

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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**MEDICAL REVIEW(S)**



Department of Health and Human Services  
Food and Drugs Administration  
Center for Drug Evaluation and Research  
Division of Nonprescription Drug Products

Medical Officer's Memo - NAI

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**NDA:** 207920  
**Sponsor:** Pfizer  
**Drug:** esomeprazole magnesium  
**Submit date:** 10/16/2015  
**Received date:** 10/16/2015  
**Review date:** 10/27/2015  
**Study Title:** A Cohort Study on the Association between Acid-suppressing Drugs in Pregnancy and Asthma in the Offspring  
**Study:** D9612N00018  
**Reviewer:** Elizabeth A. Donohoe, M.D.  
**Team Leader:** Frank Becker, M.D.

**NOTE: This review is meant to replace the "NAI" comments submitted into DARRTS 10/27/2015; those comments were inadvertently cut off.**

This submission contains a final study report for study D9612N00018, an observational study on the association between acid-suppressing drugs in pregnancy and asthma in the offspring. The CDTL review for Nexium capsules (NDA 204655) that was approved OTC in 2014 made reference to a study that the sponsor was asked to do by the UK's Medicines & Healthcare products Regulatory Agency (MHRA) related to prenatal exposure to PPIs and asthma in childhood.

FDA asked the sponsor to submit, under NDA 207920, the full study report for our review.

On brief review, the report appears to align with the summary provided by the sponsor in the PBRRER submitted under NDA 204655 (Nexium 24HR Capsules) on June 12, 2015 [see sponsor's summary below].

p. 29/260:

The study.... was conducted as a retrospective cohort study using The Health Improvement Network (THIN) primary care database in the UK with the objective to estimate the association between prenatal maternal exposure to PPIs and to H2RAs and the risk of asthma during childhood. Completed pregnancies during 1996–2010 in women aged 18-45 years were identified. Pregnancies were linked to infants using family identification numbers and dates of birth. A cohort of infants exposed to PPIs and/or H2RAs prenatally was compared with an unexposed cohort matched for maternal age and date of last menstrual period (LMP, same

quarter/year). Infants were followed up from the age of 1 year until their first recorded diagnosis of asthma, death, their sixth birthday or end of follow-up (31 December 2011). Asthma cases were ascertained by manual review of anonymized electronic medical records. Cox proportional hazards models were employed to estimate hazard ratio (HR) of asthma associated with maternal use of acid-suppressing drugs during pregnancy.

2315 women were exposed during pregnancy (PPI, n=808; H2RA, n=1368; PPI+H2RA, n=139) and 7596 women were unexposed. The incidence of asthma (per 1000 person-years) in their offspring was 19.52 (95% confidence intervals [CI]: 17.37 to 23.82) in the unexposed cohort, 23.88 (18.54 to 30.75) in the PPI cohort, 32.16 (27.60 to 37.48) in the H2RA cohort and 28.65 (16.63 to 49.34) in the PPI+H2RA cohort. Compared with unexposed infants, HR for asthma in exposed infants whose mothers received prescriptions at anytime during pregnancy was 1.12 (95% CI: 0.88 to 1.44) for PPIs and 1.43 (1.20 to 1.70) for H2RAs, after adjusting for maternal primary care physician visits and referrals during the year prior to LMP date. With further adjustments for maternal co-morbidities and co-medications, HR for asthma was 1.03 (0.76 to 1.40) for PPIs and 1.32 (1.05 to 1.64) for H2RAs. There was no excess risk of asthma in infants whose mothers had prescriptions in all three trimesters of pregnancy for PPIs (HR 0.73 [95% CI: 0.23 to 2.31]) or H2RAs (1.26 [0.51 to 3.08]). The authors conclude that the analysis showed no association between prenatal exposure to PPIs and asthma in childhood, although there was a modest association for H2RAs.

Based upon the results of the study D9612N00018 which showed that there is no association between prenatal exposure to PPIs and asthma in childhood ..... and taking into account the cumulative experience, AstraZeneca

(b) (4)

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/s/  
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ELIZABETH A DONOHOE  
11/23/2015

## CLINICAL REVIEW

Application Type NDA 505(b)(1)  
Application Number(s) 207-920  
Priority or Standard Standard

Submit Date(s) February 6, 2015  
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PDUFA Goal Date December 4, 2015  
Division / Office DNDP/ODE IV

Reviewer Name(s) Elizabeth A. Donohoe, M.D.  
Review Completion Date October 15, 2015

Established Name Esomeprazole (b) (4)  
(Proposed) Trade Name Nexium 24 HR Delayed-  
Release  
Therapeutic Class Proton Pump Inhibitor  
Applicant AstraZeneca/Pfizer

Formulation(s) Delayed-release tablet  
Dosing Regimen 20 mg once daily for 14 days  
(14- day course may be  
repeated every 4 months)  
Indication(s) Frequent Heartburn (occurs 2  
or more days a week)  
Intended Population(s) Adults ≥ 18y/o

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

From the standpoint of clinical safety, this reviewer recommends approval action for NDA 207,920 Nexium 24HR® Delayed-Release Tablets for the relief of frequent heartburn, at the dose of 20mg once daily for 14 days. This decision is based, in part, on review of a single bioequivalence (BE) study comparing the proposed Nexium 24HR Tablets to the Reference drug, Nexium 24HR® Delayed-Release Capsules. This product has an acceptable safety profile and final approvability is contingent upon approval from the Clinical Pharmacology/BioPharmaceutical standpoint and incorporation of the agency'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 over-the-counter (OTC) 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).

Esomeprazole magnesium (Nexium 24HR® Delayed-Release Capsules) received FDA approval for OTC use in March 2014.

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 be addictive or to have any psychotropic or narcotic characteristics. The incidence of severe or serious adverse events (AEs) following daily administration of esomeprazole 20 mg is low.

The safety and tolerability of esomeprazole are also supported by extensive postmarketing 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. Esomeprazole was approved for OTC use in Europe in the fall of 2013 (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.

The sponsor, AstraZeneca (AZ), is proposing to market esomeprazole magnesium in tablet formulation; this is a 505(b)(1) application and the reference drug (RD) is Nexium 24HR® Delayed-Release Capsules, NDA 204,655, manufactured by AZ. The sponsor is relying on the safety and efficacy of the RD to support the safety and clinical portions of the application as well as preclinical and toxicology data. The indications and dosing of the proposed product are identical to the RD. The sponsor does not provide a rationale in support of the proposed dosage form compared to Nexium 24HR capsules.

### *Efficacy*

In support of this NDA, the sponsor conducted a bioequivalence study, comparing the pharmacokinetics of a single dose of the proposed product and Reference drug in healthy subjects. No new efficacy studies were conducted for this NDA; efficacy of this product is extrapolated based on PK data from the single dose BE study.

The BE study was conducted in the United States. The BE study is a single dose, single center, open label, randomized, 6 way crossover study with at least a 7 day washout period involving 42 healthy subjects 18 to 55 y/o under fasting and fed conditions. The inclusion and exclusion criteria are similar for both studies. The following treatments were administered for the study separated by a 7 day washout period:

- Nexium 24HR® Delayed-Release Capsules, 20 mg
- Nexium (esomeprazole (b) (4)) 24HR Delayed-Release Tablets, 20 mg

The sponsor concluded that the results of the study under fasted conditions demonstrate that the 95% confidence intervals of the relative mean AUC and Cmax of

the test to RD were within the 80-125% acceptance range for this study. Under fed conditions, the Nexium (b) (4) tablet met criteria for bioequivalence to the Nexium banded OTC capsule for AUC; however, the Test/Reference geometric mean ratio for C<sub>max</sub> was 34.1% higher for the Nexium (b) (4) tablet than the Nexium banded OTC capsule, thus not meeting the criteria for bioequivalence. Table 1 below shows results of key summary PK parameters for this study.

**Table 1. Summary of PK Results<sup>#</sup>**

Formulation	AUC <sub>inf</sub> (ng*h/mL)	AUC <sub>last</sub> (ng*h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)
20 mg Nexium Banded OTC Capsule (Fasted)	1035.5 (925.7) [53]	1012.0 (906.6) [53]	511.3 (287.5) [53]	1.9 (0.8 – 6.3) [53]	1.3 (2.1) [53]
20 mg Nexium (b) (4) Tablet (Fasted)	985.5 (802.1) [49]	976.2 (789.1) [49]	528.3 (292.1) [49]	1.8 (1.0 – 4.5) [49]	1.1 (0.5) [49]
20 mg Nexium Banded OTC Capsule (Fed)	537.9 (538.2) [50]	448.6 (359.3) [55]	154.5 (109.7) [55]	5.5 (2.9 – 12.0) [55]	2.0 (3.0) [50]
20 mg Nexium (b) (4) Tablet (Fed)	637.1 (586.8) [46]	567.1 (535.9) [49]	217.9 (162.0) [49]	4.5 (1.3 – 10.0) [49]	2.0 (4.5) [46]

AUC<sub>inf</sub> = area under the drug concentration time curve from time zero to infinity; AUC<sub>last</sub> = area under the drug concentration-time curve from time zero to time of the last measurable concentration; C<sub>max</sub> = maximum observed drug concentration; (b) (4) (b) (4) OTC = over-the-counter; SD = standard deviation; T<sub>max</sub> = time to maximum observed drug concentration; t<sub>1/2</sub> = elimination half-life

<sup>#</sup>All values presented as mean (SD) [n] with the exception of T<sub>max</sub> which is presented as median (range) [n].

[Source: modified from Sponsor's submission Full Clinical Study Report, Mod 5.3.1.2, Table 2, p.49/160.]

Note: It was not clear to this reviewer why data for certain PK parameters (AUC<sub>inf</sub> and t<sub>1/2</sub>) are missing from the Fed treatment groups. This reviewer asked the reviewer from the Office of Translational Sciences (OTS) to address this issue; OTS imputed the missing value by using the last observation value to perform a sensitivity analysis. From their analysis, the BE results for AUC<sub>inf</sub> and C<sub>max</sub> are similar with the sponsor's results. Thus, the overall conclusion won't change for the BE analysis using their imputation model.<sup>1</sup>

<sup>1</sup> Information obtained by this reviewer via email 8/26/2015.

**Table 2 summarizes the statistical comparisons for food effect. Table 2. Summary of the Statistical Comparisons for Food Effect**

Comparison	Parameter	Ratio(Test/Reference)
fed vs fasted (Nexium OTC capsule)	$AUC_{inf}$	0.539
	$C_{max}$	0.255
fed vs fasted (Nexium (b) (4) tablet)	$AUC_{inf}$	0.563
	$C_{max}$	0.317

[Source: modified from Sponsor's submission Clinical Study Report Synopsis, Mod 5.3.1.2, p.10/13.]

See the Biopharmaceutics review for a detailed analysis of the BE study.

The Division of Biopharmaceutics in the Office of Pharmaceutical Quality (OPQ) sent a consult to Office of Translational Sciences (OTS), for additional analyses; OTS determined that the BE data was adequate. The OTS review concluded that the sponsor's statistical analysis was acceptable and that it was appropriate to conduct the analyses on fasted and fed data separately. The review essentially agreed with the sponsor's data: BE except for under the fed state where  $C_{max}$  does not establish bioequivalence because the point estimate of the Test/Reference geometric mean ratio is 1.27, which is outside (0.80, 1.25). However, because the decrease in  $C_{max}$  with food intake is slightly less in the proposed product (b) (4) tablet compared to the reference OTC capsule, the proposed drug has a slightly better efficacy profile than the reference drug. See Section 5.3 for further discussion.

### Safety

A total of 46 subjects completed the study and received both Test and reference drug; 14 subjects discontinued.

The sponsor notes in their submission that relevant review articles focusing on general safety for proton pump inhibitors (PPIs) (including esomeprazole) from 01 May 2013 up until 01 September 2014 were reviewed; there were 18 articles in total. Few reports were identified that exclusively investigated safety endpoints and the short-term use of PPIs. However, some research on risk of infection with short-term use, particularly in combination with antibiotics for *Helicobacter pylori* and regarding compliance to OTC labels, was found. No other risk identified among long-term PPI users was reported as an adverse event among these short-term users. Further, the medical literature review did not identify new clinical safety issues identified regarding the use of esomeprazole at the labeled OTC dose and duration of use.

Esomeprazole has a well-established animal and human safety profile. It has been marketed at the 20 mg/day and 40 mg/day dose for prescription use for more than twelve years. Esomeprazole as an oral formulation was first approved for marketing in Sweden in 2000, and is currently approved in more than 125 countries for various acid related disorders. There is therefore a comprehensive amount of postmarketing safety information available. Safety and tolerability of esomeprazole is well established and is supported by post marketing experience from approximately 70.5 million patient-years of oral esomeprazole treatment. In addition, more than 90,000 patients/subjects have been exposed to esomeprazole in clinical trials. Adverse events (AEs) are most often mild and reversible and the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose related AEs have been identified.

*Medical Officer Comment:*

*In summary, this reviewer concludes that the risk-benefit assessment is favorable to support the approval of esomeprazole 20 mg delayed-release tablets 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**

There are no special postmarket risk evaluation and mitigation strategies recommended beyond routine pharmacovigilance.

### **1.4 Recommendations for Postmarket 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<sup>+</sup>/K<sup>+</sup>-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. Esomeprazole is acid labile and this drug product (b) (4) (b) (4) esomeprazole magnesium trihydrate into a delayed-release tablet. Nexium 24 HR tablets 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 U.S. in 2001 as Nexium® (Nexium Rx). 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. Nexium 24HR® Delayed-Release Capsules received FDA approval for OTC use in March 2014. 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 and proposed dosing is the same as for the Nexium 24HR Capsules; the proposed indication 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 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 (H<sub>2</sub>RAs) to reduce acid production (ranitidine, cimetidine, famotidine, and nizatidine)
- PPIs to block acid production:
  - omeprazole (Prilosec OTC), 2003
  - lansoprazole (Prevacid 24HR), 2009

- combination of omeprazole and sodium bicarbonate (Zegerid OTC), 2009
- esomeprazole magnesium (Nexium 24HR® Delayed-Release Capsules), 2014.

In August 2013, a drug utilization review was conducted by OSE which examined national sales of PPIs from year 2002 through year 2012. This review was prompted by a request from the Division of Drug Safety Research (DDSR) in the Office of Testing and Research (OTR) as part of their evaluation of the occurrence of hypomagnesemia in patients taking proton pump inhibitors (PPIs). From 2002 to 2012, the total number of dispensed prescriptions for proton pump inhibitors increased by 52% from (b) (4) prescriptions in year 2002 to (b) (4) prescriptions in year 2012. In year 2012, OTC sales accounted for more than one-third of omeprazole sales and 47% of lansoprazole sales.<sup>2</sup>

### 2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient esomeprazole is available under the following brand names:

Prescription (Rx):

- Nexium® Delayed-Release Capsules (esomeprazole magnesium), 20 mg and 40 mg capsules
- Nexium® Delayed-Release Oral Suspension (esomeprazole magnesium), 2.5 mg, 5mg, 10 mg, 20 mg, 40 mg packets
- Nexium I.V. ® (esomeprazole sodium) for Injection, 20 mg and 40 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.

OTC:

- Nexium 24HR® Delayed-Release Capsules, 20 mg

### 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:

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<sup>2</sup> Drug Use review, Patty Greene, Pharm D, DEPI II submitted in DARRTS 8/22/2013 [accessed under NDA 21153 Nexium capsules].

- *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 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. This conclusion was drawn based on published epidemiological studies and not on clinical trials since most of these are of 6-months duration. FDA concluded that the OTC doses of PPIs do not incur an 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. This information is included in the Nexium 24HR DR capsules labeling.
- Decreased levels of PPI: St. John's Wort and rifampin decrease the levels of PPIs. This information is not included in the Nexium 24HR DR capsules labeling.

#### *Reviews by the Office of Surveillance and Epidemiology*

Recent reviews related to safety concerns with use of PPIs by the Office of Surveillance and Epidemiology (OSE) warrant mention; the safety concerns are generally related to chronic use and do not apply to OTC use of a 14-day treatment course for frequent heartburn.

One review evaluates postmarketing reports of cutaneous lupus erythematosus (CLE) associated with proton pump inhibitors (PPIs) to provide the Division of Gastroenterology and Inborn Errors Products (DGIEP) with an update to the 2011 Division of Pharmacovigilance (DPV) Review which found an association between PPI use and CLE. In the meantime, Takeda Pharmaceuticals U.S.A, Inc. submitted Prior Approval Labeling Supplements (PAS) for Prevacid® delayed-release capsules and oral disintegrating tablets. The PAS proposed changes to Section 7.1 of the Prevacid® label to clarify the effect PPIs may have on drugs with pH-dependent absorption pharmacokinetics and an amendment proposes to (b) (4) to the Postmarketing section of the label. DPV recommended approving the proposed labeling supplement to include in labeling the (b) (4)

DPV further recommended that consideration should be given to (b) (4) in the Warnings and Precautions section of the lansoprazole label. DPV also recommended class labeling to (b) (4) for other PPIs (omeprazole, omeprazole/sodium bicarbonate, pantoprazole, esomeprazole, rabeprazole, and dexlansoprazole). The OSE review notes that they performed a cursory search of the FAERS database for reports of systemic lupus erythematosus (SLE) with PPI use because drugs have also been reported to induce SLE; they are considering summarizing these reports in a separate review.<sup>3</sup> (b) (4)

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<sup>3</sup> OSE review by Kimberly Swank, Pharm D and Lois LeGrande, MO, submitted in DARRTS 4/13/2015 under NDA 21689.

Other OSE reviews involve the potential risk of myocardial infarction (MI) with use of PPIs; the reviews were in response to consults submitted by OND's DGIEP to OSE's Division of Epidemiology-I (DEPI-I). A May 2015 review critiques the epidemiologic methods and interpretability of two recent articles on the cardiovascular safety of proton pump inhibitors to help guide potential regulatory actions. Recommendations stated that as a result of the significant limitations in both studies, DEPI-I doesn't recommend changes to current PPI labeling. The studies fail to support a causal association between PPIs and major adverse cardiovascular events (MACE), and information presented is insufficient to support regulatory decisionmaking.<sup>4</sup> A second DEPI-I review from July 2015 [Critique of Shah, NH, et al., 2015, Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population, PLoS One, DOI:10.1371/journal.pone.0124653] looked at a recently published scientific article about the use of proton pump inhibitor (PPI) medications and the subsequent occurrence of myocardial infarction. The reviewer concluded that the new information in Shah justifies neither change to the product information for the PPIs, nor enforcement of new post-marketing requirements on PPI manufacturers. DEPI-I recommended continued surveillance of the medical literature and routine pharmacovigilance for adverse cardiovascular outcomes associated with PPI use.<sup>5</sup>

*Medical Officer Comment:*

*In regards to the risk of CLE with the use of PPIs, this reviewer notes that on September 9, 2015, the UK Medicines and Healthcare Regulatory Agency (MHRA) announced<sup>6</sup> "a very low risk" of SCLE from the use of PPIs. MHRA says evidence from clinical literature and from cases reported to regulators from health care practitioners and other sources "supports a causal association between PPIs" and the condition.*

*In regards to the risk of MI with the use of PPIs, this reviewer notes a recent request from the Division of Gastroenterology and Inborn Errors Products (DGIEP) to the Division of Cardiovascular and Renal Products for input on the analysis and conclusions in the recent article by Shah, et al (referenced above) regarding the correlation of PPI usage and the risk of myocardial infarction. This consult request was linked in DARRTS to numerous Rx PPI NDAs. DGIEP states that the review will guide potential regulatory actions. The requested completion date for the consult was September 28, 2015; it was not entered in DARRTS at the time this review was completed.*

*Although the risks of CLE and MI may not be as likely with short-term use of PPIs, given the significant attention these two safety concerns have received, this reviewer believes that close follow-up of these issues is warranted.*

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4 OSE review by David Shih, MD, MS submitted in DARRTS 5/13/2015 under NDA 21153.

5 OSE review by Joel Weissfeld, MD, MPH submitted in DARRTS 7/31/2105 under NDA 21153.

6 The Tan Sheet, "UK Notes PPI Dermatitis Risk: Will FDA Make Similar Communication?," 9/10/2015.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 3 below shows a synopsis of key interactions with the Applicant during the development program.

**Table 3. Synopsis of Key Interactions with the Applicant under IND 118964 (Nexium 24 HR tablets)**

Date	Meeting Type	Key Discussion Points/Action Items
1/28/2014	Type B pre-IND	<p>The following requirements were conveyed to the sponsor:</p> <ul style="list-style-type: none"> <li>• BE bridging study with an approved product (OTC 20 mg DR capsule subsequently approved)</li> <li>• in-vitro alcohol-induced dose dumping study or justification why such a study is not feasible</li> <li>• address food-effect on PK for proposed tablet formulation</li> <li>• Safety and Efficacy data may rely on NDA 204655</li> <li>• May cross-reference the ISS in NDA 204655 up to April 30, 2013</li> <li>• Provide interim update of safety from May 1, 2013 up to cut-off date as close as possible to the submission date</li> <li>• Provide 4 month safety update</li> <li>• Waiver request for pediatric studies is appropriate</li> </ul>

According to a DARRTS review, at the 1/28/2014 meeting, the biopharmaceutics team requested that the sponsor submit their proposed protocol for review. Subsequent submission by the sponsor (via email on 4/5/2014 and via Global Submit 5/15/2014) was not formally reviewed as the study was initiated on 4/5/2014. A review by the biopharmaceutics team would be conducted upon formal submission of the NDA. This NDA was submitted on February 6, 2015.

## 2.6 Other Relevant Background Information

Pfizer is submitting a 505(b)(1) new drug application (NDA) on behalf of AstraZeneca for the tablet dosage form based on the approval of the same OTC indication for Nexium 20 mg delayed release capsules approved on March 28, 2014 (NDA 204655). The proposed tablet dosage form contains 22.3 mg esomeprazole magnesium

trihydrate which is equivalent to 20 mg esomeprazole; the OTC Nexium 24HR capsules contain the same active ingredient. Pfizer intends to cross-reference the nonclinical studies conducted with esomeprazole and omeprazole, the clinical pharmacology data submitted in AstraZeneca's prescription NDA 21153, and the clinical efficacy and safety data in support of the OTC indication from NDA 204655, SEQ 0002. No new clinical efficacy or nonclinical data have been generated in support of the proposed OTC esomeprazole tablets. As such, in order to bridge to the aforementioned package of data package, Pfizer has conducted a bioequivalence study (BE) comparing the bioavailability of the proposed 20 mg delayed release tablets to that of the reference 20 mg delayed-release capsule approved under NDA 204655.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

This NDA was submitted in electronic format.

*Medical Officer Comments:*

*The clinical sections of the PK study were well written and were of good quality. The postmarketing safety information was presented in a standard format. This reviewer sent three information requests (IR) to the sponsor: 1) request for MedWatch Forms for all deaths and serious unlabeled adverse events, 2) request for electrocardiogram data for subjects who withdrew or terminated the study early; and 3) request for a full study report of study D9612N00018, an observational study on the association between acid-suppressing drugs in pregnancy and asthma in the offspring. At the time this review was completed, the sponsor had not responded to the third IR.*

#### **3.2 Compliance with Good Clinical Practices**

The sponsor states that this study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

The sponsor further states that a signed and dated informed consent was required before any screen procedures were done. The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document (ICD). The trial was conducted at a single center in the United States.

In addition, the study drug was packaged, labeled, and shipped by Pfizer Consumer Healthcare Consumer Study Supplies. The clinical laboratory sample analyses were performed by [REDACTED] (b) (4). All pharmacokinetic (PK) samples were sent to [REDACTED] (b) (4), for analysis. Data management, data analysis, biostatistics, and medical writing were completed by the sponsor (or its designee).

A site inspection was requested to the Office of Study Integrity and Surveillance (OSIS) to evaluate the bioequivalence study. OSIS recommended accepting data without an on-site inspection because two facilities (analytical and clinical) were recently inspected and classified as No Action Indicated (NAI). See OSIS review entered in DARRTS on May 26, 2015.

### 3.3 Financial Disclosures

An FDA form 3454 was submitted certifying that the sponsor has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). There were no financial disclosures that would cast doubt on the findings of the studies.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Esomeprazole magnesium is a proton pump inhibitor which reduces gastric acid secretion through inhibition of H<sup>+</sup>/K<sup>+</sup>-ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid. Esomeprazole is acid labile and is therefore formulated as gastro-resistant tablets containing a [REDACTED] (b) (4) esomeprazole magnesium trihydrate.

Esomeprazole, the S-isomer of omeprazole, is acid labile [REDACTED] (b) (4) formulated as gastro-resistant capsules containing enteric coated pellets of esomeprazole magnesium trihydrate. In vivo conversion to the R-isomer is negligible.

Esomeprazole is the S-isomer of omeprazole, a proton pump inhibitor that specifically blocks the gastric H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme. This enzyme is responsible for acid secretion in the parietal cells of the stomach. The proposed 20 mg OTC tablet drug product is [REDACTED] (b) (4) purple, oblong, biconvex, [REDACTED] (b) (4) tablet engraved "20 mg"



on one side and "N" on the other side. The tablet (b) (4) containing the active ingredient esomeprazole as the magnesium salt. The proposed drug product provides a 20 mg dose of esomeprazole as 22.3 mg esomeprazole magnesium trihydrate. Esomeprazole degrades rapidly at low pH, so must be protected during exposure to gastric juice. The formulation was developed as (b) (4) containing the active ingredient. (b) (4)

**Table 4. Composition of Esomeprazole Magnesium Delayed Release Tablet**

				(b) (4)
	(b) (4)	(b) (4)		(b) (4)
		(b) (4)		
		(b) (4)		
	(b) (4)		(b) (4)	
		(b) (4)		
u	The at		(b) (4)	
c	Metha	(b) (4)		(b) (4)
		(b) (4)		
d	The at		(b) (4)	
e		(b) (4)		
	N/A Not a			

[Source: Sponsor's submission, Quality Overall Summary, Table 2.3.P.1-1., p.1/2]

**Table 5. Composition of [REDACTED] (b) (4)**  
**Esomeprazole Magnesium Delayed Release Tablet**

[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)
[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)
[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)
[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)
Mica	[REDACTED] (b) (4)	[REDACTED] (b) (4)
Titanium d	[REDACTED] (b) (4)	[REDACTED] (b) (4)
Polyethyle	[REDACTED] (b) (4)	[REDACTED] (b) (4)
[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)
NA Not	[REDACTED] (b) (4)	[REDACTED] (b) (4)

[Source: Sponsor's submission, Quality Overall Summary, Table 2.3.P.1-2., p.2/2]  
The Sponsor cross-references the original NDA 21153 Nexium Capsules for the chemistry information.

*Medical Officer Comment:*

*In the briefing package for the IND 118964, the sponsor stated that the proposed OTC tablet [REDACTED] (b) (4). In this NDA submission, the description of the tablet is [REDACTED] (b) (4) purple, oblong, bi-convex [REDACTED] (b) (4) tablet". The proposed esomeprazole magnesium 22.3 mg delayed-release tablets (henceforth referred to as "esomeprazole tablets") [REDACTED] (b) (4). The tablet is [REDACTED] (b) (4).*

## 4.2 Clinical Microbiology

No new information is provided.

## 4.3 Preclinical Pharmacology/Toxicology

There are no new non-clinical or toxicology data submitted to support this NDA. Nexium 24HR Tablets is relying on the preclinical and toxicology information of previous NDA submissions. The original prescription Nexium Delayed-Release Capsules' nonclinical dossier (NDA 21153, February 2001) was used for the Nonclinical Overview in Nexium 24HR Delayed-Release Capsules NDA (204655 (SEQ. 0002), Section 2.4). The original summaries/reports referenced are therefore listed in: NDA 204655 (SEQ.

0002); Nexium 24 HR Delayed-Release Capsules; NDA 21-689; Nexium® IV (esomeprazole sodium) for Injection; NDA 22-10; Nexium® (esomeprazole magnesium) For Delayed-Release Oral Suspension esomeprazole 20 mg delayed-release capsules, in support of this application.

All the non-clinical studies on the active substance esomeprazole (b) (4) were submitted and reviewed in NDA 21153. The non-clinical data supporting the clinical oral use of esomeprazole is described in the Nexium Rx Package Insert.

Since esomeprazole is the S-enantiomer of a racemate (omeprazole) that was already a marketed drug, only a limited number of nonclinical studies were performed and submitted in the prescription esomeprazole capsule (NDA 21153). There are no new nonclinical pharmacology or toxicology studies that have been conducted in support of the proposed OTC esomeprazole tablet product. The Nonclinical Overview cross-references the complete listing of the nonclinical studies that are provided in NDA 204655.

*Medical Officer Comment:*

*Esomeprazole magnesium is characterized as Pregnancy Category C. 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, 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 BE study.

##### **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<sup>+</sup>K<sup>+</sup>-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 Sand 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 (section 12.2), 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 over a 24-hour period 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 for 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 of 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 (b) (4). The absorption of esomeprazole is rapid, with peak plasma levels (C<sub>max</sub>) 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.

Esomeprazole is administered orally and intravenously. It is 97% bound to plasma proteins. Metabolism occurs extensively in the liver to inactive metabolites via CYP2C19 and to a lesser extent by CYP3A4. The metabolites lack antisecretory activity. The plasma elimination half-life is approximately 1.5 hours. Less than 1% of parent drug is excreted in the urine with the remainder excreted as inactive metabolites in both the urine and feces. Esomeprazole is metabolized by CYP2C19 and CYP3A4, and it inhibits the CYP2C19 isoenzyme. In vitro and in vivo drug interaction studies note that it is not likely to inhibit CYP3A4, CYP1A2, CYP2A6, CYP2C9, CYP2D6, or CYP2E1.

Per the oral route, esomeprazole dissolves rapidly in an acidic environment and therefore is formulated as a capsule containing enteric-coated pellets. Multiple dosing at 40 mg/day results in 90% bioavailability versus 64% after a single 40 mg dose. C<sub>max</sub> is reached within 1—3.5 hours. The AUC of esomeprazole (the S-isomer) is 80% higher than with omeprazole (both S- and R-isomer) due to decreased clearance and first-pass elimination of the S-isomer. Clinically this allows more esomeprazole to reach the site of action and may contribute to higher efficacy rates. The AUC of a single 40 mg dose of esomeprazole is decreased by 33—53% after food intake compared to fasting conditions.<sup>7</sup>

## 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

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<sup>7</sup> Clinicalpharmacology online, accessed June 4, 2015.

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<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> 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 following are the sources of clinical data submitted with this 505(b)(1) application:

- A fed/fasting study B5141002
- Summary safety analysis of Nexium from the following databases:

- Interim update of safety from May 1, 2013 up to cut-off date as close as possible to the submission date
- 4 month safety update submitted June 4, 2015.

## 5.1 Tables of Studies/Clinical Trials

The sponsor conducted a single study comparing the bioequivalence (BE) of proposed product (test; esomeprazole 20 mg (b) (4) Tablet) to the reference drug (RD; esomeprazole 20 mg Banded OTC Capsule) and effect of high-fat meal on bioavailability (BA) of RD and test. See Table 6.

**Table 6. Table of Clinical Trials**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design	Treatment Groups	Duration of Treatment	Subjects
BE, BA	B5141002  United States	Fasting BE (test v RD)  Fed BE (test v RD)  Effect of high-fat meal on BA of RD and test	6-period crossover, open-label	RD: esomeprazole 20 mg Capsule (Fasted)	Single dose	Healthy volunteers N=53
				RD: esomeprazole 20 mg Capsule (Fed)		Healthy volunteers N=49
				Test: esomeprazole 20 mg Tablet (Fasted)		Healthy volunteers N=55
				Test: esomeprazole 20 mg Tablet (Fed)		Healthy volunteers N=49

[Source: based on Sponsor's submission, Full Clinical Study Report – Protocol B5141002, Mod 5.3.1.2, Table 11, p.54/160.]

## 5.2 Review Strategy

This clinical review focuses on the clinical safety aspect of this application, primarily the safety information from the clinical trial conducted for this OTC program and

postmarketing safety information. 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 Drug Products (DNPD). 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.) The DMEPA reviewer determined that the proposed proprietary name Nexium 24HR is acceptable from both a safety and misbranding perspective. See review entered into DARRTS April 2, 2015.

### **5.3 Discussion of Individual Studies/Clinical Trials**

One in-vivo comparative BE trial was conducted to confirm BE of the Test and RD. This was an open-label, randomized, single-dose, 6-period partial replicate crossover study to assess the BE of Nexium OTC capsule (RD) and Nexium (b) (4) tablet (test) in healthy volunteers in fed and fasted conditions. Since esomeprazole is considered a highly pharmacokinetically-variable drug, the study was designed to enable a reference scaled average bioequivalence (RSAB) testing approach. Therefore, two reference treatments with Nexium 24HR Capsules (Treatment A [fasted] and Treatment C [fed]) were administered in two separate treatment periods within each subject. Treatment groups B and D include the proposed Nexium 24HR Tablets, fasted and fed, respectively. The sponsor intends for the results from this study to bridge the efficacy and safety data generated in support of the OTC esomeprazole approval to the 20 mg Nexium (b) (4) tablet, and establish suitability of the Nexium (b) (4) tablet for the proposed OTC indication of treatment of frequent heartburn

The study included healthy male and/or female subjects between the ages of 18 and 55 years, with a body mass index of 17.5 to 29.9 kg./m<sup>2</sup> and a total body weight >50 kg (110 lbs). See Figure 1 below.



**Figure 1. Treatments Administered During each Treatment Period**

(b) (4)

(b) (4)

Note: The 2 1  
periods with  
treatment per

(b) (4)

<sup>a</sup> Treatment C  
meal.

[Source: Sponsor's submission, Clinical Study Report Synopsis, Mod 5.3.1.2, Table S 1., p. 3/13.]

Subjects were randomly assigned to 1 of the following 6 treatment sequences (approximately nine subjects per sequence).

1. B-A-C-D-A-C
2. A-D-B-C-C-A
3. D-C-A-A-B-C
4. C-A-D-C-A-B
5. A-C-C-B-D-A
6. C-B-A-A-C-D

[Source: Sponsor's submission, Clinical Study Report Synopsis, Mod 5.3.1.2, p. 2/13.]

Reference Treatments (Treatment A and Treatment C) were administered in two separate treatment periods within each subject. The minimum washout between treatment periods was 7 days. Sixty subjects enrolled and 46 subjects completed this study.

Subjects were screened within 21 days prior to administration of the study drug to confirm that they met the subject selection criteria for the study. Subjects were admitted to the clinical research unit (CRU) the evening prior to dosing and were required to stay in the CRU for up to 1 day/1 night. The dose of study drugs was administered to the subjects as a single 20 mg Nexium OTC banded capsule or Nexium (b) (4) tablet given orally with 200 mL of water at the investigational site at approximately 0700 ± 1 hour on Day 1 of each treatment period. Subjects were instructed to consume the entire 200 mL of water along with the study drug. Subjects received their study drug after a 10-hour fast (Treatment A and Treatment B) or with a high-fat breakfast following a 10-hour fast (Treatment C and Treatment D). Water was allowed except within 1 hour before and 1 hour after drug administration (with the exception of water provided with drug administration). No food was allowed for at least four hours postdose. The estimated duration of the study was up to approximately 60 days (including the screening, 6 study visits, wash-out, and study completion assessments).

Pharmacokinetic (PK) blood samples were collected serially for 12 hours after dosing during each treatment period. Plasma concentrations of esomeprazole were measured with a validated LC-MS/MS assay. PK parameters following single-dose administration were derived from the concentration-time data. The primary PK parameters for the study were area under the drug concentration-time curve from time zero to infinity ( $AUC_{inf}$ ) and maximum observed drug concentration ( $C_{max}$ ). Table 7 and Table 8 summarize PK results for fasted and fed state, respectively.

**Table 7. Summary of PK Results for Fasted State<sup>#</sup>**

Formulation		AUC inf (ng*h/mL)	AUC last (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
20 mg Nexium Banded OTC Capsule	Mean SD/range n	1035.5 (925.7) [53]	1012.0 (906.6) [53]	511.3 (287.5) [53]	1.9 (0.8 – 6.3) [53]	1.3 (2.1) [53]
20 mg Nexium (b) (4) Tablet	Mean SD/range n	985.5 (802.1) [49]	976.2 (789.1) [49]	528.3 (292.1) [49]	1.8 (1.0 – 4.5) [49]	1.1 (0.5) [49]

#All values presented as mean (SD) [n] with the exception of T<sub>max</sub> which is presented as median (range) [n].

[Source: modified from Sponsor's submission, Full Clinical Study Report Mod 5.3.1.2, Table 7, p.49/160.]

**Table 8. Summary of PK Results for Fed State#**

Formulation		AUC inf (ng*h/mL)	AUC last (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	t <sub>1/2</sub> (h)
20 mg Nexium Banded OTC Capsule	Mean SD/range n	537.9 (538.2) [50]	448.6 (359.3) [55]	154.5 (109.7) [55]	5.5 (2.9-12.9) [55]	2.0 (3.0) [50]
20 mg Nexium (b) (4) Tablet	Mean SD/range n	637.1 (586.8) [46]	567.1 (535.9) [49]	217.9 (162.0) [49]	4.5 (1.3-10.0) [49]	2.0 (4.5) [46]

#All values presented as mean (SD) [n] with the exception of T<sub>max</sub> which is presented as median (range) [n].

[Source: modified from Sponsor's submission, Full Clinical Study Report Mod 5.3.1.2, Table 7, p.49/160.]

The sponsor concluded that the results of this study show that the 20 mg Nexium (b) (4) tablet is bioequivalent to the currently marketed Nexium banded OTC capsule in terms of both peak esomeprazole exposure (C<sub>max</sub>) and the extent of esomeprazole exposure (AUC) under fasted conditions. Under fed conditions, the Nexium (b) (4) tablet met criteria for bioequivalence to the Nexium banded OTC capsule for AUC; however, the Test/Reference geometric mean ratio for C<sub>max</sub> was 34.1% higher for the Nexium (b) (4) tablet than the Nexium banded OTC capsule, thus not meeting the criteria for bioequivalence.

Table 9 shows a summary of the statistical comparisons of the pharmacokinetic parameters of esomeprazole following a single dose administered as a 20 mg Nexium Banded OTC Capsule or 20 mg Nexium (b) (4) Tablet under fasted and fed conditions.

**Table 9. Summary of the Statistical Comparisons of PK Study**

Comparison	Parameter	$S_{wr}^a$	Test/ Reference GMR	90% Confidence Interval	95% Criteria Bound	Method Used
Tablet v Capsule (Fasted)	AUCinf (ng*h/mL)	0.202	0.948	(0.890, 1.010)	----	Unscaled
	Cmax (ng/mL)	0.304	1.009	----	-0.050	Scaled
Tablet v Capsule (Fed)	AUCinf (ng*h/mL)	0.351	0.994	----	-0.061	Scaled
	Cmax (ng/mL)	0.763	1.341	----	-0.156	Scaled

GMR = geometric mean ratio;  $S_{wr}$  = within-subject standard deviation of the reference product (capsule); <sup>a</sup>  
 If  $S_{wr} \geq 0.294$  then a reference scaled average bioequivalence (BE) approach is applied. BE is declared if  
 95% criteria bound <0 and the Test/Reference GMR is between (0.80, 1.25)

[Source: modified from Sponsor's submission, Full Clinical Study Report, Mod 5.3.1.2, Table 8, p.50/160]

Esomeprazole plasma concentrations in the fed state for the 20 mg capsule and 20 mg tablet are shown below in Figure 2.

**Figure 2. Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) – 20 mg Nexium Banded OTC Capsule (C) and 20 mg Nexium (b) (4) Tablet (D) in the Fed State**

(b) (4)

MUPS = multi

[Source: Sponsor's submission, Clinical Study Report Synopsis, Mod 5.3.1.2, Figure S 3., p.7/13.]

See review by the Biopharmaceutics reviewer for details related to analysis of this PK study.

The Biopharmaceutics reviewer from the Office of Pharmaceutical Quality (OPQ) consulted the Office of Translational Sciences (OTS) requesting assistance in analyzing the submitted clinical data with SAS. Specifically:

1. Is the Applicant's statistics analysis plan for Protocol B5141002 adequate to meet its goal (primary and secondary objectives)?
2. From their data presentation in this BE report, is it appropriate to conduct analyses on the fast data and fed data separately?

OTS responded to the above consult July 31, 2015. The review concluded that the sponsor’s statistical analysis was acceptable and that it was appropriate to conduct the analyses on fasted and fed data separately. The review essentially agreed with the sponsor’s data: BE except for under the fed state where  $C_{max}$  does not establish bioequivalence because the point estimate of the Test/Reference geometric mean ratio is 1.27, which is outside (0.80, 1.25). However, because the decrease in  $C_{max}$  with food intake is slightly less in the proposed product (b) (4) tablet compared to the reference OTC capsule [0.317 (~68% decreased) vs 0.255 (~75% decreased)], the proposed drug has a slightly better efficacy profile than the reference drug. See Table 10 below.

**Table 10. Summary of the Statistical Comparisons for Food Effect**

Comparison	Parameter	Ratio(Test/Reference)
fed vs fasted (Nexium OTC capsule)	$AUC_{inf}$	0.539
	$C_{max}$	0.255
fed vs fasted (Nexium (b) (4) tablet)	$AUC_{inf}$	0.563
	$C_{max}$	0.317

[Source: modified from Sponsor’s submission, Clinical Study Report Synopsis, Mod 5.3.1.2, Table S 5., p. 10/13.]

Most adverse events experienced by subjects in the trial were mild or moderate in severity; there was one serious AE reported not related to study drug. See section 7 for detailed discussion on safety findings.

*Medical Officer Comment:*

*The results of the BE study showed that the proposed product met the BE criteria compared to the RD in the fasted state, however, the  $C_{max}$  for the proposed product was greater than the  $C_{max}$  for the RD in the fed state. In the fed state, the point estimate of the Test/Reference geometric mean ratio for  $C_{max}$  is 1.27, which is outside (0.80, 1.25). Although the decrease in  $C_{max}$  with food intake is slightly less in the proposed product (b) (4) tablet compared to the reference OTC capsule [0.317 (~68% decreased) vs 0.255 (~75% decreased)], the proposed product has a slightly better efficacy profile than the reference drug.*

*Both the reference drug and the proposed drug have similar food effect (the AUC and  $C_{max}$  decreased with intake of food to a similar extent). The sponsor plans to follow the same user direction as the reference drug in their proposed labeling: (b) (4)*

*The labeling for prescription Nexium states: “the AUC after administration of a single 40 mg dose of NEXIUM is decreased by 43% to 53% after food intake compared to fasting*

conditions. NEXIUM should be taken at least one hour before meals.” Given the profound effect induced by the fed state on AUC, it is not clear to this reviewer why the prescription Nexium includes the direction to take at least one hour before meals yet the OTC Nexium 24HR Capsule (NDA 204655; IND 111185) labeling states: “before eating in the morning”. On review of related reviews in DARRTS, it appears to this reviewer that FDA agreed that the clinical trial design for the two pivotal efficacy studies to support Nexium 24HR Capsules include instructions to subjects that they take the capsule “before eating in the morning.” Note: there were no clinical pharmacology studies or food effect studies conducted under NDA 204655.

1) Under IND 111185:

- meeting minutes from May 11, 2011 include the following:

*FDA Preliminary Response:*

Your proposed Nexium OTC label directs consumers to “swallow one capsule before eating in the morning”; however, in your proposed efficacy trials, volunteers are directed to take Nexium (b) (4). Please note that your efficacy trials should support the labeling of your 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.

- The medical officer’s 30-day safety review submitted June 2, 2011 includes the statement: “For all phases of this study, double blind study medication with esomeprazole 20 mg capsule, or matching placebo will be taken once daily before eating in the morning.”

2) Under NDA 204655:

- The DGIEP review submitted February 21, 2014 includes the statement: “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 review further states: “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];  $p < 0.0001$ ).”

This reviewer supports the following user directions for the proposed product: “For better results, take at least one hour before meals”, to be consistent with Rx labeling. See section 9.2 of this review for more information.



## 6 Review of Efficacy

### **Efficacy Summary**

There are no efficacy trials conducted for this application. One PK trial was conducted comparing their proposed product, esomeprazole magnesium delayed-release tablets 20 mg and the RD, esomeprazole magnesium delayed release capsules, 20 mg. To bridge efficacy, the sponsor relies on demonstrating bioequivalence between the two products. The RD, OTC Nexium 24HR capsules, was approved as a 505(b)(2) application on 3/28/14 (AstraZeneca, NDA 204655)

### **6.1 Indication**

The indication of the proposed product is the same as that of the currently marketed OTC esomeprazole magnesium delayed-release capsules, 20 mg:

- Treats frequent heartburn (occurs two or more days a week).

#### 6.1.1 Methods

There are no efficacy trials conducted for this application. To bridge efficacy, the sponsor relies on demonstrating bioequivalence between their proposed product, esomeprazole magnesium delayed-release tablets 20 mg, and the RD, esomeprazole magnesium delayed release capsules, 20 mg. Study B5141002 was conducted as an open label, randomized, partial replicate cross-over study to investigate if the test 20 mg delayed-release tablet and the reference 20 mg delayed-release capsule are bioequivalent following single dose administration under fasting conditions.

#### 6.1.2 Demographics

The demographic characteristics of subjects enrolled in the PK study are summarized below. This study was conducted in the United States; mean age of subjects was 31 years with a range of 18 to 51 years. Of the 60 subjects who began the study, 41 (68.33%) were male and 19 (31.67%) were female. The mean BMI was 25.58kg/m<sup>2</sup>. The majority of the study population was white (51, 85%); 8 subjects (13.33%) were black and 1 subject (1/67%) was "Other". See Table 11.



**Table 11. Summary of Demographic and Baseline Characteristics**

BMI (kg/m<sup>2</sup>)  
Mean (SD)  
Median (m)

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Source: [Table 6](#)  
BMI = body

[Source: Sponsor's submission, Full Clinical Study Report, M5.3.1.2, Table 6, p. 43/160.]

**Medical Officer's Comments:**

*As this trial is a cross-over study, the characteristics of participants in terms of age, gender, race, weight and BMI are inherently the same for each arm. Overall, more males than females participated and the majority of subjects were white (87%). Given what is known about the mechanism of action of esomeprazole, no substantial differences in findings would be expected despite these demographic differences. Overall, the demographic subsets of subjects were limited by the inadequate percentage of geriatric subjects. Of the fourteen subjects that withdrew, nine were male and five were female; 11 were white and three were black.*

**6.1.3 Subject Disposition**

Of the 60 subjects who started the study, 46 subjects completed all 6 treatment periods and 14 subjects discontinued from the study. The subjects who withdrew from the study

withdrew due to the following reasons: no longer willing to participate (8 subjects), AEs (5 subjects) and a protocol violation (1 subject). See Table 12.

### Table 12. Subject Disposition and Evaluation Groups

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Randomized  
Completed  
Discontinued

[Source: modified from Sponsor's submission, Clinical Study Report Synopsis, M5.3.1.2, Table S2., p. 5/13.]

There does not appear to be any particular pattern to the subjects who discontinued relative to the assigned treatment group.

#### 6.1.4 Analysis of Primary Endpoint(s)

No pivotal efficacy studies were conducted for this NDA. A PK study was conducted to establish bioequivalence between the proposed product and RD. See section 5.3 of this review and the Biopharmaceutics review for complete analysis of the PK study.

#### 6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

#### 6.1.6 Other Endpoints

Not applicable.

#### 6.1.7 Subpopulations

Not applicable.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

#### 6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

## 7 Review of Safety

### **Safety Summary**

The sponsor supports safety of the NDA by the safety information obtained from the PK study, postmarketing information for esomeprazole (including Nexium 24 HR Capsules) and an updated literature review.

The sponsor's original submission includes post-marketing data from:

- AstraZeneca's safety database for prescription esomeprazole covering the period for 01 May 2013 through 01 September 2014; and
- Pfizer's safety database for non-prescription esomeprazole covering the period from 27 May 2014 through 01 September 2014.

The sponsor also references the Integrated Summary of Safety (ISS) submitted in NDA 204655 (for the cumulative time period through 31 December 2012) and the 4-month Safety Update (additional data from 01 January 2013 through 30 April 2013). According to the sponsor, the ISS included worldwide post-marketing data from the global marketing of prescription esomeprazole (cumulatively through 31 December 2012) and evaluation of specific safety topics, worldwide literature review, and data from external global safety databases. The sponsor references additional safety data submitted under NDA 204655; see Section 8, Postmarketing Safety.

Associated literature searches were conducted for the time period of this report (01 May 2013 through 01 September 2014).

The sponsor also submitted a 4 Month Safety Update covering the period 02 September 2014 through 01 January 2015 with safety data from both the AstraZeneca and Pfizer databases as well as an updated literature search.

The postmarketing data are discussed in detail in section 8 of this review. Information from the literature searches are discussed in section 9 of this review.

Nexium capsules were approved for marketing in the United States in February 2001.<sup>8</sup> Consumers have been safely self-treating heartburn with over-the-counter (OTC) proton pump inhibitors (PPIs) beginning in 2003 in the US when omeprazole (Prilosec OTC) was approved to treat frequent heartburn. The safety profile of esomeprazole has been well established for both Rx and OTC use.

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<sup>8</sup> Clinicalpharmacology online, accessed 5/04/2015.

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.

Many of the above safety concerns are associated with long term use. As the indication for Nexium OTC is for a 14 day treatment period, these safety concerns are of less importance for OTC consumers. Nexium 24HR OTC capsules was approved for marketing in March 2014; the Drug Facts Label, under “Stop use and ask a doctor if” includes “you get diarrhea” to address the safety concern related to *Clostridium difficile* associated diarrhea.

On 31 October 2014, Pfizer received an OTC proton pump inhibitor (PPI) class labeling request from the FDA to add mycophenolate mofetil to the Drug Facts Warnings section of the approved Nexium 24HR capsule labeling in NDA 204655. This request has been included in the labeling for the proposed tablet product that is the subject of this application.

The sponsor states that over 80,000 subjects have been exposed to esomeprazole as of 10 March 2014 (from AstraZeneca studies). Since first approval for marketing esomeprazole in 2000, US exposure is approximately 41 million patient-years and since the launch of the OTC capsules, more than (b) (4) capsules have been delivered to wholesalers in the U.S.

Safety Conclusions:

Both Nexium 20 mg banded OTC capsule and Nexium 20 mg (b) (4) tablet formulations, under fed and fasted conditions, were well-tolerated with no unexpected safety findings. No deaths occurred during this study. Of the 60 subjects enrolled in the study, twelve (20.0%) subjects experienced a total of 29 treatment-emergent AEs. Four subjects reported an AE after receiving the 20 mg Nexium banded OTC capsule

(fasted), five subjects reported after receiving the 20 mg Nexium (b) (4) tablet (fasted), four subjects reported after receiving the 20 mg Nexium banded OTC capsule (fed), and three subjects reported after receiving the 20 mg Nexium (b) (4) tablet (fed). Some subjects reported AEs in more than one treatment group. All AEs were mild or moderate in severity. Of the 12 (20.0%) subjects who reported treatment-emergent AEs, six subjects had treatment-related AEs. The most frequently reported all-causality treatment-emergent AEs were nausea (n=5, 8.3%) and headache (n=5, 8.3%). In general, AEs were similar across formulation and administration conditions. Overall, reported AEs were numerically fairly similar for both formulations under fed and fasted conditions.

There was one serious adverse event (SAE); a subject who had received Nexium (b) (4) tablet (fasted) experienced an SAE (wrist fracture), which was considered not related to the study drug.

Five subjects discontinued study treatment due to AEs. Of those subjects, four subjects discontinued study treatment due to non-related AEs (vessel puncture site pain, nausea/vomiting, wrist fracture/excoriation, and influenza-like illness) and one discontinued study treatment due to a related AE (swollen tongue).

The observed safety results were consistent with the known safety profile of the study drug and as outlined in the product label.

After review of the information submitted in this NDA, no new safety concerns were identified regarding the safety of esomeprazole magnesium for OTC use. The safety profile of the proposed product is expected to be comparable to that of the currently marketed OTC esomeprazole magnesium product.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor submitted safety results from the PK study and from postmarketing safety information for esomeprazole. The latter will be discussed in detail in section 8 of this review. It should be noted that this is a 505(b)(1) application, and it relies on the Reference drug for safety and efficacy of esomeprazole.

Although there was a single PK study conducted for this submission, the study design was unique in that it involved a six-period crossover design involving fed and fasted conditions. The Biopharmaceutics reviewer from the Office of Pharmaceutical Quality (OPQ) consulted the Office of Translational Sciences (OTS) requesting assistance in analyzing the submitted clinical data with SAS. Specifically:

1. Is the Applicant's statistics analysis plan for Protocol B5141002 adequate to meet its goal (primary and secondary objectives)?
2. From their data presentation in this BE report, is it appropriate to conduct analyses on the fast data and fed data separately?

OTS responded to the above consult July 31, 2015. The review essentially agreed with the sponsor's data: BE except for under the fed state where  $C_{max}$  does not establish bioequivalence because the point estimate of the Test/Reference geometric mean ratio is 1.27, which is outside (0.80, 1.25).

The sponsor did present safety results (incidence of adverse events) from fed and fasted periods of this study separately. See sections 7.3 and 7.4.

#### 7.1.2 Categorization of Adverse Events

Adverse events from the PK study were coded using the MedDRA 17.0 dictionary and were tabulated by MedDRA preferred term (PT) and system organ class (SOC) system. All AEs were collected as well as any changes in laboratory or vital signs that may have constituted an AE. AEs were assessed according to frequency, severity, seriousness and suspected causality. The incidence and the total number of reports of AEs were presented for each treatment and for all treatments combined.

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

Not applicable.

### 7.2 Adequacy of Safety Assessments

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

The PK study was designed so that subjects received 4 treatments: Nexium 24HR Capsules 20mg, fed and fasted (Reference) and Nexium 24HR Tablets 20 mg, fed and fasted (Test). Subjects were exposed to the Reference treatment periods twice and to the Test treatment periods once. Forty-six subjects completed all 6 treatment periods of the study and 14 subjects discontinued from the study.

#### 7.2.2 Explorations for Dose Response

Not applicable. The dose proposed for this OTC indication is based on the currently approved dose of Nexium 24HR Capsules OTC.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

### 7.2.4 Routine Clinical Testing

A medical history was obtained for all subjects during Screening as well as a complete medication history of all prescription or nonprescription drugs and dietary and herbal supplements taken within 28 days prior to the planned first dose. In addition, a History of drug, alcohol and tobacco use, Full Physical examination, Height, weight, and BMI, Supine blood pressure (BP), pulse rate (PR) and respiratory rate (RR) and Standard supine 12-lead electrocardiogram (ECG) were conducted.

Following at least a 4-hour fast, blood and urine specimens were collected for the following: Safety laboratory tests (including urinalysis)& serology for screening of HIV, Hepatitis B, and Hepatitis C; Urine drug test; Serum FSH concentration for any female who has been amenorrheic for at least 1 year; and Serum (screening only) or urine human chorionic gonadotropin (hCG) for all females of childbearing potential.

A brief physical examination, medical history, vital signs (supine BP, PR and RR), pregnancy test, urine drug screen, and review of concomitant were done at each of the six study periods. Each study period was separated by at least 7 days.

Study completion procedures were conducted after all Period 6 Day 1 assessments were completed. These included a brief physical exam, BP, PR, RR and a urine pregnancy test for females of childbearing potential, assessment of symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?", review of concomitant medications and discharge from clinical research unit.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

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

The evaluation of adverse events by the sponsor was appropriate for this single-dose fasting and fed PK study as the proposed OTC Nexium tablets will be labeled for short-term use. More serious adverse events from PPI use (including esomeprazole) are more likely to occur when used at higher doses and for longer durations which is considered prescription use.

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 (hypochlorydria) 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 tablets 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.

### **7.3 Major Safety Results**

#### **7.3.1 Deaths**

There were no deaths in the PK study.

#### **7.3.2 Nonfatal Serious Adverse Events**

One SAE was reported; it was not related to the study drug. The subject reported a wrist fracture after a motorcycle accident; this subject also discontinued study treatment.

#### **7.3.3 Dropouts and/or Discontinuations**

Five subjects discontinued study treatment due to adverse events; these included pain at puncture site, nausea/vomiting, flu-like symptoms, swollen tongue (mild) and wrist fracture as noted previously. Four of the five subjects discontinued after Period 1; one discontinued after Period 4 (subject with wrist fracture). Nine subjects discontinued due to other reasons (eight were no longer willing and there was one protocol violation).

#### **7.3.4 Significant Adverse Events**

There were no other significant adverse events in the PK study.

#### **7.3.5 Submission Specific Primary Safety Concerns**

There were no other significant adverse events in the PK study.

### **7.4 Supportive Safety Results**

As per the protocol, AEs were assessed throughout the study after enrollment both prior to dosing and after dosing during each treatment period. Of the 60 subjects that were enrolled in Study B5141002, 12 subjects reported 29 treatment-emergent AEs.



Table 13 presents a Summary of adverse events for Study B5141002.

**Table 13. Summary of Adverse Events (Study B5141002)**

Number of Subj  
 Number of Subj  
 Discontinuation  
 Number of Subj  
 Source: Table 1  
 A: 20 mg of Ne  
 C: 20 mg of Ne  
 AE = adverse e  
<sup>a</sup>Related: relate

(b) (4)  
 (b) (4)  
 (b) (4)

[Source: Sponsor's submission, Full Clinical Study Report, Mod 5.3.1.2, Table 10, p. 52/160.]

#### 7.4.1 Common Adverse Events

The incidence of all-causality treatment-emergent AEs occurring in at least 2% of the 60 enrolled subjects is presented in Table 14. Gastrointestinal disorders and nervous system disorders were the System Order Class (SOCs) with the most frequently reported AEs.

**Table 14. Incidence of Adverse Events (Study B5141002) in  $\geq$  2% of Subjects by Treatment, in Decreasing Frequency**

Adverse Event (Preferred Term)	Total N=60 N (%)	A: 20 mg Capsule Fasted N=53 n (%)	B: 20mg Tablet Fasted N=49 n (%)	C: 20mg Capsule Fed N=55 n (%)	D: 20mg Tablet Fed N=49 n (%)
No. of Subjects (total)	12 (20.0)	4 (7.5)	5 (10.2)	4 (7.3)	3 (6.1)
Nausea	5 (8.3)	2 (3.8)	2 (4.1)	1 (1.8)	1 (2.0)

Headache	5 (8.3)	3 (5.7)	2 (4.1)	1 (1.8)	2 (4.1)
Vomiting	2 (3.3)	0	2 (4.1)	0	1 (2.0)

[Source: modified from Sponsor's submission, Full Clinical Study Report, M5.3.1.2, Table 11, p. 54/160.]

All twelve subjects reported mild AEs; two of those subjects also reported with moderate AEs. The moderate AEs included: a subject reporting a wrist fracture of moderate severity after receiving 20 mg Nexium (b) (4) tablet (fasted) and a subject reporting moderate back pain after receiving Nexium 20 mg banded OTC capsule (fed).

In the two treatments with Capsule 20 mg, there were six treatment emergent AEs in Treatment A (fasted) and eight for Treatment C (fed). The two treatments with Tablets 20 mg involved nine treatment emergent AEs in Treatment B (fasted) and six in Treatment D (fed). Generally, the sponsor attributes an AE as "related" if it occurred within 12 hours of the previous dose. Of the 12 subjects who experienced AEs, seven subjects appeared to have AEs related to study treatment. AEs attributed to study treatment include headache (five events), nausea (three events), vomiting (two events), dizziness (one event), and swollen tongue (one event). One subject experienced headache and nausea twice, one subjects experienced headache twice and one subject experienced vomiting twice.

*Medical Officer Comment:*

*The most commonly reported treatment emergent AEs appear to mirror the known safety profile for esomeprazole, the most frequent being headache and gastrointestinal disorders, such as nausea and vomiting, and are mild and transient in nature. The AEs are known events with esomeprazole.*

*No treatment associated SAEs occurred during any treatment phase of the PK study.*

7.4.2 Laboratory Findings

Clinical laboratory evaluations were performed at Screening (hematology and serum chemistry; Human Immunodeficiency Virus, Hepatitis B, and Hepatitis C) testing to verify subject eligibility requirements. Urine drug screens were performed on Day 0 of each treatment period. Laboratory data collected at Screening were used for inclusion and exclusion criteria, considered source data, and not included in the study database.

No data was submitted regarding abnormal laboratory values.

7.4.3 Vital Signs

Vital signs (Supine BP, PR and RR) were recorded at screening and at each subsequent period. The mean (SD) change from screening in systolic blood pressure

was -2.2 (9.1) mmHg, diastolic blood pressure was -1.9 mmHg (6.8), heart rate was -0.2 (8.1) beats per minute, and respiration rate was 0 (2) breaths per minute. No subject had vital sign values that were considered clinically significant.

A total of 57 (95.0%) of subjects underwent physical examination, and none of the subjects had physical exam findings that were considered clinically significant changes from baseline. Physical examinations were not performed for 3 (5.0%) subjects after they discontinued early from the study and were considered protocol deviations.

#### 7.4.4 Electrocardiograms (ECGs)

According to the submitted protocol, ECGs were done at screening and in the case of subject withdrawal or early discontinuation from study. However, in section 12.5 of the protocol, the sponsor states that an ECG was only performed at Screening and at the end of the study (or at the time of early discontinuation from the study). Case Report Forms (CRFs) were provided only for the five subjects that discontinued due to adverse events. The CRFs indicate that for three of the subjects, the ECGs were “normal” at screen and at termination; however, ECGs for subject ID 10032 [10011065] and subject ID 10009 [10011169] were not done at termination. It is not clear if ECGs were done on all subjects at end of study.

An Information Request (IR) was sent to the sponsor July 16, 2015 to provide an analysis of the ECG data and to clarify if ECGs were done on all subjects at end of study.

The sponsor responded to the above IR on July 31, 2015. They stated that “Section 12.5 of the protocol contains a typographical error stating that ECGs would be performed in all subjects at the end of the study”. ECGs were only done at baseline and in the case of early subject withdrawal/discontinuation. Of the 14 subjects who discontinued, three were lost to follow-up and, therefore, those early termination ECGs were not done. The sponsor provided ECG data (including PR, QRS and QTc intervals) for baseline and early termination readings for the remainder 11 subjects. None of the individual absolute or changes from baseline values were outside of the protocol defined thresholds of concern. Further, none of the values or changes from baseline was deemed to be clinically significant by the investigator. Criteria for values of QTc requiring further evaluation in the protocol were defined as an absolute value of  $\geq 500$  msec or a change from baseline of  $> 45$  msec. Similarly, values of potential concern for PR interval were defined as  $\geq 300$  msec or a  $\geq 25\%$  increase from baseline if baseline  $> 200$  msec or  $\geq 50\%$  increase from baseline if baseline  $\leq 200$  msec. For the QRS complex, values of potential concern were defined as  $\geq 140$  msec or change from baseline  $\geq 50\%$ .

The sponsor further stated that the totality of the experience with esomeprazole shows no evidence of trends in QT prolongation, increases in PR interval or increases in the

QRS complex. Pre-clinical tolerability evaluations of esomeprazole have provided no indications of adverse ECG effects.

*Medical Officer Comments:*

*Data related to subjects ECGs do not reflect any safety concerns. Of note, the submission for NDA 2046559 (Nexium Delayed Release Capsules, approved March 28, 2014) included data for electrocardiograms conducted at baseline only 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

Not applicable to this submission.

### **7.5 Other Safety Explorations**

The sponsor did not conduct additional studies to evaluate safety of the product.

#### 7.5.1 Dose Dependency for Adverse Events

No assessments of dose-dependency for AEs were conducted for this submission. 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 for this submission. The label of Nexium Rx however, indicates that the occurrence of AEs is increased with longer treatment duration.

#### 7.5.3 Drug-Demographic Interactions

As this trial is a cross-over study, the characteristics of participants in terms of age, gender, race, weight and BMI are inherently the same for each arm. See section 6.1.2.

*Medical Officer Comments: It should be noted that there were no subjects  $\geq 65$  years of age, therefore the data is not conducive for drawing conclusions in this particular population subset based on this study.*

#### 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

The sponsor did not perform studies to evaluate drug-drug interactions. However, per the protocol, exclusion criteria included: Use of prescription or nonprescription drugs within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study medication. Dietary supplements must be discontinued 14 days prior to the first dose of study medication. Herbal supplements must be discontinued 28 days prior to the first dose of study medication. As an exception, acetaminophen may be used at doses of  $\leq 1$  g/day. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

##### *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 24HR DFL under "ask a doctor or pharmacist before use if you are taking": warfarin, clopidogrel or cilostazol, prescription antifungal or anti-yeast medicines, digoxin, diazepam, tacrolimus or mycophenolate mofetil, prescription antiretrovirals, methotrexate.<sup>10</sup> This section of the proposed DFL is the same as that approved for Nexium 24HR Capsules.*

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<sup>10</sup> DailyMed, accessed 6/26/2015.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

There were no carcinogenicity studies performed for this NDA application.

#### *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.”*
- *“In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs. 10% controls).”*
- *“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

The sponsor did not conduct studies that provide data on human reproduction and pregnancy. However, the review by CDTL L. Furlong, MD for NDA 204655 (Nexium 24HR Capsules) submitted in DARRTS 3/2/2014 states:

The applicant notes two observational studies linking prenatal exposure to PPIs to an increased risk of asthma. Both studies have limitations. At the request of the UK’s regulatory authority (MHRA), the applicant is performing an observational study and a cohort study investigating the possible association

between pregnancy exposures and childhood asthma. Study results will be available in the fourth quarter of 2014.

Comments: Proposed labeling for pregnancy states “If pregnant or breast-feeding, ask a health professional before use.” This is consistent with other OTC PPIs, is also consistent with other OTC drugs that are Pregnancy Category B or C in the Rx labeling, and is acceptable to me.

When completed, the ongoing observational and cohort studies of asthma should be submitted to the applicant’s esomeprazole NDAs for FDA review.

According to the PBRER submitted under NDA 204655, Nexium 24HR Capsules:

AstraZeneca has been requested by MHRA to perform an observational study on the association between acid-suppressing drugs in pregnancy and asthma in the offspring. Based upon the results of the study D9612N00018 which showed that there is no association between prenatal exposure to PPIs and asthma in childhood, see Section 8.1, and taking into account the cumulative experience, (b) (4).  
(b) (4).

This submission’s (NDA 207920) Interim Update of Safety states that the Regulatory Authority in UK (MHRA) requested that AstraZeneca perform an observational study on the association between acid suppressing drugs in pregnancy and asthma in the offspring. A cohort study using the THIN database in the UK between 1995 and 2010 conducted by AstraZeneca concluded that the previously suggested modest association between prescription of any acid-suppressive drug during pregnancy and asthma in the offspring may be explained by underlying environmental or genetic factors in the families.

Prescription Nexium is classified as Pregnancy Category C It is recommended that pregnant and lactating women seek the advice of a health care professional before use.

According to the sponsor, in total, since launch up to 01 September 2014, when taking all cases regarding pregnancy regardless of source, seriousness and causality into consideration, AstraZeneca has received 729 cases of pregnancy (including paternal exposure and child cases with placental exposure). Information below reflects data submitted with the 4MSU, from launch of the prescription product through 01 January 2015. AstraZeneca has received 746 cases of pregnancy; outcomes were unknown for 486 cases.

There were 267 pregnancy outcomes reported. Of these, there were:

- 10 intrauterine deaths/stillbirths
- 1 ectopic pregnancy

- 4 terminations due to fetal defects (trisomy 18, alobar holoprosencephaly, congenital hand malformation, limb reduction defect)
- 8 babies have been born with congenital malformations (hypospadias, syndactyly, cleft palate/lip, anotia, mild haemangiomas, heart disease congenital, suspected hypospadias, kidney duplex, pelvic kidney and congenital hydronephrosis).
- 33 spontaneous abortions
- 22 elective terminations (fetal defects unknown)
- 4 transplacentally exposed children with AEs after being born
- 14 babies reported to being non-healthy (not congenital malformations) at birth. In 1 report oligohydramnios was reported, but pregnancy outcome was unknown.
- 171 healthy babies have been born.

The sponsor further states that the number of known pregnancy outcomes in AstraZeneca's safety database was limited; however, the cases did not indicate any causal relationship between esomeprazole and complications during pregnancy. As for most cases received from marketed use, detailed information is often scarce and confounding factors such as concurrent disease and/or other concomitant medication might exist. The sponsor references a study (Jensen et al, 2004) that cites a congenital malformation rate of 2.8% in a background population was presented when analyzing a cohort of >1200 consecutive pregnancies.

The sponsor states that by 01 January 2015, AstraZeneca had received 30 cases concerning drug exposure of esomeprazole via breast milk. Five of the 30 cases contained AEs (decreased appetite and decreased activity, rash, food intolerance, vomiting and abdominal pain), while 25 cases had no reported symptoms. However, the excretion of esomeprazole in milk has not been measured, thus it is not known whether esomeprazole is excreted in human milk.

The Pfizer OTC database contained 4 cases in which terms related to pregnancy and lactation were reported. Two cases involved pregnancy and in both cases outcomes were unknown. Other clinical events (AEs) reported with the pregnancy cases were: Gastroesophageal reflux disease, Barrett's oesophagus, Pancreatitis, Anxiety, Nervousness, Dysuria, Dyspnoea, Feeling abnormal, and Blood cholesterol abnormal. In 2 other cases, Lactation disorder was reported and both cases described spontaneous lactation with an unknown outcome. All of these cases were non-serious and none were medically confirmed. In the 4MSU, there were 6 additional cases in which terms related to pregnancy and lactation were reported with the use of oral non-prescription esomeprazole. The details for each of these 6 cases were limited. No clinical AEs were reported. All of these cases were considered non-serious and none were medically confirmed. Five cases related to pregnancy, outcomes unknown, and one case related to lactation.



*Medical Officer Comments:*

*It is difficult to draw any definitive conclusions as to a safety assessment with respect to pregnancy outcomes due to limited information, confounders and because the denominator for the use of the drug in this population is not known. 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 fully 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 language applies to drugs of Pregnancy (b) (4) Category C. See 21CFR 201.63 Pregnancy/breast feeding warning.*

*The pregnancy outcomes from the AZ database are consistent with those mentioned in the review by J. Filie, MD for the initial OTC switch, Nexium Capsules NDA 204665.*

*At the time this review was written, a copy of the final study report for Study D9612N00018 had not been submitted to FDA for review. An Information Request requesting submission of this study report was sent to the sponsor on October 7, 2015.*

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

*Medical Officer Comment:*

*The sponsor made reference to an Agreed initial Pediatric Study Plan (iPSP) dated January 28, 2014 submitted by AstraZeneca (AZ) for esomeprazole magnesium delayed-release tablets (henceforth referred to as "esomeprazole tablets" or "20 mg delayed-release tablet") to Pre- Investigational New Drug (PIND) Application 118,964 (SEQ. 0004) and confirmed by the Agency on February 27, 2014. As noted in the Agreed iPSP, AZ requested a full waiver for pediatric studies for the over-the-counter (OTC) treatment of heartburn and to exclude use in the pediatric population (all ages 0 to < 18 years of age). Following confirmation of the Agreed iPSP from the Agency on February 27, 2014, AZ received approval on March 28, 2014 for OTC Nexium24HR (esomeprazole magnesium) delayed-release capsules (NDA 204655) and was granted a full pediatric waiver.*

*The OTC indication for Nexium 24HR 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 PK study.

According to the sponsor, AstraZeneca's database contained 43 cases (from the total dataset of 4898 cases, 0.9%) reporting 75 events in association with an overdose. Thirty-six of the 75 events used the preferred term "overdose"; three were serious, 33 were non-serious. Twenty-nine of these 43 cases contained no safety-related adverse event (other than the overdose term) in connection with the reported overdose. The majority of the remaining 14 cases were non-serious (10, 23.2%). Thirty-six events used the preferred term "overdose"; three were serious, 33 were non-serious. Case outcome was recovered/recovering for 6 cases (13.9%) and not recovered for 4 cases (9.3%); outcome was unknown for 3 cases (7.0%). One patient died and this case is described further below.

Case 2013SE41109 involved a 76-year-old male with a history of hypertension, diabetes, hypercholesterolemia and atrial fibrillation who suffered an ischaemic stroke. The information is limited and it is not clear if an overdose/drug-drug interaction occurred. Causality with esomeprazole is considered unlikely.

The Pfizer OTC database reported 23 counts of "overdose" PT term reported of a total of 1871 counts. The sponsor states that no new safety trends or patterns were identified from this review of cases reporting....overdose.

*Medical Officer Comment:*

*According to the Nexium Rx label, there was limited experience of doses exceeding 240 mg. The Rx 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.*

#### **7.7 Additional Submissions / Safety Issues**

Not applicable.

### **8 Postmarket Experience**

This section includes data from the sponsor's initial submission of February 2015; detailed information submitted with the 4 Month Safety Update of June 4, 2015 is not

included in the discussions under sections 8.1 or 8.2 as it would not add to or change the overall analysis.

The sponsor states that the esomeprazole oral formulation is currently approved in over 125 countries, for various acid-related disorders. According to the sponsor, as of January 1, 2015, more than 80,000 subjects have been exposed to esomeprazole in clinical trials. The worldwide postmarketing prescription exposure exceeds 102 million patient years with a corresponding US exposure of approximately 42 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. Since the launch of the non-prescription product, more than (b) (4) capsules and tablets have been delivered to wholesalers worldwide, corresponding to an estimated exposure of over 2.5 million patient-years. The U.S. accounts for over 99% of the distribution of non-prescription oral esomeprazole.

Adverse events (AEs) reported in the postmarketing databases are most often mild or reversible and the safety profile is similar for different formulations and treatment indications with different age groups and populations. There have been no withdrawals for either safety or regulatory reasons.

The sponsor submitted an Interim Update of Safety which included the Nexium prescription database (May 1, 2013 through September 1, 2014) and OTC Nexium 24HR database (May 27, 2014 through September 1, 2014) as well as an updated literature review (May 1, 2013 through September 1, 2014). The Sponsor references NDA 204655 for efficacy and safety, including a summary of esomeprazole safety information from five databases (Sponsor's post-marketing database, AERS, WHO Vigibase, AAPCC/NPDS, and DAWN).

Esomeprazole has a well-established safety profile and has been marketed for prescription use for many years. Esomeprazole was first approved on 10 March 10, 2000 and in the US in February, 2001; substantial post-marketing safety information is available.

The sponsor's submission includes post-marketing data from:

- AstraZeneca's safety database for prescription esomeprazole covering the period for 01 May 2013 through 01 September 2014;
- Pfizer's safety database for non-prescription esomeprazole covering the period from 27 May 2014 through 01 September 2014; and

A 4 Month Safety Update (MSU) covering the period 02 September 2014 through 01 January 2015 with data from both the AstraZeneca and Pfizer databases was submitted June 5, 2015. In the 4 MSU, the sponsor states that no studies relevant to this proposed indication were performed during that reporting period and no analyses of

clinical study data were performed. The sponsor noted that due to the volume of post-marketing cases and associated AE terms, all searches could not be conducted at one single time point. Some minor differences in overall number of cases and AE terms can be noted between different tables, due to the dynamic nature of post-marketing safety databases which are updated on a daily basis. Consequently, the total number of cases/AE terms may change due to updates although the same time period relevant for all searches was used (02 September 2014 through 01 January 2015). The total of cases for the post-marketing database queries may vary resulting from queries at different points in time.

Note: there are limitations of post-marketing adverse drug event reporting as reports are submitted voluntarily and the magnitude of underreporting is unknown.

*Medical Officer comment:*

*Review of NDA 204655 submission by Dr. Jane Filie noted that there were no new or unexpected safety findings from the reports from the FDA/AERS and WHO databases except for cases involving drug eruptions such as Stevens Johnson syndrome and of Toxic epidermal necrolysis [TEN]; the reports were confounded by multidrug use and these conditions are listed under section 6.2 Postmarketing experience in the Nexium Rx labeling. 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. Further, information from DAWN and NPDS does not indicate that there is any safety concern in connection to use of esomeprazole, the abuse potential for esomeprazole is very low and there is no evidence that esomeprazole is subject to abuse.*

## **8.1 AstraZeneca's Global Postmarketing Database (Prescription)**

### **8.1.1 Overall analysis**

The sponsor provided data for case reports for use of oral prescription esomeprazole received from 01 May 2013 through 01 September 2014. The reporting did not include intravenous or OTC use with the exception of the pregnancy search.

Overall, there were a total of 4898 cases involving 14,496 AE terms with the use of oral prescription esomeprazole. A total of 1611 (32.9%) of these cases with 7320 associated events were reported from the US. Overall, there were 1316 (26.9%) serious non-fatal cases, of which 430 (32.7%) originated from the US. There were 60 (1.2%) cases that reported a fatal outcome and 17 (28.3%) of these were from the US. Overall, reporting was comparable among medically confirmed sources (2621, 53.5%) and consumers (2272, 46.4%). In contrast, in the US, the majority of the cases (1396 [86.9%]) originated from consumers whereas only 211 (13.1%) were from medically confirmed sources. The total number of AE terms reported for prescription esomeprazole for all SOC for global and US cases were 14,456 and 7,300, respectively,

for all groups combined (serious non-fatal cases, non-serious cases and cases that reported a fatal outcome). Cases classified as serious may also contain non-serious events.

The mean age of fatal cases in the U.S. was 65 yo (range: 50-84 yo); serious non-fatal AEs mean age was 58 yo (range: 11-94 yo); non-serious AEs mean age was 59 yo (range 0-94 yo).

**Table 15. Selected Characteristics of Prescription Esomeprazole Cases: US**

prescription terms  
Age, years

Age group  
n (%)

Gender  
n (%)

<sup>a</sup>May include both serious and non-serious AE terms

<sup>b</sup>Sum of all categories with the exception of totals where data for overall were available.

[Source: Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 4, p.16/79]

The 4 Month Safety Update (MSU) submitted June 4, 2015 reported no new or unexpected safety findings. Of the 4898 global cases that were included in the interim safety analysis provided with NDA 207920, there were 126 (2.6%) cases for which follow-up information was received during the 4 MSU. Of the 126 cases reporting follow-up information during this period, 30 (23.8%) cases originated from the US. Globally, this follow-up information was received for 66 serious non-fatal cases, 56 nonserious cases and 4 cases with a fatal outcome. The profile of reported events is consistent with the safety profile observed in the initial cases. No new safety concerns were identified.

During the 4 MSU, there were a total of 930 cases involving 2739 AE terms with the use of oral prescription esomeprazole. A total of 354 (38.1%) of these cases with 1385 associated events were reported from the US. 287 were serious cases; there were four deaths, one death occurred in the U.S. AEs by PT term are similar for the 4 MSU as for the initial submission for both the non-fatal and fatal cases.

### 8.1.2 Deaths

Overall, there were 60 cases (of 4898, 1.2%) with fatal outcome associated with 274 AE terms for prescription esomeprazole. A total of 17 of these cases (28.3%) with 73 associated AEs originated from the US. Of the 60 cases with fatal outcome, 43 (71.7%) were medically confirmed and 17 (28.3%) were non-medically confirmed. Age was reported for 48 of the 60 deaths; mean age was 69.9 years, with a range of 28-98 years of age.

Globally, in five of the fatal cases, the event of “Fall” was reported. These five patients were reported to have died, but the cause of death was not attributed to the fall. The mean age for the patients was 77 years (age was not reported for 1 case). In four of the five fatal fall cases, several concomitant conditions such as cardiomyopathy, cardiac failure, chronic obstructive pulmonary disease and arrhythmias were present and the causal relationship with esomeprazole could not be established. In one of the cases, the sponsor states that information was too limited to make a causal assessment.

#### **Table 16. Most Frequently Reported AEs with Prescription Esomeprazole by PT for 60 Fatal Cases: Global (Count >3)**

<u>AE Preferred Term</u>
Death
Fall
General phy
Renal failure
Septic shock
Therapy ces
Cardiac arre
Interstitial h
Multi-organ

[Source: modified from Sponsor’s submission, Interim Update of Safety, Mod 5.3.5.3, Table 10, p. 24/79.]

#### **Table 17. Most Frequently Reported AEs with Prescription Esomeprazole by PT for 17 Fatal Cases: US (Count ≥2)**

Bone disorder  
 Chronic obstructive pulmonary disease  
 Completed studies  
 Diarrhoea  
 Multiple fractures  
 Rheumatoid arthritis  
Total

[Source: Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 11, p. 25/79.]  
 Of the 274 AEs reported for the 60 deaths globally, the most frequent AEs by SOC were:

• General disorders and administration site disorders	40 (14.6%)
• Nervous System Disorders	20 (7.3%)
• Infections and Infestations	20 (7.3%)
• Respiratory, thoracic and mediastinal disorders	19 (6.9%)
• Gastrointestinal disorders	17 (6.2%)
• Cardiac disorders	16 (5.8%)
• Injury, poisoning and procedural complications	16 (5.8%)
• Musculoskeletal and connective tissue disorders	15 (5.5%)
• Blood and lymphatic system disorders	14 (5.1%)
• Vascular disorders	13 (4.7%)
• Investigations	13 (4.7%)
• Metabolism and nutrition disorders	<u>13 (4.7%)</u>
	78.6%

[Source: modified from Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 5, p. 18/79.]

Of the 73 AEs reported for the 17 deaths in the U.S., the most frequent AEs by SOC were:

• General disorders and administration site disorders	11 (15.1%)
• Musculoskeletal and connective tissue disorders	11 (15.1%)
• Gastrointestinal disorders	8 (11%)
• Injury, poisoning and procedural complications	8 (11%)
• Neoplasms benign, malignancy and unspecified	7 (9.6%)
• Cardiac Disorders	6 (8.2%)
• Respiratory, thoracic and mediastinal disorders	<u>6 (8.2%)</u>
	78%

[Source: modified from Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 6, p. 19/79.]

There were four deaths during the 4 MSU for prescription esomeprazole; one was in the U.S. The four deaths involved 43 AEs with the most frequent PTs ( $\geq 2$ ) being diarrhea,

general physical health deterioration, multi-organ failure and acute renal failure. This is similar to findings reported in the Interim Update of Safety. One death may have involved interaction with methotrexate in a 33 yo patient with a history of juvenile destructive chronic polyarthritis and arterial hypertension.

The sponsor concludes that there has been no evidence of safety issues originating from the esomeprazole cases with fatal outcomes. The patients are most often severely ill already prior to esomeprazole treatment and there are no trends or pattern in reporting that would indicate a relationship between esomeprazole and fatal outcomes.

*Medical Officer Comment:*

*The AE PTs associated with the fatal cases seemed to differ between the global and US reported cases. The common SOCs associated with the fatal cases globally are similar to those SOCs noted in the review for Nexium OTC Capsules. The 17 U.S. cases include AE PTs osteoporosis, bone disorder and multiple fractures; the musculoskeletal and connective tissue disorders SOC comprised 15.1% of the 73 total AEs. Globally, that SOC comprised 5.5% of the total 274 AEs for 60 deaths.*

*An Information Request was sent to the sponsor May 27, 2015 requesting submission of the Adverse Event Forms for all reported deaths from the prescription database. The sponsor responded June 5, 2015; upon review of the MedWatch forms, this reviewer did not find that they provided any additional valuable information. Most of the summaries concluded that there was limited information, multiple comorbidities or polypharmacy involved. The AEs reported for these deaths are generally already known about the study drug.*

*A review of the 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.*

### 8.1.3 Serious Adverse Events – Non-Fatal

Of the 4898 cases reported globally for prescription esomeprazole, 1316 (26.9%) were nonfatal serious cases associated with 6007 AE terms (may include both serious and non-serious AE terms).

For serious non-fatal reports for prescription esomeprazole globally, the most commonly reported adverse events by PT (>1%) include:

- intentional drug misuse 124 (2.1%)
- Off-label use 100 (1.7%)
- GERD 94 (1.6%)
- Fall 77 (1.3%)



- Osteoporosis 72 (1.2%)

[Source: modified from Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 8, p. 21/79.]

Of the 1316 non-fatal serious cases, 430 cases (32.7%) with 3442 associated events originated from the US.

For serious non-fatal reports for prescription esomeprazole in the U.S., the most commonly reported adverse events by PT ( $\geq 1.9\%$ ) include:

- intentional drug misuse 103 (3%)
- GERD 82 (2.4%)
- Off-label use 73 (2.1%)
- Osteoporosis 70 (2.0%)
- Fall 66 (1.9%)

[Source: modified from Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 9, p. 22/79.]

The sponsor states that the most commonly reported PT Intentional drug misuse is not primarily related to safety/adverse reaction of esomeprazole, but often reflects situations where the patients are not able to receive their medication as intended and/or were out of medication and as a result might experience manifestations of symptoms actually related to the underlying disease for which they were being treated. For cases of fall, there is generally a range of several terms reported. In many cases, falls occur in elderly patients under treatment with multiple medications and with medical history or concurrent diseases such as dizziness, vertigo, hypertension and orthostatic hypotension.

*Medical Officer Comment:*

*The non-fatal SAEs, as indicated by PT terms, are similar for the global and U.S. reports and reflect the known profile of esomeprazole. The pattern of reported AE terms was similar for both the cases received globally and for those received from the US.*

#### 8.1.4 Common Adverse Events

More than half of the cases were events reported from the following 5 SOCs: Gastrointestinal disorders, General disorders and administration site disorders, Nervous system disorders, Skin and subcutaneous tissue disorders and Musculoskeletal and connective tissue disorders (55.1% globally, 55.1% for the US, respectively). Most of the commonly reported AE terms were either considered to reflect the underlying disease or represented terms which are included in the product labeling.

#### 8.1.5 Analyses by age, gender and race

Information regarding age was available in most (69.1%) of the cases. The overall AE pattern was similar between different age groups within the patient population treated

with prescription esomeprazole. The sponsor states that overall, there were no trends or pattern indicating differences or clustering of events due to any age-related factors.

Data regarding age were available for 3383 (69.1%) cases globally and ranged from 0-109 years of age. Information regarding gender was available in 92.7% of the cases. There were overall more cases reported for females than males, 54.9% versus 37.9%.

Information regarding ethnic origin was available in less than half (44.1%) of the cases globally. The majority of cases were for Caucasians (32.8%). Of the remaining cases, ethnic origin was reported as: Asian/Chinese (4.9%), African/Black (3.0%), Hispanic (2.0%), and Other/Native American (1.4%). Adverse events were similarly distributed across the different groups of ethnic origin. Overall, less than half of the cases (44.1%) contained information with regard to ethnic origin, thus making it difficult to draw any firm conclusions of AE pattern.

#### 8.1.6 Dose and Time to Onset

Information regarding dose was available in 29.6% and 29.5% among the global and US cases, respectively. There were no relevant differences in AE patterns between dose groups (defined as 20 mg, 40 mg and other/unknown) with prescription esomeprazole. The most frequently reported events were gastrointestinal (Diarrhoea, Nausea, Dyspepsia, Abdominal pain, and Vomiting) together with other terms also known to be associated with esomeprazole such as Headache, Rash, Dizziness and Pruritus. Time to onset categories were defined as 0-14 days, 15-120 days, ≥121 days, and Unknown. Information regarding time to onset was available in a similar proportion of cases in both the global and US populations (40.2% and 40.8%, respectively). Information regarding dose and time to onset was available in a limited amount of the cases, precluding a meaningful assessment.

#### 8.1.7 Summary of Information from prescription post-marketing database

There were no new or unexpected safety findings following review of the cases from AstraZeneca's safety database for prescription esomeprazole, including the data from the 4 MSU.

### **8.2 Pfizer's Postmarketing Database (OTC)**

#### 8.2.1 Overall Analysis

The sponsor provided data from the Pfizer Safety Database (PSD) with non-prescription esomeprazole as the suspect drug from the launch date (27 March 2014) through 01 September 2014. The AE terms are presented by SOC and PT according to the MedDRA dictionary, version 17.0. Cases were analyzed by age, gender and ethnic origin as well as by dose and time to onset.

Overall, there were a total of 668 cases involving 1871 AE terms with the use of nonprescription esomeprazole. All except one case were reported from the US. One consumer received medication in the US; however, the AE occurred while the consumer was traveling in Canada.

The majority of cases were non-serious (598, 89.5%) and non-medically confirmed (644, 96.4%). There were 70 (10.5%) serious cases. There were no cases that reported a fatal outcome. Case outcome was unknown for the majority of cases (533, 79.8%). Six hundred and twenty-five cases were spontaneous (93.6%), 40 cases were solicited (6.0%) and 3 cases were from clinical studies (0.4%).

### Table 18. Selected Characteristics of Non-Prescription Esomeprazole Cases

Total number of c  
Total number of a  
Age, years

Age group  
n (%)

Gender  
n (%)

<sup>a</sup>May include both serious and non-serious AE terms  
[Source: modified from Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 19, p. 38/79.]

The 4 Month Safety Update (MSU) submitted June 4, 2015 reported no new or unexpected safety findings. Of the 668 cases containing data through 01 September 2014 that were included in the interim safety analysis and submitted as part of NDA 207920, there were 273 (40.9%) cases for which follow-up information was received during the 4 MSU. Of the 273 cases, 214 (78.4%) were considered non-serious and 59 (21.6%) were considered serious. The pattern of reported events was consistent with the safety profile presented in the initial NDA submission and in line with the current non-prescription product labeling.

During the 4 MSU, there were a total of 998 cases involving 2983 AE terms with the use of oral nonprescription esomeprazole. All except 8 cases were reported from the U.S. A total of 119 (12%) of these were serious cases with 794 associated events. Of the 998 cases, 757 (75.9%) case outcomes were not known. Reports of AEs by PT term

are similar for the 4 MSU as for the initial submission for all non-fatal cases. There were reports of 2 deaths with nonprescription esomeprazole in the 4 MSU.

### 8.2.2 Deaths

There were no cases reporting a fatal outcome in association with non-prescription esomeprazole from the initial submission, however, there were reports of two deaths in the 4 MSU. Both fatal cases had esophageal cancer and there was limited information available to assess for a causal relationship.

Case 2014334202 involved a consumer who reported on behalf of his/her brother who died of esophageal cancer “because he wouldn’t take his Nexium as prescribed”. Case 2014358032 involved a consumer who reported on behalf of her husband who died of Stage 4 esophageal cancer approximately 6 weeks after he was diagnosed. He had reflux for a short while and treated it with OTC medications. Both cases contained limited information on therapy start date, cause of death, autopsy findings, circumstances leading to death, relevant medical history, concurrent disease or concomitant medications which makes a causal relationship assessment difficult.

### 8.2.3 Serious Adverse Events – Non-Fatal

Of the 668 cases reported for non-prescription esomeprazole, there were 70 serious cases that reported 546 events (may include both serious and non-serious AE terms).

The mean age of patients comprising the serious subset of cases was 62 years old. The majority of the serious cases (68, 97.1%) were non-medically confirmed; reporting source was unknown for three cases (4.3%) and medically confirmed for two cases (2.9%). The most frequently reported SOCs were Gastrointestinal disorders (112, 20.5%), followed by General disorders and administration site conditions (81, 14.8%), Surgical and medical procedures (71, 13.0%) and Injury, poisoning and procedural complications (43, 7.9%).

The sponsor states that all 70 serious cases had medical history or concurrent medical conditions. Case outcome was unknown for 31 cases (44.3%), not recovered/not resolved for 30 cases (42.9%), recovered/resolved for seven cases (10.0%), and recovering/resolving for two cases (2.9%).

The most frequently reported clinical AEs were Gastroesophageal reflux disease (17, 3.1%), Dyspepsia (12, 2.2%), Nausea (12, 2.2%) and Malaise (11, 2.0%). Most of the frequently reported clinical events for the serious cases were either considered to reflect the underlying disease or represented terms which are listed as Adverse Drug Reactions (ADRs) for esomeprazole in the product labelling. Table 19 below presents most frequently reported AEs with OTC Nexium 24HR for serious cases.

**Table 19. Most Frequently Reported Adverse Events with Non-Prescription Esomeprazole by PT for Serious Cases (Cut-Off  $\geq$  1%)**

weight decreased  
Dyspnoea  
Abdominal discomfort  
Chest pain  
Dizziness  
Dysphonia  
Vomiting  
Abdominal pain upper  
Myocardial infarction  
Total

Note: totals are for all cases, not just data shown in the table.

[Source: Sponsor's submission, Mod 5.3.5.3, Interim Update of Safety, Table 23, p.44/79.]

According to the sponsor, the most commonly reported term "Intentional drug misuse" is not primarily related to safety/adverse reaction of esomeprazole, but often reflects situations where patients intentionally and inappropriately used non-prescription esomeprazole not in accordance with the authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply. Examples relating to misuse described situations where consumers took medication intended for others (using neighbor's/wife's/husbands medication) or that they sometimes took one extra dose or decreased daily dose. There was no evidence of any new safety issues from the cases reporting intentional drug misuse.

"Drug ineffective" described cases when the reporter clearly communicated an assessment that the therapeutic effect was absent or less than expected. The majority of these cases were from consumers who had previous experience with prescription PPIs. The duration of use was not provided for vast majority of the cases.

"Drug dose omission" described situations where patients were not able to receive their medication or were out of medication. "Drug dose omission" mostly involved patients who ran out of esomeprazole. "Off label use" refers to situations where a physician prescribed non-prescription esomeprazole for medical purposes outside the conditions of the label/instructions.

*Medical Officer Comments:*

*An Information Request was sent to the sponsor May 27, 2015 requesting submission of the Adverse Event Forms for all unlabeled Serious AEs from the non-prescription database. The sponsor responded June 5, 2015; of note, 27 reports for serious, unexpected events for OTC Nexium were submitted and one report of a death (79 yo female with multiple co-morbidities). The MedWatch form for the death was dated 6/1/2015 for event date 3/9/2011 (prior to approval of OTC Nexium). This consumer had a history of heart disease and atrial fibrillation and had taken multiple medications; cause of death was not known. On brief review of the 27 reports by this reviewer, just a few appeared to be clearly associated with Nexium 24HR OTC 20 mg. Many involved consumers who did not take the medication as labeled (e.g., twice a day), and consumers taking multiple medications including other PPIs and/or a complicated medical history.*

*Events included blood in the stool or rectum (four cases); bleeding ulcer (two cases); cancer of esophagus (one), gastric cancer (one); deafness (two; 62 yo and 71 yo); myocardial infarction (one; limited information). The remainder 15 cases appeared to be due to the underlying condition (e.g., gastritis) or unrelated (e.g., fall off a ladder, anxiety). None appear to be clearly related to use of Nexium OTC.*

#### 8.2.4 Common Adverse Events

Table 20 below presents the most frequently reported AEs with OTC Nexium 24HR.

**Table 20. Most Frequently Reported Adverse Events with Non-Prescription Esomeprazole by PT (cut off 5%)**

Preferred Term	Count	Percentage
Intentional drug misuse	329	49.3
Drug ineffective	164	24.6
Drug ineffective for unapproved indication	55	8.2
Gastroesophageal reflux disease	48	7.2
Dyspepsia	45	6.7
Malaise	44	6.6
Nausea	43	6.4
Drug dose omission	42	6.3
Abdominal pain upper	39	5.8
Diarrhoea	34	5.1
Off label use	34	5.1

[Source: modified from Sponsor's submission, Mod 5.3.5.3, Interim Update of Safety, Table 21, p.40/79.] There were five cases of drug interactions reported, all of which were non-serious and two of which were medically confirmed. There were three females and one male; gender was unknown in two cases. The AEs reported in these five cases were: Malaise, Gastrointestinal disorder, Feeling abnormal and Pain. The suspected drugs with which the drug interactions were reported were: etanercept, lorazepam, levothyroxine, and citalopram. Additional details for these cases were not provided. Of note, there were no cases of reporting an interaction with mycophenolate mofetil during this reporting period.

### 8.2.5 Analyses by age, gender and race

In the majority of cases, age was unknown (386, 57.8%) and there were limited cases (n=nine) of non-prescription use in children; the AEs reported for children aged 0-17 yo were all non-serious. Where age was available, in general, the overall AE pattern was similar among different age groups within the adult population treated with nonprescription esomeprazole. According to the sponsor, many of the most frequently reported terms reflected the patient's underlying disease that is the reason for treatment; or other terms known to be associated with esomeprazole therapy such as diarrhea, abdominal pain, nausea, vomiting, malaise, headache, rash and dizziness. See Table 21.

**Table 21. Most Frequently Reported Adverse Events with Non-Prescription Esomeprazole by PT and Age Group: Global (total >5%)**

Preferred

Intentional  
Drug ineffe  
Drug ineffe  
indication  
Gastrooesop  
Dyspepsia  
Malaise  
Nausea  
Drug dose c  
Abdominal  
Off label us  
Diarrhea

[Source: modified from Sponsor's submission, Interim Update of Safety, Mod 5.3.5.3, Table 24, p.47/79.]

There were nine cases involving children (age ranging from nine months to 16 years of age). Of these nine cases, four were girls and three were boys; in two cases, gender was unspecified. Associated events reported in two or more cases included Intentional drug misuse (six), Accidental exposure to the product by child (two), Upper abdominal pain (two), and Tremor (one). A 15-year-old girl had been receiving prescription esomeprazole (40 mg for 10 months). She was then transitioned to non-prescription esomeprazole 20 mg per day; the outcome was unknown. There was an overdose reported with a seven year old girl, where the dose strength and the outcome were not reported. In two cases, the children had a pertinent medical history (abdominal disorders and/or GERD); however, it was unclear whether they were instructed to take the non-prescription product by their treating physician. In one case, the boy was prescribed non-prescription esomeprazole for his esophageal ulcer. Limited information was available for case outcome for all the cases. Non-prescription esomeprazole is not indicated for children and the non-prescription esomeprazole label contains clear instructions for use in adults. No new safety concerns were identified.

The sponsor states that there were no trends or pattern indicating differences or clustering of events due to any age-related factors.

Information regarding gender was available in 93.1% of the cases. There were overall more cases received from females than males, 63.2% versus 29.9%. With regard to reported PTs, Gastroesophageal reflux disease, Diarrhoea, Malaise, Dyspepsia, Abdominal pain, Nausea and Vomiting were among the most commonly reported event terms for both men and women.

Approximately one third (35.5%) of the cases contained information with regard to ethnic origin. The majority of cases (205, 30.7%) were in patients of Caucasian ethnic origin. Of the remaining cases, ethnic origin was reported as: Black (16 cases, 2.4%), Native American/Other (8 cases, 1.2%), Hispanic (7 cases, 1.0%), and Asian (1 case, 0.1%). Due to the low case counts in various ethnic groups, it is difficult to draw any firm conclusions of AE pattern in association with ethnicity. With regard to reported PTs, Gastroesophageal reflux disease (GERD), Dyspepsia, Malaise, Nausea, Abdominal pain, and Diarrhoea were among the most commonly reported event terms across various ethnic groups.

#### 8.2.6 Dose and Time to Onset

Time to onset was unknown (595, 74.5%) in the majority of cases, precluding a meaningful assessment. When time to onset was reported, the most common time to onset of the first event was  $\leq 1$  day (93, 11.6%), followed by pre-therapy (27, 3.4%), more than a year (22, 2.8%), between 7 days and  $\leq 1$  month (18, 2.3%), post-therapy (17, 2.1%), between 1 month and  $\leq 6$  month (10, 1.3%), greater than 6 month but less than a year (1, 0.1%), and more than 1 year (22, 3.3%). Analysis and evaluation of these cases was complicated by the fact that consumers often reported a non-specific period of use. For example, where time to onset was  $> 1$  year, consumers reported taking esomeprazole without specifying non-prescription or prescription.

Information with regard to dose was available for 362 (54.2%) of 668 cases. Of the cases that reported dose information, 52 (7.2%) reported a first total daily dose of 20 mg, 249 (37.3%) reported a first total daily dose  $>20$  mg, and 61 (9.1%) reported a dose of other or indeterminate value. Nineteen of the 668 cases (2.8%) reported a dosage ranging from  $>50$ -100 mg. In each of these 19 cases, the patients were using either prescription esomeprazole and/or non-prescription esomeprazole at doses greater than the approved 20 mg dose regimen as indicated in the label for the non-prescription product.

#### 8.2.7 Summary of Information from OTC post-marketing database



There were no new or unexpected safety findings following review of the cases from Pfizer's safety database for non-prescription esomeprazole, including the data from the 4 MSU. Most of the commonly reported AE terms were either considered to reflect the underlying disease or represented terms which are listed as ADRs for esomeprazole in the product labelling. When stratified by age, no consistent age-group dependent pattern emerged. There were limited cases (n=9) of nonprescription use in children. With respect to gender, there were no apparent differences in the overall distribution of adverse event between men and women. Due to the low case counts in various ethnic groups, it is difficult to draw any firm conclusions of AE pattern in association with ethnicity.

*Medical Officer Comments:*

*The adverse events reported are consistent with the known safety profile of the product and no new trends or patterns have been found. In conclusion, the benefit-risk profile of nonprescription esomeprazole continues to be positive.*

## 9 Appendices

### 9.1 Literature Review/References

#### Literature Review for Esomeprazole Active Ingredient (May 1, 2013 through September 1, 2014)

The sponsor submitted a literature review for esomeprazole; for the review articles the search specified "proton pump inhibitor" and "review" in title or abstract in publications in humans during the time period 10 March 2000 through 01 September 2014. 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.

According to the publications that were identified, the following diseases or conditions may be related to the long term use of PPIs: gastric cancer, infections (such as pneumonia and enteric infections including *Clostridium difficile* infection), vitamin B12 deficiency, hypomagnesemia, hypocalcaemia, osteoporotic fractures, interaction with clopidogrel and rebound acid hypersecretion (RAHS). Data relating to short-term PPI use were emphasized when duration of use was known

Few reports were identified that exclusively investigated safety endpoints and the short-term use of PPIs. However, some research on risk of infection with short-term use, particularly in combination with antibiotics for H. pylori and regarding compliance to OTC labels, was found. A Cochrane systematic meta-analysis identified 68 clinical trials where PPIs were used for a short duration (7 to 14 days) in combination with antibiotics for H. pylori eradication. One publication of these 68 trials (1.5%) reported infections in

3.3% (26/788) of *H. pylori* patients treated with rabeprazole or omeprazole plus amoxicillin and clarithromycin. No further information was provided on the nature of infection in the meta-analysis (Yuan et al, 2013) or in the original report (Vakil et al, 2004). No other risk identified among long-term PPI users was reported as an adverse event among these short-term users (Yuan et al, 2013).

The following topics were originally reviewed by AstraZeneca and were included in the summary due to their potential seriousness, together with an evaluation of potential for any safety concern for data available through 01 September 2014. Topics included neoplasm, interstitial nephritis, *Clostridium difficile*, pneumonia, potential interactions with clopidogrel, potential interactions with mycophenolic acid, osteoporosis/osteoporotic fractures, poor nutrient absorption [magnesium and calcium, Vitamin B12, iron deficiency], cardiac events, rebound acid hypersecretion.

The sponsor states that in an article by Haag et al (2009), relevant papers, including national and international guidelines, were reviewed and recommendations were made for appropriate use of OTC PPI therapy. The authors concluded “OTC treatment of typical reflux symptoms (acid regurgitation, heartburn) with antacids and H2RAs is now accepted as safe and results in short term relief of symptoms. There is no evidence of additional risk with OTC PPIs compared to these existing OTC therapies and PPIs are significantly more efficacious”. The sponsor further states that similar conclusions were reached by more recent authors (Corleto et al, 2014). In summary, no new areas of concern regarding the safety profile of esomeprazole were identified.

The sponsor’s 4 MSU included an updated literature search and a total of 468 articles were identified. Reports selected for further review were publications which contained information on a safety topic pertinent to the OTC product and/or short-term use. Nine reports were examined closely involving neoplasm, respiratory infections, nutrient absorption (magnesium) and cardiac events and interaction with clopidogrel. According to the sponsor, a review of the scientific literature did not identify any new safety information regarding the use of esomeprazole.

Of note, in a recent response by the agency to a Citizens Petition regarding requested revision to the labeling for PPIs due to certain safety concerns, the agency believes that the potential serious risks associated with short-term use of a PPI (interaction with clopidogrel, mycophenolate mofetil, methotrexate, risk of *C. difficile*) have been addressed in OTC labeling.<sup>11</sup> Other risks are either associated with long-term use or are not well established.

*Medical Officer Comments:*

*Information related to the literature search does not alter the known safety profile of esomeprazole.*

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<sup>11</sup> FDA response of Oct. 31, 2014 to Public Citizens’ Citizens Petition postmarked Oct. 6, 2011.

## 9.2 Labeling Recommendations

Formal labeling review is undertaken by the IDS team in DNDP; see the review by Mary Vienna. The DMEPA reviewer determined that the proposed proprietary name Nexium 24HR is acceptable. The sponsor's proposed Drug Facts Label and Principal Display Panel (PDP) for Nexium 24HR tablets are shown in Figures 3 and 4, respectively.

### *Medical Officer Comment:*

*The Drug Facts Label is similar to that of the reference drug, Nexium 24HR Capsules, except for the Inactive Ingredients and revised content under (b) (4). The Sponsor does not seek any additional claims than what has been allowed for other approved OTC PPIs, including Nexium 24HR Capsules. 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 on the Drug Facts Label ("Stop use and ask a doctor if ...you get diarrhea"). In addition, the class labeling changes requiring methotrexate and mycophenolate mofetil to be included under the section "Ask a doctor or pharmacist before use if you are taking:" are included.*

*The comments below were discussed at the team meeting on September 1, 2015.*

- *The phrase (b) (4) will be removed.*
- *The (b) (4) in the established name needs to be resolved.*
- *Instructions to consumers to "swallow 1 tablet with a glass of water before eating in the morning" vs taking one hour before eating; current labeling for the Rx product states: "NEXIUM should be taken at least one hour before meals."*

*A meeting was held October 9, 2015 to discuss unresolved labeling issues; see the review by Mary Vienna for full details. These issues will be further discussed with the sponsor and will also impact labeling for Nexium 24HR Capsules.*

- *The (b) (4) in the established name on the Principle Display Panel (PDP).  
The group decided that use of "esomeprazole (b) (4) and "20 mg" is the preferred option for the PDP (b) (4)*
- *Instructions to consumers regarding when to take the medication in relation to meals.  
The group decided to include wording such as "For better results, take at least one hour before meals", to be more consistent with Rx labeling.*

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH A DONOHOE  
10/26/2015

FRANCIS E BECKER  
10/26/2015

Clinical Investigator Financial Disclosure Review

Application Number: 207920

Submission Date(s): February 6, 2015

Applicant: Pfizer

Product: Nexium (esomeprazole magnesium) delayed release tablets, 20 mg

Reviewer: Elizabeth A. Donohoe, M.D.

Date of Review: October 15, 2015

Covered Clinical Study (Name and/or Number): B5141002

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>13</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 style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u></p> <p style="padding-left: 40px;">Significant payments of other sorts: <u>N/A</u></p> <p style="padding-left: 40px;">Proprietary interest in the product tested held by investigator: <u>N/A</u></p> <p style="padding-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u></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 applicant has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21 CFR Part 54 and as recommended in the guidance for

industry: Financial Disclosure by Clinical Investigators.<sup>1</sup> The applicant states that it's financial disclosure information covers the time period from the study start date through one year after the completion of the study. The applicant notes that their disclosure reports information for clinical investigators as that term is defined in 21 CFR Part 54. The applicant provided certification for 13 of the 13 investigators listed in the covered study. Due Diligence activities were required for 0 of the 13 investigators. The information provided does not raise questions about the integrity of the data or the approvability of the application.

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<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm341008.pdf>

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/s/  
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ELIZABETH A DONOHOE  
10/26/2015

FRANCIS E BECKER  
10/26/2015

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 207920**

**Applicant: Pfizer**

**Stamp Date: 2/06/2015**

**Drug Name: Nexium 24 HR DR Tablets**     **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			See DNNDP labeling comments
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Relies on NDA 204655 and 4MSU through 4/13/13; also M5.3.5.3; ISS includes Interim Update of Safety: [4.1]- AZ post market safety update 5/2013-9/2014; [4.2.2] – Pfizer OTC database 5/27/2014-09/01/2014
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Relies on NDA 204655
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				Defer to OCP
15.	Describe the scientific bridge (e.g., BA/BE studies)				Defer to OCP
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product			X	Dose and schedule relies on NDA 204655

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908





## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MedDRA (v.12 or later) coding dictionary was used.
27.	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			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			See M5.3.1.2 Study Report Body, Full Clinical Study Report 12.2.3.1, 12.3.1.1
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Sponsor states that in vitro assessment of alcohol induced dose dumping is not feasible for this dosage form [defer to CMC]
30.	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	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requesting waiver for <18 y/o., per 3/28/14 t-con meeting minutes
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	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.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Per 3/28/14 t-con meeting minutes
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse			X	

<sup>2</sup> 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
	drop-outs) as previously requested by the Division?				
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			See M1.3.4
<b>GOOD CLINICAL PRACTICE</b>					
42.	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			See M5.3.1.2 Protocol or Amendment, 12.1

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES**

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

*None.*

Elizabeth A. Donohoe, M.D.  
 \_\_\_\_\_  
 Reviewing Medical Officer

March 26, 2015  
 \_\_\_\_\_  
 Date

Francis Becker, M.D.  
 \_\_\_\_\_  
 Clinical Team Leader

\_\_\_\_\_  
 Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH A DONOHOE  
03/26/2015

FRANCIS E BECKER  
03/26/2015