 | 0.5 | 360 | 0.6 |
| Nerv | Cerebrovascular accident | 1 | 0.0 | 351 | 0.7 | 352 | 0.6 |
| Skin | Urticaria | 249 | 2.3 | 73 | 0.2 | 322 | 0.5 |
| Resp | Cough | 41 | 0.4 | 267 | 0.6 | 308 | 0.5 |
| Resp | Throat irritation | 13 | 0.1 | 288 | 0.6 | 301 | 0.5 |
| Gastr | Flatulence | 51 | 0.5 | 238 | 0.5 | 289 | 0.5 |
| Gastr | Dry mouth | 92 | 0.9 | 190 | 0.4 | 282 | 0.5 |
| Inv | Weight decreased | 29 | 0.3 | 245 | 0.5 | 274 | 0.5 |
| Neopl | Neoplasm malignant | 1 | 0.0 | 271 | 0.6 | 272 | 0.5 |
| Gastr | Dysphagia | 27 | 0.2 | 244 | 0.5 | 271 | 0.5 |
| Vasc | Hypertension | 26 | 0.2 | 242 | 0.5 | 268 | 0.5 |
| | Total Terms^a (col %) | 10803 | 100.0 | 47920 | 100.0 | 58723 | 100.0 |

[Source: ISS, Table 28, p. 74 (109)]

Medical Officer Comment: The frequency of each PT seems to vary slightly between the US and ex-US cases but the general pattern of the non-serious case reports does not differ from what has been reported in the Sponsor's post-marketing database and AERS, and supports the findings of safety for esomeprazole.

8.3.4 Adverse events by age, gender and ethnic origin

There were no relevant differences in AE patterns between different age groups. The most commonly occurring AE terms were gastrointestinal (nausea, diarrhea, abdominal pain) together with other terms known to be associated with esomeprazole such as pruritus, rash, headache, urticaria and dizziness. Overall, there were no trends or indicating differences or clustering of events due to any age-related factors.

Age data were available in 86.7% of the reported cases. The fatal terms most commonly reported, Stevens Johnson syndrome and toxic epidermal necrolysis, appeared more frequently in the age group 18-65 years. For the remaining fatal terms there were no apparent differences between the respective age categories, see Table 19 below. There was only one case report with fatal outcome among patients <18 years of age.

Table 19. WHO Vigibase Number of case reports by seriousness and age group (exUS)

| Age group | Not serious | | Non-fatal serious | | Fatal serious | | No outcome data | | Total exUS cases | |
|----------------------------|-------------|--------------|-------------------|--------------|---------------|--------------|-----------------|--------------|------------------|--------------|
| | N | % | N | % | N | % | N | % | N | % |
| <12 | 34 | 2.3 | 15 | 1.3 | 1 | 1.4 | 17 | 0.7 | 67 | 1.3 |
| 12-17 | 12 | 0.8 | 3 | 0.3 | 0 | 0.0 | 9 | 0.4 | 24 | 0.5 |
| 18-65 | 813 | 54.5 | 578 | 50.7 | 27 | 36.5 | 1368 | 56.7 | 2786 | 54.4 |
| >65 | 432 | 29.0 | 434 | 38.1 | 43 | 58.1 | 651 | 27.0 | 1560 | 30.5 |
| No age data | 200 | 13.4 | 109 | 9.6 | 3 | 4.1 | 368 | 15.3 | 680 | 13.3 |
| Total cases (col %) | 1491 | 100.0 | 1139 | 100.0 | 74 | 100.0 | 2413 | 100.0 | 5117 | 100.0 |
| Total cases (row %) | 1491 | 29.1 | 1139 | 22.3 | 74 | 1.4 | 2413 | 47.2 | 5117 | 100.0 |

Source: ISS, Appendix 4, Table 8, p. 76)

As for gender, there were more reports received for females (56.6% than males (40.2%). The reported terms were similar between both groups with pruritus, rash, nausea, headache, urticaria, diarrhea, dizziness and abdominal pain being the most commonly reported AEs. Information regarding ethnic origin was not available in the datasets derived from the WHO database.

8.3.5 Adverse events by dose and time to onset

The information regarding dose and time to onset was available in a large number of the case reports which might be due to the fact that the majority of cases were medically confirmed reports.

Information regarding dose was available in 65.3% of the reports. There were no relevant differences in AE patterns between dose groups (defined as 20 mg, 40 mg and others/unknown). The most commonly reported AE terms were pruritus, rash, headache, nausea, diarrhea, urticaria, dizziness, and abdominal pain, all representing terms known to be associated with esomeprazole therapy. No dose response pattern was identified from the available data.

Information regarding time to onset was available in 48.5% of the reports. “Time to onset categories” were defined as 0- 14 days, 15-120 days, \geq 120 days, and Unknown. The most commonly occurring AEs in all categories were gastrointestinal (nausea, diarrhea, abdominal pain) together with other terms known to be associated with esomeprazole such as pruritus, headache, rash, urticaria and dizziness. The AE profile was unaffected by treatment duration.

In summary, there were no new or unexpected safety findings following review of the case reports from the WHO database. In general the types of AEs were similar to those previously reported AEs with the use of esomeprazole both during clinical trials and post-marketing use and most of them reflect listed AEs for esomeprazole. Many of the commonly reported AE terms, either reflect the underlying disease or represent terms that are in the Nexium Rx label. The case reports with fatal outcome were distributed across a range of SOCs. No age-group dependent pattern emerged from the reports. The majority of the serious and fatal reports were in the 18-65 and > 65 age ranges. There were no apparent differences in the overall distribution of AE between genders, or between dose groups, or in relation to the time to onset of AEs.

The pattern of reported AE terms differed from the Sponsor’s post-marketing database and AERS, with respect to the most commonly PT for fatal cases. TEN and SJS, which are included as AEs in the Nexium Rx label, were the events most commonly reported in WHO/ Vigibase. A possible explanation might be the fact that a relatively larger proportion of reports (75%) were received from health professionals which perhaps would be more likely to report such type of cases. For more discussion on TEN and SJS see section 8.1.7.

8.4 National Poison Data System

With regard to overdose and abuse information derived from the NPDS and DAWN databases, the available information does not indicate that there is any safety concern in connection to use of esomeprazole. The results from NPDS confirm that the risk of organ toxicity is low, by either accidentally or deliberately exceeding the maximum daily dosage. Esomeprazole is not known to produce euphoric, stimulant, sedative or other addictive effects most commonly associated with abuse or misuse. There is no evidence from the DAWN data that esomeprazole is subject to abuse. Drowsiness was one of the most common CE term, which was not so frequent in other databases but it is on the Nexium Rx label.

Case records in this database reflect exposures to esomeprazole from 2001-2011 and they are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, an inhalation, or a topical exposure, etc), or request information.

Exposures do not necessarily represent a poisoning or overdose. Clinical Events (CEs) were analyzed by age, gender, dose, time to onset, management site, reason for exposure, medical outcome and esomeprazole case status (all cases, primary drug, only drug). CEs were also categorized by causality: Not related, Unknown if Related, Related. It should be noted that the terminology used for CEs does not follow MedDRA, but is specific to NPDS and is limited to approximately 130 terms.

There were 21,566 human exposures for esomeprazole with 9,379 associated CE terms during the reporting period. Of the 21,566 exposures (all cases where esomeprazole was a mentioned drug), 70.6% reported esomeprazole as the primary drug (EPD) and 64.1% reported “esomeprazole as the only drug” ingested (EOD). In a majority of exposures no CE was reported, as shown in Table 20 below:

Table 20. NPDS Esomeprazole exposures

| Causality: Dose | Not Related | | Unknown If Related | | Related | | Total | |
|---------------------|-------------|--------------|--------------------|--------------|------------|--------------|-------------------------|--------------|
| | n | % | n | % | n | % | n | % |
| 20 mg | 16 | 2.8 | 4 | 0.7 | 9 | 1.0 | 29 | 1.4 |
| 40 mg | 32 | 5.7 | 33 | 6.0 | 41 | 4.5 | 106 | 5.2 |
| Other doses/unknown | 517 | 91.5 | 516 | 93.3 | 863 | 94.5 | 1896 | 93.4 |
| Total col% | 565 | 100.0 | 553 | 100.0 | 913 | 100.0 | 2031^a | 100.0 |
| Total row% | 565 | 27.8 | 553 | 27.2 | 913 | 45.0 | 2031^a | 100.0 |

EOD population = all cases where esomeprazole was the only drug (n=13824)

a Of the in total 13824 cases, 1408 (10.2%) cases reported 2031 Clinical Events and 12416 (89.8%) cases did not report a Clinical Event

(Source: ISS, Appendix 5, Table 25, p. 44)

This review focuses on the cases in which esomeprazole was the only drug of exposure (EOD). For the case reports where esomeprazole was reported as EOD, no deaths occurred. Overall, there were 18 reports of death in cases which esomeprazole was not the only drug, with 159 CEs, all occurred within the age range 18-76 years. Out of the 18 case reports, all were reported as intentional, 17 were reported as suspected suicide and one was reported as abuse. Ten reports (55.6%) occurred in females and 8 reports (44.4%) occurred in males. All case reports included several ingested substances, ranging from 2 to 13.

The most frequently reported clinical effects in the EOD population were vomiting (15.3%), other (15.0%), nausea (8.6%), abdominal pain (7.2%) and drowsiness/lethargy (6.6%). Drowsiness was one of the most common CE term, which was not so prominent on other databases but it is a labeled AE in the Nexium Rx label. Table 21 below shows the number of CE by causality in the EOD population.

Table 21. NPDS Events by causality and clinical event term, EOD pop.(cut-off 1%)

| Causality: Clinical Event Term | Not Related | | Unknown If Related | | Related | | Total | |
|-----------------------------------|-------------|------|--------------------|------|---------|------|-------|------|
| | n | % | n | % | n | % | n | % |
| Vomiting | 67 | 11.9 | 51 | 9.2 | 192 | 21.0 | 310 | 15.3 |
| Other | 104 | 18.4 | 103 | 18.6 | 98 | 10.7 | 305 | 15.0 |
| Nausea | 22 | 3.9 | 44 | 8.0 | 108 | 11.8 | 174 | 8.6 |
| Abdominal Pain | 36 | 6.4 | 49 | 8.9 | 61 | 6.7 | 146 | 7.2 |
| Drowsiness/lethargy | 31 | 5.5 | 38 | 6.9 | 65 | 7.1 | 134 | 6.6 |
| Dizziness/vertigo | 25 | 4.4 | 28 | 5.1 | 44 | 4.8 | 97 | 4.8 |
| Headache | 19 | 3.4 | 35 | 6.3 | 38 | 4.2 | 92 | 4.5 |
| Diarrhea | 18 | 3.2 | 17 | 3.1 | 37 | 4.1 | 72 | 3.5 |
| Tachycardia | 13 | 2.3 | 14 | 2.5 | 30 | 3.3 | 57 | 2.8 |
| Throat irritation | 12 | 2.1 | 15 | 2.7 | 20 | 2.2 | 47 | 2.3 |
| Rash | 5 | 0.9 | 14 | 2.5 | 23 | 2.5 | 42 | 2.1 |
| Agitated/irritable | 21 | 3.7 | 14 | 2.5 | 7 | 0.8 | 42 | 2.1 |
| Oral irritation | 3 | 0.5 | 6 | 1.1 | 29 | 3.2 | 38 | 1.9 |
| Erythema/flushed | 7 | 1.2 | 13 | 2.4 | 17 | 1.9 | 37 | 1.8 |
| Pruritus | 5 | 0.9 | 11 | 2.0 | 20 | 2.2 | 36 | 1.8 |
| Cough/choke | 7 | 1.2 | 7 | 1.3 | 22 | 2.4 | 36 | 1.8 |
| Chest pain (incl. noncardiac) | 20 | 3.5 | 7 | 1.3 | 5 | 0.5 | 32 | 1.6 |
| Confusion | 10 | 1.8 | 7 | 1.3 | 11 | 1.2 | 28 | 1.4 |
| Dyspnea | 12 | 2.1 | 7 | 1.3 | 9 | 1.0 | 28 | 1.4 |
| Fever/hyperthermia | 20 | 3.5 | 2 | 0.4 | 0 | 0.0 | 22 | 1.1 |
| Pain (not dermal, GI, ocular) | 11 | 1.9 | 7 | 1.3 | 3 | 0.3 | 21 | 1.0 |
| Tremor | 10 | 1.8 | 7 | 1.3 | 3 | 0.3 | 20 | 1.0 |

EOD population = all cases where esomeprazole was the only drug

[Source: ISS, Table 35, p. 85 (109)]

Clinical events resulted only in minor or moderate clinical effects when the only ingested substance was esomeprazole. These were also predominantly unintentional (58.4%) and were managed on site (66.9%) rather than in a healthcare facility.

Of the EOD population of 13,824, only 1,408 (10.2 %) reported CEs. In cases where the only ingested substance was esomeprazole, the CEs were categorized as having one of the following medical outcomes: no effect (24.6%), minor clinical effect (29.4 %), moderate clinical effect (5.2%), major clinical effect (0.0%) and no follow-up (40.8 %).

Of all cases reported, 8.3 % of the CEs occurred in children younger than 3 years and 2.8 % occurred in children aged 3 - <6 years. Overall, children aged <20 years and adults ≥20 years accounted for 20.5% and 79.2 % of the CEs, respectively. A majority of the CEs were reported in females (64.9 %.) The most frequently reported time to onset was >3 months (14.9%), however, in a majority of cases time to onset was unknown (76.7 %.)

Data for the doses were limited: among the reports in which esomeprazole was the only drug (2,031) there were only 135 reports with dose information: 29 reports with 20 mg (1.4 %), 106 reports with 40 mg (5.2 %), and 1,896 Other doses/Unknown. Because of the large proportion of cases with unknown doses it is difficult to draw a definitive conclusion but the numbers suggest that more CEs were associated with the 40 mg dose compared with the 20 mg dose, which is higher than the proposed OTC dose.

8.4 Drug Abuse Warning Network

The DAWN database was downloaded for year 2004 to 2010 (last year available) for all cases where any PPI was in any of the drug mention fields. DAWN provides demographic and visit-level information on emergency department (ED) visits resulting from substance misuse or abuse, adverse reactions to drugs taken as prescribed, accidental ingestion of drugs, drug-related suicide attempts, and other drug-related medical emergencies. Cases involving esomeprazole in any of the 22 drug mentions fields were compared to PPIs as a whole. Comparisons were also made for cases where a PPI was the sole drug mentioned. Cases were analyzed by age, gender and ethnic origin.

A total of 9,334 cases were available for analysis, 1,680 (18%) of them involving esomeprazole. The number of cases where a PPI was the only drug mentioned was 2,142 and of these cases, esomeprazole was the PPI mentioned in 380 (17.7%) cases. The distribution of reasons for the ED visits for esomeprazole did not vary substantially from the distribution observed for all the PPI cases reported. The primary reason for the ED visit for both esomeprazole (69.6%) and PPIs in general (71.9%) were for adverse reactions. These proportions increased to 90.0% and 90.3% respectively when PPIs were the only drug involved (see Table 22 below).

Table 22. DAWN Reason for ED visit- PPI only drug involved

| | All PPIs | | Esomeprazole | |
|----------------------|-------------|-------------|--------------|-------------|
| | Number | Percent | Number | Percent |
| Suicide Attempt | 19 | 0.89% | 1 | 0.26% |
| Seeking Detox | 1 | 0.05% | 0 | 0.00% |
| Adverse Reaction | 1934 | 90.29% | 342 | 90.00% |
| Overmedication | 66 | 3.08% | 9 | 2.37% |
| Malicious Poisoning | 1 | 0.05% | 1 | 0.26% |
| Accidental Ingestion | 87 | 4.06% | 23 | 6.05% |
| Other | 34 | 1.59% | 4 | 1.05% |
| Totals | 2142 | 100% | 380 | 100% |

[Source: ISS, Table 41, p. 90 (109)]

In over 80% of these cases, for both esomeprazole and PPIs in general, the patients were discharged home. There was an alcohol mention in 6.3% of the esomeprazole cases and 5.9% for PPIs overall. Suicide attempts when PPIs were the only drug involved were infrequent, accounting for about one percent of all the cases. There were nineteen (of 2,142) cases for all PPIs and one (of 380) cases for esomeprazole. In general, the abuse potential for esomeprazole is very low and there is no evidence from the DAWN data that esomeprazole is subject to abuse. Of note it is not surprising that of the 87 accidental ingestions involving all PPIs, 75 of them occurred in the pediatric population: 71 in children 5 years of age or younger (81.6 % of the 87 accidental ingestions)

9 Appendices

9.1 Literature Review/References

The Sponsor conducted a literature search using Embase. For the review articles the search specified “proton pump inhibitor” and “review” in title or abstract in publications in humans during the time period March 10, 2000 to December 31, 2012. The actual search terms were: 'proton pump inhibitor':ab,ti AND review:ab,ti AND [humans]/lim AND [10-3-2000]/sd NOT[1-1-2013]/sd.

The articles addressed several safety topics during long term treatment with PPIs such as infections (such as pneumonia and enteric infections including *Clostridium difficile*, *Salmonella* and *Campylobacter* infection), vitamin B12 deficiency, iron deficiency, hypomagnesemia, osteoporotic fractures, interaction with clopidogrel and rebound acid

hypersecretion, interstitial nephritis. Some of the articles discuss hypergastrinemia, gastric polyps and whether there is a risk for gastric cancer and/or gastric carcinoids, some discuss the risk of colon cancer during long-term treatment with PPIs (Sheen et al 2011, Yang & Metz 2010, Lodato et al 2009, McCarthy 2010, Vakil 2012, Thomson et al 2010).

Except for colon cancer risk, for which the available published data is inconclusive at this time, all other safety concerns are addressed in various sections of the Nexium Rx label. With the exception of infections that may occur with short-term use, all the other safety concerns posed by the articles have been associated with long-term use of PPIs.

9.2 Information Regarding Potential Drug Interactions

The Sponsor provided a summary of the known drug interactions that occur with esomeprazole and which are already addressed in the Nexium Rx label. There are no new drug interactions with esomeprazole that have required additional labeling to the Rx product. The proposed OTC label does contain cautionary language alerting consumers to not use esomeprazole with certain drugs. However, the interaction with MTX, was recently added to the PPIs Rx label, but has not been added to any of the OTC PPI labels and has not been included in the Sponsor's proposed OTC label for Nexium 24HR. This will be discussed in section 9.3 Labeling Recommendations.

9.3 Labeling Recommendations

In a review dated April 17, 2013, the proprietary name Nexium 24HR was deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology.

Formal labeling review is undertaken by the IDS team in DNCE. The figures below show the proposed Drug Facts label for Nexium 24HR and the proposed Principal Display Panel.

Figure 1 Proposed Drug Facts Label Nexium 24HR

(b) (4)



Figure 2: Proposed Principal Display Panel (PDP) Nexium 24HR

(b) (4)

The Sponsor does not seek any additional claims than what has been allowed for other approved OTC PPIs. Language addressing the concerns regarding drug interactions, as well as signs and symptoms of serious conditions are on the label. Class labeling addressing the risk of *C. difficile* diarrhea is already on the Drug Facts (“Stop use and ask a doctor if ...you get diarrhea”).

From the clinical perspective this reviewer makes the following recommendations not specifically for esomeprazole, but for the entire class of OTC PPIs:

- Because of the recent class labeling change to warn regarding concomitant use of esomeprazole and MTX, I recommend adding MTX to the list on the section “Ask a doctor or pharmacist” to be consistent with the Nexium Rx label. Under the section “Ask a doctor or pharmacist before use if you are taking:”...(after prescription antiretrovirals)
 - Methotrexate (arthritis medicine)

- The other recommendation would be regarding the cautionary language regarding underlying cardiac symptoms. The current label contains bullets under “Ask a doctor before use if you have:
 - heartburn with **lightheadedness, sweating, or dizziness**
 - chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
 - frequent **chest pain**

This section does not convey the seriousness and urgency to seek medical attention if an ischemic cardiac event is imminent and it implies that the patient can wait until asking a healthcare professional to use this medicine while experiencing these symptoms. Because signs and symptoms of ischemic cardiac events and GERD overlap, and because unlike other drugs for the relief of heartburn, PPIs do not provide immediate relief, consumers may delay seeking medical attention for a serious condition.

This reviewer recommends moving these bullets to a higher level of warning. According to CFR 201.66 (c)(5)(iii): *“Do not use”, followed by all contraindications for use with the product. These contraindications are absolute and are intended for situations in which consumers should not use the product unless a prior diagnosis has been established by a doctor or for situations in which certain consumers should not use the product under any circumstances regardless of whether a doctor or health professional is consulted.”*

The following is this reviewer’s recommended labeling:

“DO NOT USE:

- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools
- if you have heartburn with **lightheadedness, sweating, or dizziness**
- if you have chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- if you have frequent **chest pain**
- **These symptoms may be signs of a serious condition. See your doctor.**

Because these proposed changes to the OTC labeling are not in any of the currently marketed OTC PPIs this reviewer’s opinion is that Nexium 24 HR may be approved with the currently proposed labeling and the labeling changes recommended should be proposed as a class labeling change for all OTC PPIs. This reviewer defers this decision to management.

9.3 Advisory Committee Meeting

There is no Advisory Committee meeting for this NDA.

9.4 Tables and Figures

Table 23. Combined Data (D961RC00001 and D961RC00002) - Number (%) of Subjects who had at Least 1 AE by PT and SOC in Treatment Period (Safety analysis set)

| System organ class / Preferred Term | Number(%) of subject | |
|---|-------------------------------|--------------------|
| | Esomeprazole 20 mg (N=333) | Placebo (N=324) |
| subjects with any AE | 40 (12.01) | 31 (9.57) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 1 (0.30) | 0(0.00) |
| ANAEMIA | 1 (0.30) | 0(0.00) |
| CARDIAC DISORDERS | 0(0.00) | 1 (0.31) |
| CORONARY ARTERY DISEASE | 0(0.00) | 1 (0.31) |
| GASTROINTESTINAL DISORDERS | 8 (2.40) | 13 (4.01) |
| ABDOMINAL PAIN | 0(0.00) | 1 (0.31) |
| CONSTIPATION | 3 (0.90) | 2 (0.62) |
| DIARRHOEA | 2 (0.60) | 3 (0.93) |
| DRY MOUTH | 1 (0.30) | 2 (0.62) |
| DYSPEPSIA | 0(0.00) | 1 (0.31) |
| FLATULENCE | 1 (0.30) | 0(0.00) |
| GASTROINTESTINAL PAIN | 1 (0.30) | 0(0.00) |
| NAUSEA | 2 (0.60) | 4 (1.23) |
| SWOLLEN TONGUE | 0(0.00) | 1 (0.31) |
| VOMITING | 0(0.00) | 2 (0.62) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 (0.60) | 3 (0.93) |
| OEDEMA PERIPHERAL | 1 (0.30) | 0(0.00) |
| PAIN | 0(0.00) | 3 (0.93) |
| PYREXIA | 1 (0.30) | 1 (0.31) |
| HEPATOBIILIARY DISORDERS | 0(0.00) | 1 (0.31) |
| CHOLELITHIASIS | 0(0.00) | 1 (0.31) |
| INFECTIONS AND INFESTATIONS | 10 (3.00) | 5 (1.54) |
| ARTHRITIS INFECTIVE | 0(0.00) | 1 (0.31) |
| BRONCHITIS | 2 (0.60) | 0(0.00) |
| GASTROENTERITIS VIRAL | 1 (0.30) | 0(0.00) |
| NASOPHARYNGITIS | 2 (0.60) | 2 (0.62) |
| SINUSITIS | 2 (0.60) | 1 (0.31) |
| UPPER RESPIRATORY TRACT INFECTION | 2 (0.60) | 1 (0.31) |
| URINARY TRACT INFECTION | 1 (0.30) | 0(0.00) |
| VAGINITIS BACTERIAL | 1 (0.30) | 0(0.00) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 4 (1.20) | 3 (0.93) |
| EXCORIATION | 1 (0.30) | 0(0.00) |
| FOOT FRACTURE | 0(0.00) | 1 (0.31) |
| HEAD INJURY | 1 (0.30) | 0(0.00) |

| | | |
|--|------------|-----------|
| LIGAMENT SPRAIN | 0(0.00) | 1 (0.31) |
| LIMB INJURY | 1 (0.30) | 0(0.00) |
| MUSCLE STRAIN | 0(0.00) | 1 (0.31) |
| SCRATCH | 1 (0.30) | 0(0.00) |
| INVESTIGATIONS | 10 (3.00) | 5 (1.54) |
| BLOOD CREATINE INCREASED | 1 (0.30) | 0(0.00) |
| BLOOD CREATININE INCREASED | 0(0.00) | 1 (0.31) |
| BLOOD GLUCOSE DECREASED | 2 (0.60) | 1 (0.31) |
| BLOOD GLUCOSE INCREASED | 2 (0.60) | 3 (0.93) |
| BLOOD URINE PRESENT | 1 (0.30) | 0(0.00) |
| EOSINOPHIL COUNT DECREASED | 0(0.00) | 1 (0.31) |
| HAEMATOCRIT DECREASED | 1 (0.30) | 0(0.00) |
| HAEMOGLOBIN DECREASED | 2 (0.60) | 0(0.00) |
| HEPATIC ENZYME INCREASED | 0(0.00) | 1 (0.31) |
| LYMPHOCYTE COUNT DECREASED | 1 (0.30) | 0(0.00) |
| MEAN CELL VOLUME ABNORMAL | 0(0.00) | 1 (0.31) |
| MONOCYTE COUNT DECREASED | 1 (0.30) | 0(0.00) |
| NEUTROPHIL COUNT INCREASED | 1 (0.30) | 1 (0.31) |
| PROTEIN URINE PRESENT | 1 (0.30) | 1 (0.31) |
| RED BLOOD CELL COUNT DECREASED | 0(0.00) | 1 (0.31) |
| WHITE BLOOD CELL COUNT DECREASED | 1 (0.30) | 0(0.00) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 3 (0.90) | 2 (0.62) |
| BACK PAIN | 0(0.00) | 1 (0.31) |
| COSTOCHONDRITIS | 1 (0.30) | 0(0.00) |
| MUSCLE SPASMS | 1 (0.30) | 0(0.00) |
| MUSCULOSKELETAL CHEST PAIN | 0(0.00) | 1 (0.31) |
| MYALGIA | 1 (0.30) | 0(0.00) |
| NERVOUS SYSTEM DISORDERS | 5 (1.50) | 1 (0.31) |

| | | |
|---|-----------|-----------|
| DIZZINESS | 0(0.00) | 1 (0.31) |
| HEADACHE | 1 (0.30) | 0(0.00) |
| LOSS OF CONSCIOUSNESS | 1 (0.30) | 0(0.00) |
| MIGRAINE | 1 (0.30) | 0(0.00) |
| SOMNOLENCE | 1 (0.30) | 0(0.00) |
| TREMOR | 1 (0.30) | 0(0.00) |
| PSYCHIATRIC DISORDERS | 3 (0.90) | 0(0.00) |
| ANXIETY | 1 (0.30) | 0(0.00) |
| NERVOUSNESS | 1 (0.30) | 0(0.00) |
| PANIC ATTACK | 1 (0.30) | 0(0.00) |
| RENAL AND URINARY DISORDERS | 2 (0.60) | 2 (0.62) |
| HAEMATURIA | 1 (0.30) | 0(0.00) |
| POLLAKIURIA | 0(0.00) | 1 (0.31) |
| PROTEINURIA | 1 (0.30) | 1 (0.31) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 2 (0.60) | 0(0.00) |
| BREAST PAIN | 1 (0.30) | 0(0.00) |
| OVARIAN CYST | 1 (0.30) | 0(0.00) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 5 (1.50) | 1 (0.31) |
| COUGH | 2 (0.60) | 1 (0.31) |
| NASAL CONGESTION | 1 (0.30) | 1 (0.31) |
| RESPIRATORY TRACT CONGESTION | 1 (0.30) | 0(0.00) |
| RHINORRHOEA | 1 (0.30) | 0(0.00) |
| SNEEZING | 1 (0.30) | 0(0.00) |
| THROAT TIGHTNESS | 1 (0.30) | 0(0.00) |
| WHEEZING | 0(0.00) | 1 (0.31) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 1 (0.30) | 3 (0.93) |
| BLISTER | 1 (0.30) | 0(0.00) |
| DRY SKIN | 0(0.00) | 1 (0.31) |
| RASH | 0(0.00) | 1 (0.31) |
| SWELLING FACE | 0(0.00) | 1 (0.31) |
| VASCULAR DISORDERS | 1 (0.30) | 0(0.00) |
| HAEMATOMA | 1 (0.30) | 0(0.00) |

(Source: ISS, Appendix 1, Table 2, p. 5)

Table 24. Combined Data (D961RC00001 and D961RC00002) - Most Frequent AEs (> 0.5%) by PT in Treatment Period (Safety analysis set)

| Preferred Term | Number (%) of subjects ^a | |
|-----------------------------------|-------------------------------------|-----------------|
| | Esomeprazole 20 mg (N=333) | Placebo (N=324) |
| subjects with any AE | 19 (5.7) | 20 (6.2) |
| CONSTIPATION | 3 (0.9) | 2 (0.6) |
| BRONCHITIS | 2 (0.6) | 0 (0.0) |
| HAEMOGLOBIN DECREASED | 2 (0.6) | 0 (0.0) |
| BLOOD GLUCOSE DECREASED | 2 (0.6) | 1 (0.3) |
| COUGH | 2 (0.6) | 1 (0.3) |
| SINUSITIS | 2 (0.6) | 1 (0.3) |
| UPPER RESPIRATORY TRACT INFECTION | 2 (0.6) | 1 (0.3) |
| BLOOD GLUCOSE INCREASED | 2 (0.6) | 3 (0.9) |
| DIARRHOEA | 2 (0.6) | 3 (0.9) |
| NASOPHARYNGITIS | 2 (0.6) | 2 (0.6) |
| NAUSEA | 2 (0.6) | 4 (1.2) |
| DRY MOUTH | 1 (0.3) | 2 (0.6) |
| PAIN | 0 (0.0) | 3 (0.9) |
| VOMITING | 0 (0.0) | 2 (0.6) |

^a Sorting is done on decreasing frequency of Esomeprazole 20mg

AEs experienced by at least 1% of the patients in any treatment group are included in this table.

Subjects with multiple AEs were counted once for each preferred term

[Source: Sponsor's ISS, Table 7, p. 24 (109)]

Table 25. AZ SOCs for all AEs by Seriousness (Global)

| SOC Abbrev | Fatal outcome | | Serious Non-Fatal cases | | Non-serious cases | | Overall cases | |
|---|---------------|--------------|-------------------------|--------------|-------------------|--------------|---------------|--------------|
| | n | % | n | % | n | % | n | % |
| Gastr | 87 | 4.4 | 7711 | 18.0 | 39253 | 33.2 | 47051 | 28.9 |
| Genrl | 869 | 43.5 | 4618 | 10.8 | 18352 | 15.5 | 23839 | 14.6 |
| Inj&P | 75 | 3.8 | 4548 | 10.6 | 10932 | 9.3 | 15555 | 9.5 |
| Nerv | 83 | 4.2 | 3482 | 8.1 | 10103 | 8.6 | 13668 | 8.4 |
| Musc | 23 | 1.2 | 2333 | 5.4 | 6472 | 5.5 | 8828 | 5.4 |
| Resp | 102 | 5.1 | 2155 | 5.0 | 5699 | 4.8 | 7956 | 4.9 |
| Psych | 37 | 1.9 | 2083 | 4.9 | 5307 | 4.5 | 7427 | 4.6 |
| Skin | 33 | 1.7 | 1352 | 3.2 | 5993 | 5.1 | 7378 | 4.5 |
| Inv | 15 | 0.8 | 1607 | 3.7 | 3871 | 3.3 | 5493 | 3.4 |
| Infec | 88 | 4.4 | 1575 | 3.7 | 2426 | 2.1 | 4089 | 2.5 |
| Surg | 11 | 0.6 | 1680 | 3.9 | 1106 | 0.9 | 2797 | 1.7 |
| Metab | 30 | 1.5 | 1098 | 2.6 | 1456 | 1.2 | 2584 | 1.6 |
| Card | 179 | 9.0 | 1580 | 3.7 | 814 | 0.7 | 2573 | 1.6 |
| Eye | 3 | 0.2 | 843 | 2.0 | 1326 | 1.1 | 2172 | 1.3 |
| Neopl | 192 | 9.6 | 1930 | 4.5 | 44 | <0.1 | 2166 | 1.3 |
| Vasc | 36 | 1.8 | 1013 | 2.4 | 1092 | 0.9 | 2141 | 1.3 |
| Renal | 34 | 1.7 | 642 | 1.5 | 813 | 0.7 | 1489 | 0.9 |
| Blood | 33 | 1.7 | 885 | 2.1 | 404 | 0.3 | 1322 | 0.8 |
| Ear | 0 | 0.0 | 284 | 0.7 | 735 | 0.6 | 1019 | 0.6 |
| Hepat | 55 | 2.8 | 607 | 1.4 | 282 | 0.2 | 944 | 0.6 |
| Repro | 3 | 0.2 | 179 | 0.4 | 739 | 0.6 | 921 | 0.6 |
| Immun | 7 | 0.4 | 310 | 0.7 | 502 | 0.4 | 819 | 0.5 |
| SocCi | 0 | 0.0 | 183 | 0.4 | 174 | 0.2 | 357 | 0.2 |
| Endo | 1 | 0.1 | 162 | 0.4 | 144 | 0.1 | 307 | 0.2 |
| Cong | 3 | 0.2 | 47 | 0.1 | 22 | <0.1 | 72 | <0.1 |
| Preg | 0 | 0.0 | 48 | 0.1 | 15 | <0.1 | 63 | <0.1 |
| <i>Tot No of AE terms</i> | <i>1999</i> | <i>100.0</i> | <i>42955</i> | <i>100.0</i> | <i>118076</i> | <i>100.0</i> | <i>163030</i> | <i>100.0</i> |
| <i>Tot No of Cases</i> | <i>1352</i> | | <i>12059</i> | | <i>55621</i> | | <i>69032</i> | |
| <i>Tot No of AE terms / Tot No of Cases</i> | <i>1.5</i> | | <i>3.6</i> | | <i>2.1</i> | | <i>2.4</i> | |

[(Source: ISS, Table 13, p. 48 (109))]

Table 26. AZ SOCs for all AEs by Seriousness (US)

| SOC Abbrev | Fatal outcome | | Serious Non-Fatal cases | | Non-serious cases | | Overall cases | |
|---|---------------|--------------|-------------------------|--------------|-------------------|--------------|---------------|--------------|
| | n | % | n | % | n | % | n | % |
| Gastr | 54 | 3.2 | 6638 | 18.9 | 30941 | 33.3 | 37633 | 29.0 |
| Genrl | 821 | 49.3 | 3921 | 11.2 | 15640 | 16.8 | 20382 | 15.7 |
| Inj&P | 67 | 4.0 | 4351 | 12.4 | 10510 | 11.3 | 14928 | 11.5 |
| Nerv | 63 | 3.8 | 2837 | 8.1 | 6854 | 7.4 | 9754 | 7.5 |
| Musc | 15 | 0.9 | 1986 | 5.7 | 5108 | 5.5 | 7109 | 5.5 |
| Resp | 84 | 5.0 | 1850 | 5.3 | 4818 | 5.2 | 6752 | 5.2 |
| Psych | 31 | 1.9 | 1683 | 4.8 | 4151 | 4.5 | 5865 | 4.5 |
| Inv | 7 | 0.4 | 1134 | 3.2 | 2765 | 3.0 | 3906 | 3.0 |
| Infec | 69 | 4.1 | 1420 | 4.0 | 2110 | 2.3 | 3599 | 2.8 |
| Skin | 3 | 0.2 | 381 | 1.1 | 3099 | 3.3 | 3483 | 2.7 |
| Surg | 8 | 0.5 | 1626 | 4.6 | 965 | 1.0 | 2599 | 2.0 |
| Card | 151 | 9.1 | 1405 | 4.0 | 601 | 0.6 | 2157 | 1.7 |
| Neopl | 176 | 10.6 | 1847 | 5.3 | 32 | 0.0 | 2055 | 1.6 |
| Metab | 25 | 1.5 | 754 | 2.1 | 1131 | 1.2 | 1910 | 1.5 |
| Vasc | 27 | 1.6 | 855 | 2.4 | 844 | 0.9 | 1726 | 1.3 |
| Eye | 2 | 0.1 | 698 | 2.0 | 805 | 0.9 | 1505 | 1.2 |
| Renal | 20 | 1.2 | 402 | 1.1 | 533 | 0.6 | 955 | 0.7 |
| Ear | 0 | 0.0 | 244 | 0.7 | 548 | 0.6 | 792 | 0.6 |
| Immun | 4 | 0.2 | 177 | 0.5 | 402 | 0.4 | 583 | 0.4 |
| Renro | 2 | 0.1 | 117 | 0.3 | 334 | 0.4 | 453 | 0.3 |
| Blood | 8 | 0.5 | 202 | 0.6 | 228 | 0.2 | 438 | 0.3 |
| Hepat | 25 | 1.5 | 223 | 0.6 | 160 | 0.2 | 408 | 0.3 |
| SocCi | 0 | 0.0 | 172 | 0.5 | 167 | 0.2 | 339 | 0.3 |
| Endo | 1 | 0.1 | 127 | 0.4 | 121 | 0.1 | 249 | 0.2 |
| Cong | 1 | 0.1 | 36 | 0.1 | 21 | <0.1 | 58 | <0.1 |
| Preg | 0 | 0.0 | 13 | <0.1 | 6 | <0.1 | 19 | <0.1 |
| Tot No of AE terms | 1664 | 100.0 | 35099 | 100.0 | 92894 | 100.0 | 129657 | 100.0 |
| Tot No of Cases | 1186 | | 8564 | | 42411 | | 52161 | |
| Tot No of AE terms / Tot No of Cases | 1.4 | | 4.1 | | 2.2 | | 2.5 | |

[(Source: ISS, Table 14, p. 49 (109))]

Table 27. AZ PTs Fatal Cases (Global- cut-off 0.5%)

| AE Preferred Term | Case Count | Percentage |
|---------------------------------------|-------------|---------------|
| Death | 789 | 39.47 |
| Myocardial infarction | 56 | 2.80 |
| Neoplasm malignant | 39 | 1.95 |
| Pneumonia | 30 | 1.50 |
| Lung neoplasm malignant | 29 | 1.45 |
| Cardiac disorder | 25 | 1.25 |
| Chronic obstructive pulmonary disease | 25 | 1.25 |
| Cardiac failure congestive | 23 | 1.15 |
| Cardiac arrest | 21 | 1.05 |
| Cerebrovascular accident | 19 | 0.95 |
| Completed suicide | 17 | 0.85 |
| Renal failure | 17 | 0.85 |
| Drug dose omission | 15 | 0.75 |
| Hepatic failure | 15 | 0.75 |
| Sepsis | 15 | 0.75 |
| Malaise | 14 | 0.70 |
| Cardiac failure | 13 | 0.65 |
| Hepatic neoplasm malignant | 13 | 0.65 |
| Pancreatic carcinoma | 13 | 0.65 |
| Respiratory failure | 13 | 0.65 |
| Toxic epidermal necrolysis | 13 | 0.65 |
| Oesophageal carcinoma | 12 | 0.60 |
| Drug interaction | 10 | 0.50 |
| Hepatic cirrhosis | 10 | 0.50 |
| Road traffic accident | 10 | 0.50 |
| Toxicity to various agents | 10 | 0.50 |
| Total: | 1999 | 100.00 |

Case reports with fatal outcome, may include both serious and non-serious AE terms.
 The totals are those for the entire dataset, not just the data displayed in the table.

[Source: ISS, Table 18, p. 55 (109)]

Table 28. AZ PTs Fatal Cases (US cut-off 0.5%)

| AE Preferred Term | Case Count | Percentage |
|---------------------------------------|-------------|---------------|
| Death | 766 | 46.03 |
| Myocardial infarction | 47 | 2.82 |
| Neoplasm malignant | 39 | 2.34 |
| Lung neoplasm malignant | 29 | 1.74 |
| Pneumonia | 26 | 1.56 |
| Chronic obstructive pulmonary disease | 25 | 1.50 |
| Cardiac disorder | 23 | 1.38 |
| Cardiac failure congestive | 22 | 1.32 |
| Cerebrovascular accident | 18 | 1.08 |
| Cardiac arrest | 17 | 1.02 |
| Completed suicide | 15 | 0.90 |
| Drug dose omission | 15 | 0.90 |
| Malaise | 14 | 0.84 |
| Cardiac failure | 12 | 0.72 |
| Hepatic neoplasm malignant | 12 | 0.72 |
| Pancreatic carcinoma | 12 | 0.72 |
| Renal failure | 12 | 0.72 |
| Respiratory failure | 10 | 0.60 |
| Sepsis | 10 | 0.60 |
| Hepatic failure | 9 | 0.54 |
| Oesophageal carcinoma | 9 | 0.54 |
| Road traffic accident | 9 | 0.54 |
| Toxicity to various agents | 9 | 0.54 |
| Total: | 1664 | 100.00 |

Case reports with fatal outcome, may include both serious and non-serious AE terms.
The totals are those for the entire dataset, not just the data displayed in the table.

[Source: ISS, Table 18, p. 55 (109)]

Table 29. AZ SAEs PT (Global >0.5%)

| AE Preferred Term | Case Count | Percentage |
|----------------------------------|------------|------------|
| Drug dose omission | 1 564 | 3.64 |
| Gastrooesophageal reflux disease | 1 116 | 2.60 |
| Malaise | 974 | 2.27 |
| Cerebrovascular accident | 602 | 1.40 |
| Dyspepsia | 578 | 1.35 |
| Myocardial infarction | 563 | 1.31 |
| Vomiting | 519 | 1.21 |
| Fall | 511 | 1.19 |
| Neoplasm malignant | 468 | 1.09 |
| Intentional drug misuse | 408 | 0.95 |
| Abdominal pain upper | 405 | 0.94 |
| Pain | 405 | 0.94 |
| Nausea | 374 | 0.87 |
| Dyspnoea | 366 | 0.85 |
| Chest pain | 343 | 0.80 |
| Hypertension | 339 | 0.79 |
| Drug ineffective | 336 | 0.78 |
| Diarrhoea | 325 | 0.76 |
| Pneumonia | 293 | 0.68 |
| Headache | 290 | 0.68 |
| Off label use | 272 | 0.63 |
| Diabetes mellitus | 257 | 0.60 |
| Abdominal discomfort | 252 | 0.59 |
| Hiatus hernia | 246 | 0.57 |
| Weight decreased | 227 | 0.53 |
| Dizziness | 214 | 0.50 |
| Cardiac disorder | 213 | 0.50 |
| Depression | 213 | 0.50 |

(Source: From ISS, Appendix 2, Table 6, p. 147)

Table 30. AZ SAEs PT (US >0.5%)

| AE Preferred Term | Case Count | Percentage |
|---------------------------------|------------|------------|
| Drug dose omission | 1 547 | 4.41 |
| Gastroesophageal reflux disease | 1 075 | 3.06 |
| Malaise | 927 | 2.64 |
| Cerebrovascular accident | 592 | 1.69 |
| Dyspepsia | 544 | 1.55 |
| Myocardial infarction | 541 | 1.54 |
| Fall | 476 | 1.36 |
| Neoplasm malignant | 465 | 1.32 |
| Vomiting | 439 | 1.25 |
| Intentional drug misuse | 389 | 1.11 |
| Pain | 376 | 1.07 |
| Abdominal pain upper | 329 | 0.94 |
| Hypertension | 310 | 0.88 |
| Chest pain | 307 | 0.87 |
| Dyspnoea | 277 | 0.79 |
| Pneumonia | 272 | 0.77 |
| Drug ineffective | 270 | 0.77 |
| Nausea | 265 | 0.76 |
| Diabetes mellitus | 250 | 0.71 |
| Off label use | 246 | 0.70 |
| Hiatus hernia | 236 | 0.67 |
| Abdominal discomfort | 233 | 0.66 |
| Diarrhoea | 227 | 0.65 |
| Cardiac disorder | 212 | 0.60 |
| Gastric disorder | 203 | 0.58 |
| Adverse event | 198 | 0.56 |
| Headache | 196 | 0.56 |
| Weight decreased | 187 | 0.53 |
| Depression | 176 | 0.50 |
| Road traffic accident | 176 | 0.50 |
| Dysphagia | 174 | 0.50 |

(Source: From ISS, Appendix 2, Table 8, p. 242)

Table 31. AERS AEs by PT and Seriousness (cut-off 0.5%)

| SOC abbr ^b | MedDRA Preferred term | Not serious | | Non-fatal serious | | Fatal serious | | All cases | |
|-----------------------|--|--------------|----------------|-------------------|-------------|---------------|------------|--------------|------------|
| | | N | % ^a | N | % | N | % | N | % |
| Inj&P | Drug dose omission | 5570 | 12.0 | 1013 | 2.7 | 6 | 0.3 | 6589 | 7.6 |
| Gastr | Gastroesophageal reflux disease | 2774 | 6.0 | 814 | 2.1 | 6 | 0.3 | 3594 | 4.1 |
| Genrl | Malaise | 1681 | 3.6 | 674 | 1.8 | 12 | 0.5 | 2367 | 2.7 |
| Gastr | Dyspepsia | 1668 | 3.6 | 415 | 1.1 | 3 | 0.1 | 2086 | 2.4 |
| Genrl | Drug ineffective | 1436 | 3.1 | 627 | 1.6 | 10 | 0.4 | 2073 | 2.4 |
| Musc | Osteoporosis | 1405 | 3.0 | 139 | 0.4 | 3 | 0.1 | 1547 | 1.8 |
| Inj&P | Multiple fractures | 1239 | 2.7 | 23 | 0.1 | 0 | 0.0 | 1262 | 1.5 |
| Gastr | Vomiting | 796 | 1.7 | 437 | 1.1 | 15 | 0.6 | 1248 | 1.4 |
| Gastr | Abdominal pain upper | 881 | 1.9 | 346 | 0.9 | 4 | 0.2 | 1231 | 1.4 |
| Genrl | Pain | 708 | 1.5 | 324 | 0.9 | 2 | 0.1 | 1034 | 1.2 |
| Gastr | Abdominal discomfort | 771 | 1.7 | 210 | 0.6 | 2 | 0.1 | 983 | 1.1 |
| Gastr | Nausea | 556 | 1.2 | 403 | 1.1 | 13 | 0.5 | 972 | 1.1 |
| Gastr | Diarrhoea | 454 | 1.0 | 370 | 1.0 | 7 | 0.3 | 831 | 1.0 |
| Nerv | Headache | 423 | 0.9 | 307 | 0.8 | 0 | 0.0 | 730 | 0.8 |
| Genrl | Chest pain | 437 | 0.9 | 285 | 0.7 | 1 | 0.0 | 723 | 0.8 |
| Psych | Intentional drug misuse | 351 | 0.8 | 263 | 0.7 | 5 | 0.2 | 619 | 0.7 |
| Resp | Dyspnoea | 260 | 0.6 | 331 | 0.9 | 14 | 0.6 | 605 | 0.7 |
| Surg | Off label use | 383 | 0.8 | 202 | 0.5 | 3 | 0.1 | 588 | 0.7 |
| Inj&P | Fall | 184 | 0.4 | 380 | 1.0 | 6 | 0.3 | 570 | 0.7 |
| Gastr | Gastric disorder | 414 | 0.9 | 152 | 0.4 | 0 | 0.0 | 566 | 0.7 |
| Psych | Insomnia | 389 | 0.8 | 172 | 0.5 | 2 | 0.1 | 563 | 0.6 |
| Gastr | Aphagia | 424 | 0.9 | 108 | 0.3 | 2 | 0.1 | 534 | 0.6 |
| Gastr | Abdominal pain | 235 | 0.5 | 228 | 0.6 | 6 | 0.3 | 469 | 0.5 |
| Nerv | Dizziness | 231 | 0.5 | 235 | 0.6 | 1 | 0.0 | 467 | 0.5 |
| Resp | Throat irritation | 379 | 0.8 | 80 | 0.2 | 0 | 0.0 | 459 | 0.5 |
| Metab | Diabetes mellitus | 263 | 0.6 | 188 | 0.5 | 5 | 0.2 | 456 | 0.5 |
| Genrl | Feeling abnormal | 353 | 0.8 | 100 | 0.3 | 1 | 0.0 | 454 | 0.5 |
| Gastr | Dysphagia | 302 | 0.7 | 146 | 0.4 | 6 | 0.3 | 454 | 0.5 |
| Card | Myocardial infarction | 4 | 0.0 | 405 | 1.1 | 44 | 1.8 | 453 | 0.5 |
| Resp | Cough | 303 | 0.7 | 139 | 0.4 | 2 | 0.1 | 444 | 0.5 |
| Vasc | Hypertension | 175 | 0.4 | 240 | 0.6 | 12 | 0.5 | 427 | 0.5 |
| Nerv | Cerebrovascular accident | 1 | 0.0 | 414 | 1.1 | 12 | 0.5 | 427 | 0.5 |
| Inv | Weight decreased | 220 | 0.5 | 192 | 0.5 | 6 | 0.3 | 418 | 0.5 |
| Inj&P | Incorrect dose administered | 339 | 0.7 | 77 | 0.2 | 1 | 0.0 | 417 | 0.5 |
| Gastr | Hiatus hernia | 217 | 0.5 | 177 | 0.5 | 2 | 0.1 | 396 | 0.5 |
| | Total terms^c (col %) | 46261 | 100 | 38054 | 100 | 2383 | 100 | 86698 | 100 |
| | Total terms^c (row %) | 46261 | 53.4 | 38054 | 43.9 | 2383 | 2.7 | 86698 | 100 |
| | Total cases^c (row %) | 16472 | 60.4 | 9973 | 36.6 | 818 | 3.0 | 27263 | 100 |

^a Unless otherwise indicated, the percent basis is the total number of preferred terms in each seriousness category. Terms with >10 events and a relative reporting rate >20% higher than the corresponding overall rate are highlighted in bold.

^b System Organ Class

^c The totals are those for the entire dataset, not just the data displayed in the table

[Source: ISS, Table 24, p. 66 (109)]

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

/s/

JANE FILIE
02/19/2014

LESLEYANNE FURLONG
02/19/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|------------------------|---|------------|-----------|-----------|---|
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | See DGIEP's comments |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | See DGIEP's comments. |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | X | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | | | X | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | X | | | Nexium is an approved Rx product since 2001 & indicated for up to ^(b) ₍₄₎ months use. |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | X | | | MedDRA (v.12 or later) coding dictionary was used. |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | | | X | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | X | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | | | X | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | AZ is requesting a pediatric waiver for <18 y/o. |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the | X | | | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|--|
| | abuse liability of the product? | | | | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | X | There were no foreign study sites in this NDA. |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | | | X | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | | | | See DGIEP Comments |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | | | | Defer to Stats |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Lolita A. Lopez, M.D.

7-11-2013

Reviewing Medical Officer

Date

Lesley-Anne Furlong, M.D.

7-11-2013

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

LOLITA A LOPEZ
07/12/2013

LESLEYANNE FURLONG
07/12/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---------------|---|-----|----|----|--|
| | Pivotal Study #2: D961RC00002 Indication: Frequent heartburn | | | | |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | Studies appear to be adequate and well-controlled and conducted in accordance with GCPs. |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | Endpoints appear to conform to recommendations from the Agency during pre-submission interactions with the Sponsor |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | X | No foreign study sites |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)? | | | X | Previously established during NDA filings for prescription Nexium |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | | | X | OTC indication is limited to 14-day course |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | X | | | OTC indication is limited to 14-day course |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested | | | X | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|---|
| | by the Division)? | | | | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | X | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)? | | | X | No consumer behavioral studies required |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | X | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | See statistical reviewer's comments |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | See statistical reviewer's comments |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | | | | Defer to statistics reviewer |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

None.

| | |
|----------------------------|-----------|
| Farrokh Sohrabi, MD | 7-12-2013 |
| Reviewing Medical Officer | Date |
| Robert Fiorentino, MD, MPH | 7-12-2013 |
| Clinical Team Leader | Date |

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

/s/

FARROKH SOHRABI
07/12/2013

ROBERT FIORENTINO
07/15/2013