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*APPLICATION NUMBER:*

**204655Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

NDA 204655

Esomeprazole magnesium delayed release capsules for frequent heartburn

### Cross-Discipline Team Leader Review

<b>Date</b>	2-March-2014
<b>From</b>	Lesley-Anne Furlong
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	204655
<b>Related IND Prescription NDA</b>	111,185 21153 (also held by AstraZeneca LP)
<b>Applicant</b>	AstraZeneca LP
<b>Date of Submission</b>	30-May-2013
<b>PDUFA Goal Date</b>	30-Mar-2014
<b>Proposed Proprietary Name / Established (USAN) names</b>	Nexium 24 HR/esomeprazole magnesium
<b>Dosage forms / Strength</b>	Delayed release capsules/20 mg
<b>Proposed Indication(s)</b>	<ol style="list-style-type: none"><li>1. Treats frequent heartburn (occurs 2 or more days a week)</li><li>2. Not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect</li></ol>
<b>Recommended:</b>	<i>Approval contingent on satisfactory labeling and no approval issues from the CMC and biostatistics reviews, which were pending when this review was finalized.</i>

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## 1. Introduction

This is a summary review of a new drug application for nonprescription marketing of esomeprazole magnesium delayed-release capsules to treat frequent heartburn. The proposed proprietary name is Nexium 24HR. The current prescription brand name is Nexium.

## 2. Background

While esomeprazole would be a new over-the-counter (OTC) active ingredient, proton pump inhibitors (PPIs) and the proposed indication are familiar to U.S. consumers. OTC omeprazole and lansoprazole were approved in 2003 and 2009, respectively.

Nexium was approved in the United States as a prescription product in 2001 and is indicated for the treatment of gastroesophageal reflux disease (GERD), risk reduction of NSAID-associated gastric ulcers, H.pylori eradication, and hypersecretory conditions including Zollinger-Ellison syndrome (NDA 21153). Prescription labeling allows for adult oral doses ranging from 20 mg once daily to 40 mg twice daily. The proposed over-the-counter (OTC) dose is the lowest adult prescription dose, 20 mg once daily.

The safety and efficacy of esomeprazole 20 mg should be similar to the safety and efficacy of omeprazole 20 mg (the approved OTC dose for omeprazole). Esomeprazole is the S-isomer of omeprazole, which is a racemic mixture of S- and R- isomers. Both isomers are prodrugs that are converted in the acidic compartment of the parietal cell to the same active moiety, an achiral sulphenamide.

The proposed label provides dosing instructions for adults 18 years and older; this is consistent with the other OTC PPI labels. FDA has taken the position that symptoms of heartburn in children should be evaluated by a healthcare provider for safety reasons. In contrast, prescription labeling for Nexium provides pediatric dosing for the GERD indication down to 1 month of age.

Esomeprazole is currently approved in more than 125 countries. According to the applicant, postmarketing experience exceeds 80 million patient-years, and over 91,000 subjects have been exposed to esomeprazole in clinical trials. Nonprescription Nexium was approved in the European Union in Sep 2013; the applicant plans to launch the nonprescription product as "Nexium Control" in Europe in early 2014.

For this application, the main interactions occurred between AstraZeneca and FDA occurred under IND 111,185 and included:

- 13-May-2011: Preliminary responses to questions in a PIND meeting package were sent to AstraZeneca. FDA generally agreed with clinical trial design for the proposed OTC product. FDA also agreed that consumer studies would not be necessary unless the label presented new elements that might impact consumer use. A proposal for submission of stability data was acceptable. AstraZeneca deemed the FDA responses satisfactory, and the meeting was cancelled at their request.

- 22-Jul-2011: FDA provided an advice letter regarding two clinical studies (Studies D96RC00001 and D96RC00002) for the treatment of frequent heartburn
- 15-Jan-2013: FDA sent preliminary responses to AstraZeneca's questions about NDA content and format. The questions were part of a preNDA meeting package. AstraZeneca deemed the FDA responses satisfactory, and the meeting was cancelled at their request.

To support the application, the applicant conducted two identical phase 3 clinical trials that evaluated safety and efficacy in subjects with frequent heartburn. The applicant also submitted a bioequivalence waiver supported by dissolution data and an IVIVC similarity assessment comparing the OTC capsule to the prescription capsule. The difference between the prescription capsule and the proposed OTC capsule is [REDACTED] (b) (4)

The submission contains two phase 3 study reports, both entitled "A Phase III Multi-Center Randomized, Double Blind, Placebo-Controlled, Parallel Group Trial of 14 Day Treatment with Esomeprazole 20 mg Once Daily in Subjects with Frequent Heartburn." In addition, the applicant has provided an analysis of postmarketing safety data and the literature. A four-month safety update was submitted on 27-Sep-13.

In writing this summary review, I have considered the following primary FDA reviews:

- Dr. Alice (Chi-Ming) Tu's label, labeling and packaging review
- Dr. Stephen Langille's product quality microbiology review
- Dr. Jane Filie's clinical safety review
- Dr. Robert Dorsam's pharmacology/toxicology review
- Dr. Tien-Mien Chen's biopharmaceutics review
- The regulatory labeling review of Mary Vienna, RN, MHA
- Dr. Farrokh Sohrabi's clinical review of efficacy
- The environmental assessment of James P. Laurensen, Office of Pharmaceutical Quality

The following were pending when this review was finalized:

- Dr. Sheldon Markofsky's CMC review, including final determinations on inspections
- Dr. Wen Jen Chen's biostatistics review

### 3. CMC/Device

Figure 1 illustrates that the product is a sealed, two-piece, hard gelatin capsule. The capsule is identical to the prescription capsule except for a radial gelatin band covering the junction of the cap and base of the capsule. The gelatin band serves as a tamper-evident seal.

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**Figure 1. Image of Nexium 24 HR**



Source: applicant's submission

Dr. Dr. Tien-Mien Chen recommended approval from a biopharmaceutics perspective. I have read his review and concur. Dr. Chen's recommendation was contingent on the applicant committing to tightening the dissolution acceptance criterion from  $Q = \frac{(b)}{(4)}\%$  at 30 minutes to  $Q = \frac{(b)}{(4)}\%$  at 30 minutes and updating the drug specification section of the application. The applicant made the commitment on 20-Feb-2014 and updated the drug product specification section of the application on 25-Feb-2014.

The biopharmaceutics section of the application included

- A comparative dissolution profile
- A biowaiver request
- An IVIVC simulation for plasma PK profiles

Dr. Chen concluded that dissolution of the esomeprazole capsules was not affected by the tamper band, and the simulation of plasma profiles supported the biowaiver.

The capsule contains enteric coated esomeprazole pellets. AstraZeneca intends to produce: 2-count sample bottle, 14-count bottle, 28-count (2x14 count bottles) and a 42-count (3x14 count bottles). The 42-count size represents a full year of maximum OTC therapy, and is the largest count size approved for the other OTC PPIs, which are similarly packaged in 14-count bottles with up to three bottles in one carton.

At the time this review was finalized, the CMC review had not been finalized; however, the CMC review team had not conveyed any approvability issues at team meetings.

Dr. Stephen Langille reviewed the product quality microbiology and recommended approval.

The applicant's environmental assessment (EA) was reviewed by FDA toxicologist James P. Laurenson. Dr. Laurenson determined the EA was adequate and concluded that approval of Nexium 24HR is not expected to have a significant impact on the human environment.

#### **4. Nonclinical Pharmacology/Toxicology**

Dr. Dorsam recommended approval from a pharmacology/toxicology perspective. The reader is referred to Dr. Dorsam's review for a detailed description of the pharmacology/toxicology profile of esomeprazole. There were no new nonclinical data in the submission.

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Prescription labeling notes that the carcinogenic potential of Nexium was assessed in studies using omeprazole. In two 24-month oral carcinogenicity studies in rats, omeprazole at doses about 0.7 to 57 times the human dose of 20 mg/day produced gastric enterochromaffin cell (ECL) hyperplasia and carcinoids in a dose-related manner in both male and female rats. This was also observed for other PPIs and appears to be a class effect.

During the review cycle for the current application (4-Feb-2014), the applicant submitted changes in labeling involving the pregnancy section of prescription labeling; the changes were made at the behest of the FDA and are currently under review. The Pregnancy Category (b) (4) C, and information about a preclinical study done by a different sponsor was added to the pregnancy section. The information noted that changes in bone morphology were observed in the offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 33 times an oral human dose of 40 mg.

Overall, however, the reproductive data are reassuring. Heartburn is a common condition in pregnancy; substantial and reassuring observational human data including over 1200 women are noted on current Rx labeling. The Rx labeling that is under review describes four observational studies including over 3000 women exposed to omeprazole during the first trimester of pregnancy. The studies did not detect any specific pattern of congenital anomalies that would suggest human teratogenicity. Studies with esomeprazole in rats (treated with doses up to 57 times the human dose) and in rabbits (treated with doses up to 35 times the human dose) have revealed no evidence of impaired fertility or harm to the fetus.

However, as with most drugs, there are no adequate and well-controlled studies of Nexium use in pregnancy. The excretion of esomeprazole in breast milk has not been studied.

The applicant notes two observational studies linking prenatal exposure to PPIs to an increased risk of asthma. Both studies have limitations (b) (4)

*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) (4) C in the Rx labeling, and is acceptable to me.*

(b) (4)

## 5. Clinical Pharmacology/Biopharmaceutics

Prescription (Rx) labeling states that Nexium should be taken at least one hour before meals because the area under the curve (AUC) is decreased after food intake by 45 to 53%; however, for the heartburn indication, dosing in the phase 3 studies was identical to the proposed OTC directions: capsules were swallowed whole with a glass of water once a day before eating in the morning.

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*Comment: The proposed OTC dosing instructions are the same as those used in the clinical trials to support the heartburn indication and are acceptable.*

Rx labeling notes the following:

- Dose adjustment in the elderly is unnecessary.
- No dose adjustment is needed for patients with mild to moderate liver insufficiency; a dose of 20 mg daily should not be exceeded in subjects with severe liver insufficiency.
- No adjustments are needed for patients with renal insufficiency.
- Gender-based dosing is unnecessary.

Current Rx labeling identifies the following drug-drug interactions (DDIs):

- Changes in the serum concentrations (increases and decreases) of certain antiretrovirals used to treat patients with human immunodeficiency virus
- Possible interference with absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, atazanavir, iron salts, and digoxin)
- Decrease in exposure to the active metabolite of clopidogrel
- Decrease in diazepam concentration
- Changes in prothrombin time in patients taking warfarin
- Increase in the concentration of cilostazol (dose reduction of cilostazol is recommended)
- May increase serum levels of tacrolimus
- May increase serum levels of methotrexate

*Comments: Proposed labeling for DDIs is the same as omeprazole labeling and addresses all but the interaction with iron salts and methotrexate under the header “Ask a doctor or pharmacist before use if you are taking.”*

*Regarding iron salts, a short-term decrease in absorption of iron salts does not raise a clinical concern and has not been added to the OTC PPI labels.*

*The interaction with methotrexate was added to Rx labeling for PPIs in 2012 based on a review of literature and AERS reports. Rx labeling notes that use of PPIs with methotrexate, primarily high dose methotrexate, may elevate levels of methotrexate. I agree with Dr. Filie that methotrexate should be added to the OTC label under the header “Ask a doctor or pharmacist before use if you are taking” because increased levels of methotrexate could cause adverse effects. This is a class effect; if added to OTC esomeprazole labeling it should also be added to the lansoprazole and omeprazole OTC labels.*

## 6. Clinical Microbiology

Not applicable

## 7. Clinical/Statistical- Efficacy

The applicant demonstrated efficacy for the frequent heartburn indication in two Phase 3 clinical trials, Study D961RC00001 and Study D961RC00002 (called Study 1 and Study 2 in this review). The studies are briefly summarized here; details can be found in Dr. Sohrabi's review.

Both studies were randomized, double-blind, placebo-controlled studies in subjects with frequent heartburn, which was defined as heartburn occurring two or more days a week. The treatment duration was 14 days. There was a seven-day run-in period during which subjects had to be compliant in reporting heartburn symptoms daily for at least five days. Subjects were 18 years of age and older and could not have a diagnosis of GERD.

A total of 657 subjects were treated in both studies. A total of 333 subjects received esomeprazole 20 mg and 324 received placebo. The safety analysis included all 657 randomized subjects who took at least one dose of placebo or esomeprazole. The efficacy analysis used the full analysis set (FAS), defined as all randomized subjects who took at least one dose of treatment, had a valid baseline heartburn assessment, and had at least one valid post-baseline assessment. The FAS included a total of 651 subjects. The treatment groups were well balanced for baseline characteristics.

The primary efficacy variable was percentage of heartburn-free 24-hour days defined as the number of days when the subject had a heartburn severity score of zero during days 1 to 14, divided by 14. Both studies showed a statistically significant higher percentage of heartburn-free days in subjects treated with esomeprazole compared with placebo. Results were similar for both studies.

Table 1 summarizes the efficacy data by individual study. The overall difference between groups was 14%, or about 2 additional heartburn-free days over 14 days for the esomeprazole group compared with the placebo group.

**Table 1. Percentage of heartburn-free 24-hour days during 14 days of treatment by ANCOVA between esomeprazole 20 mg and placebo (Full analysis set)**

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

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

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

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

Source: Dr. Sohrabi's DGIEP review, Table 8, adapted from Sponsor's Table 10, page 34, Summary of Clinical Efficacy

*Comment: The effect of esomeprazole is comparable to the effect of lansoprazole in earlier trials of similar design. Lansoprazole 15 mg (Prevacid 24HR, NDA 22327) had a similar placebo-subtracted effect on the percentage of heartburn-free days (difference of 14% in one study and 21% in the other for 2-3 additional heartburn-free days over 14 days for the lansoprazole group compared with the placebo group.) The OTC omeprazole NDA used a different primary endpoint.*

A sensitivity analysis wherein subjects with missing data days were assumed to have heartburn was supportive of the primary endpoint.

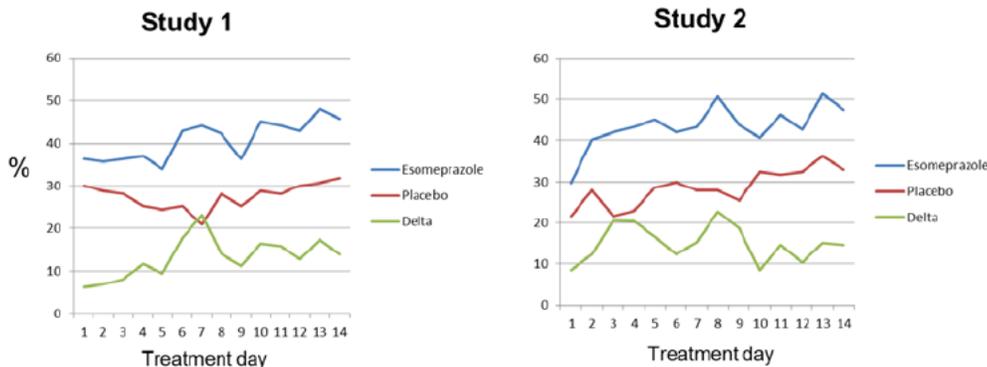
There were a five pre-specified secondary endpoints in both studies. The reader is referred to Dr. Sohrabi's review for details.

Dr. Sohrabi discussed the proposed labeling claim, (b) (4) may take 1 to 4 days for full effect, (b) (4)

None of the prespecified secondary analyses evaluated heartburn free subjects in the first 24 hours. (b) (4)

he data on heartburn-free days are nicely illustrated in Figure 2 , reproduced from Dr. Sohrabi's review:

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



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

Dr. Sohrabi evaluated the clinical reviews for OTC omeprazole and OTC lansoprazole and found that:

- the treatment difference favoring omeprazole over placebo in the first 24 hours was 17% in one trial and 15% in the other
- the treatment difference favoring lansoprazole over placebo in the first 24 hours was 17% in one trial and 13% in the other
- the treatment difference favoring esomeprazole over placebo in the first 24 hours was only 8% in one trial and 6% in the other

*Comment: I concur with Dr. Sohrabi that the esomeprazole data do not rigorously support the labeling claim (b) (4) I recommend removing this phrase. The applicant may object as removal could result in a marketing disadvantage. The applicant may be able to provide data from PK/PD studies to support the language. For example,*

*if the applicant can provide PK data showing highly similar PK of the common active metabolite of the prodrugs, esomeprazole and omeprazole, this may be reasonable support to allow the claim that*

(b) (4)

Subgroup analyses on gender, age, and race did not raise any efficacy concerns. Although point estimates of effects varied across different subgroups, particularly racial and ethnic subgroups, these analyses did not show statistically significant differences among subgroups. Efficacy trended positive in all groups evaluated.

## 8. Safety

The applicant states that as of 31-Dec-2012, more than 91,000 subjects have been exposed to esomeprazole in clinical trials, and worldwide prescription exposure exceeded 80 million patient-years. No new safety signals or trends were found in the two Phase 3 studies submitted for the present application, and no new safety concerns were identified in the postmarketing review.

Prescription labeling identifies known hypersensitivity to PPIs as the only contraindication to Nexium use. The warnings and precautions on labeling either are not relevant to short-term OTC use or are adequately covered by proposed OTC labeling. Esomeprazole is not a drug of abuse.

Prescription labeling identifies the most commonly occurring adverse reactions in association with Nexium use as headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth.

### 8.1 Safety in Clinical Trials

No new safety signals were detected in the two clinical trials performed for this application.

The applicant pooled the safety data from the two phase 3 trials. Of 657 subjects in these two trials, 333 received at least 1 dose of esomeprazole 20 mg and 324 subjects received placebo. Both studies had the same design. Each had a 14-day treatment period and a 7-day follow-up period.

The treatment groups were well-balanced for demographic characteristics. The median duration of exposure was 14 days.

There were no on-treatment deaths or serious adverse events (SAEs). There were three discontinuations for adverse events (AEs): one subject in the esomeprazole arm discontinued for sinusitis and two subjects in the placebo arm discontinued (one for cholelithiasis and one for nasopharyngitis). A total of 40 (12%) of subjects in the esomeprazole arms experienced at least 1 treatment-emergent AE (TEAE); 31 (10%) of subjects in the placebo arm experienced a TEAE. The most frequently reported AE in the esomeprazole arm during the treatment period was constipation (n=3); during the follow-up period, nausea (n=4). Subgroup analysis by race, gender, age, and ethnicity did not detect a different safety profile among subgroups.

*Comment: The symptoms of cardiac ischemia and GERD overlap somewhat; chest pain is a symptom of both conditions. In her review, Dr. Filie describes two subjects who had serious cardiac events*

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*during the run-in phase of the trials. A 45-year old male who had baseline non-specific ST-T wave changes on his ECG was dispensed placebo during the run-in phase and suffered an acute cardiac arrest resulting in death. A 60-year-old male with a history of cardiac disease, heartburn, and a normal ECG had a well-documented myocardial infarction during the washout period before the placebo run-in phase of the trial. Of note, these two subjects suffered serious cardiac events while they were under the care of physician investigators, and not under simulated OTC conditions.*

## **8.2 Postmarketing Safety**

Overall, the analysis of postmarketing data did not reveal new safety signals or any safety signals suggesting that esomeprazole has risks that distinguish it from omeprazole and lansoprazole, the PPIs that are already approved for OTC use.

In general, it is difficult to determine causality or incidence from spontaneously reported postmarketing cases. The spotty quality of the case reports, under-reporting due to the voluntary nature of reporting, the lack of a control group, use of concomitant medication, and various biases and confounders make it difficult to jump from association to causality.

Esomeprazole was first approved in the United States in Feb-2001. As of 31-Dec-2012, Sanofi estimates that worldwide exposure exceeded 80 million patient-years and U.S. exposure was about 36 million patient-years.

The postmarketing safety review included analysis of data in five different safety databases

1. Sanofi's internal safety database (Sapphire) (10-Mar-2000 through 31-Dec-2013)
2. FDA Adverse Events Reporting System (AERS) (Feb-2001 through second quarter 2012)
3. World Health Organization (WHO)/Vigibase (Nov-2000 through Oct-2012)
4. American Association of Poison Control Centers (AAPCC)/National Poison Data System (2001-2011)
5. Drug Abuse Warning Network (DAWN) (2004 to 2010, the last available year)

There is a much overlap among the first three databases. For esomeprazole, the largest general database was the Sapphire database, briefly described below. Dr. Filie provides a detailed description of postmarketing data from all databases in her review. Findings were similar across the databases. Postmarketing surveillance, both by FDA (FAERS) and the applicant, has been ongoing since prescription Nexium entered the market. Most if not all of the serious U.S. cases have been previously submitted for FDA review.

The applicant also provided a literature review and evaluation of specific safety topics, also analyzed by Dr. Filie.

### Sapphire Database:

In the Sapphire database, there were 69,032 case reports involving 163,030 AE terms. U.S. reports comprised 52,161 cases and 129,657 AEs. Most of the reports came from consumers and were not medically confirmed.

Focusing on U.S. cases, there were 1186 fatal outcomes and 8564 serious AEs. The average age for all cases was 60 years; for fatal cases, 68 years. Most frequently reported AEs by PT for fatal cases are shown in Table 2. A total of 315 cases were medically confirmed. The applicant provided MedWatch forms for the fatal cases.

*Comment: I have reviewed a sampling of the MedWatch forms reporting U.S. deaths and have not found any cases where the death is clearly linked to drug use. Most of the cases have too few details to draw any conclusions. The following is a sample narrative to illustrate the difficulty: "A 74 year old had been receiving Nexium via the Patient Assistance Program. He expired. The date and cause of death were not reported."*

The applicant states that most of the cases with "death" reported as an AE come from patients participating in data collection programs that do not actively solicit AE data. Analyses by gender, race, and age did not reveal any unusual subgroup patterns.

The applicant subjected case reports of myocardial infarction, cerebrovascular accident, and neoplasm to "extended medical review." For the most part, reports contained limited information. For malignancy, there was no clustering in specific types of malignancy. Case reports for cardiovascular events did not provide a clear link to drug use.

**Table 2. Most frequent reported AEs by PT for fatal U.S. cases (cut-off 1%)**

AE Preferred Term	Case Count	Percentage
Death	766	46.03
Myocardial infarction	47	2.82
Neoplasm malignant	39	2.34
Lung neoplasm malignant	29	1.74
Pneumonia	26	1.56
Chronic obstructive pulmonary disease	25	1.50
Cardiac disorder	23	1.38
Cardiac failure congestive	22	1.32
Cerebrovascular accident	18	1.08
Cardiac arrest	17	1.02

Source: Applicant's Summary of Clinical Safety, eCTD section 2.7.4, page 54

The most frequently reported AEs (>2%) for serious cases, excluding death, included drug dose omission (3.6% of reports), GERD (2.6%), and malaise (2.27%).

The most frequently reported AEs were typical of either the underlying diseases or the known AEs related to esomeprazole, such as diarrhea, nausea, and headache. There were no important differences in AE patterns between dose groups defined as 20 mg, 40 mg, and other/unknown.

The applicant and Dr. Filie concluded that there were no new or unexpected findings in the review of the Sapphire database; I concur.

### AAPCC's National Poison Data System:

The AAPCC's National Poison Data system contained 21,566 reported exposures with 9379 associated clinical event (CE) terms. The most common CE was drowsiness/lethargy (15%), vomiting (7.5%), tachycardia (6.9%) and nausea (4.9%). In cases where the only ingested substance was esomeprazole, the CEs were characterized as having no effect (25%), minor effect (30%), or moderate effect (5.2%). None had major clinical effect.

There were 18 reports of deaths, all of which were reported as intentional and included ingestion of multiple drugs.

### Four-month Safety Update

On 27-Sep-2013, AstraZeneca submitted a four-month safety update that included postmarketing AE reports received by AstraZeneca from 1-Jan-2013 through 30-Apr-2013 and a summary of the literature search covering the same time interval. The estimated patient exposure was 3 million patient-years worldwide and 1 million patient-years in the United States. The mean age of patients in postmarketing case reports was 60 years of age.

Overall, there were 28 fatal cases associated with 79 AE terms. Sixteen fatal cases originated the United States. The mean age of U.S. patients in the fatal case reports was 68 years old, with a range of 50-90 years. "Death" was (unhelpfully) the most commonly only reported event term. For the U.S. cases, no event other than death (n=10) was reported more than twice. Events involving the cardiovascular system were reported in U.S. reports (cerebrovascular accident (n=2), myocardial infarction (n=2), cerebral thrombosis (n=1)).

*Comment: GERD and myocardial infarction share chest pain as a presenting symptom. While it is possible that some of the cases of myocardial infarction could have been misdiagnosed as GERD in the prescription setting, it is not possible to determine whether this happened from the scant data in postmarketing reports. Myocardial infarction certainly does occur regardless of PPI use in older adults, and the average age in the case reports was 60 years (and 68 years for fatal cases).*

## **8.2 Special Safety Topics**

### Abuse Potential

No potential for abuse or misuse has been identified from the postmarketing data, including the DAWN Data. No signals for abuse have been identified in clinical trials and esomeprazole is not known to produce neuropsychiatric effects.

### Overdose

Exceeding recommended doses has not been clearly associated with a significant safety issue. There were 229 cases reports of overdose in the Sapphire data base: 35 were serious, including 3 with fatal outcome. Causality could not be ascertained due to confounding by multiple other drugs and/or

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limited information. Rx labeling states that the “The symptoms described in connection with deliberate Nexium overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful.” Review of data from AAPCC’s National Poison Data System was consistent.

## 9. Advisory Committee Meeting

Not applicable

## 10. Pediatrics

The application triggers the Pediatric Research Equity Act because of the new indication. The applicant is requesting a waiver for all pediatric populations. The proposed labeling is for adults 18 years and older. The Agency has waived pediatric studies for the other OTC PPIs because “it would not be safe to use this medication OTC in the pediatric population since the underlying causes for heartburn in children should be evaluated by a healthcare professional.”<sup>1</sup> I concur with the request for a waiver of pediatric studies. Proposed labeling states “children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.” The labeling is consistent with prior OTC PPI labels and is acceptable to me.

The pediatric plan was present to FDA Pediatric Review Committee (PeRC) on January 22, 2014 and the PeRC agreed with a full waiver “because the product would be ineffective and/or unsafe for pediatric patients.”

## 11. Other Relevant Regulatory Issues

The application contains a signed debarment certification and the appropriate certifications regarding financial interests for all the clinical investigators who contributed to the covered studies submitted in the application.

Dr. Sohrabi, in consultation with the Office of Scientific Investigations, determined that no site inspections were necessary for the clinical trials.

The application is a 505(b)(1) application.

## 12. Labeling

Only a few highlights of labeling are discussed in this section. Detailed review of labeling can be found in the DNRD (Mary Vienna, RN, MHA) and DMEPA (Dr. Tu) labeling reviews. Proposed labeling is almost identical to the labeling of OTC omeprazole and, like OTC omeprazole, includes a

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<sup>1</sup> See, for example, Dr. Leonard-Segal’s summary review for lansoprazole, NDA 22327, 11-May-2009

package insert. The Appendix contains my proposed edits to the text in Drug Facts Label and Package Insert.

The proprietary name is Nexium 24HR was acceptable to DMEPA and is acceptable to me.

The rest of the proposed labeling is highly similar to the Drug Facts Labeling (DFL) for Prilosec OTC (NDA 21229) and Prevacid 24HR (NDA 22327), two drugs in the same class with the same indication. The package insert (PI) seems to repeat much of the material on the Drug Facts labeling and its purpose is unclear to me; nonetheless, it is similar to package inserts for other OTC PPIs.

Dr. Tu evaluated labeling and had several formatting recommendations around an inaccurately-depicted graphic image of the capsule and formatting of proprietary and established names. I concur with her recommendations.

Dr. Tu also provided a comment for the Division to consider about the depiction of the established name on container and carton labeling: “esomeprazole magnesium delayed-release capsules, 22.3 mg.” Dr. Tu asks if the mg amount should be 20 mg, the amount of esomeprazole delivered by esomeprazole magnesium capsules. Dr. Tu’s proposal is a clearer presentation to me and I would like to see the change. The Rx label uses 20 mg, the amount of active moiety, and prescribers are accustomed to prescribing Nexium as 20 or 40 mg tablets. Also, there are other salts of PPIs that could eventually find their way to the OTC marketplace, and the subtleties of molecular weights of salts and active moieties are not helpful to consumers. OTC products are not consistent in this matter: for example, Advil Liqui-gels has a PDP that lists only the mg amount of the active moiety. On the other hand, Prilosec OTC has the mg amount of the salt appearing on the principle display panel (PDP). On balance, I think that the mg amount (20 mg) of the active moiety should be displayed with the established name on the container and carton labeling.

In her regulatory labeling review, Mary Vienna noted that the product graphic on labeling matches the prescription product, rather than the proposed product with its tamper-resistant band. She recommends that the graphic be removed or be changed to an accurate depiction of the proposed product; I concur. This inaccurate graphic appears multiple times on labeling and should be removed or corrected.

Mary Vienna also recommend removing the phrase (b) (4) which appears on the package insert (PI). The (b) (4) doesn’t appear on any approved omeprazole labeling or PIs (the historically approved ones, as OTC omeprazole products no longer contain a PI).

The (b) (4) does appear on the PI for Prevacid; however, the Prevacid application contained data to support (b) (4). Nonetheless, although the Prevacid application proposed the (b) (4) on the PDP, this was not approved – not for lack of clinical data, but because of difficulties defining (b) (4) and (b) (4) could be a symptom of clinical conditions that should be treated by a physician (see the Leonard-Segal/Griebel summary review, 5/11/2009). For these reasons, I concur with the recommendation to remove the (b) (4) phrase.

While I concur with the remaining DNRD recommendations, I also think that, except for the section called “Tips for Managing Heartburn,” the PI is unnecessary and the applicant could be offered the option of removing it from all package sizes. The only information on the PI that isn’t promotional or doesn’t repeat what is already on the DFL is found in the “Tips” section. This section is buried near the end of the PI in otherwise duplicative text where it is unlikely to be read. FDA approved the removal of the PI for Prilosec OTC (omeprazole) on 9-Sep-2009 under NDA 21229, S-013. For

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Prilosec OTC, the “Tips” section was placed on the outer carton labeling when the PI was eliminated. This seems like a reasonable approach to me. Alternatively, the PI could delete be much simplified to include the “Tips” section and little else.

In her review, Dr. Filie has two recommendations, both of which, if implemented, would apply to all OTC PPIs:

- 1) Add methotrexate to the list of drugs that follows the DFL header “Ask a doctor or pharmacist before use if you are taking.”
- 2) Move symptoms of cardiac ischemia out of the DFL header “Ask a doctor before use if you have” and elevate them to the header “Do not use,” followed by text indicating that these symptoms can be signs of a serious condition and the consumer should see the doctor.

I concur with Dr. Filie’s recommendations, and suggest that they be conveyed to the sponsors of all OTC PPIs as class labeling changes, either during labeling negotiations for Nexium 24 HR or shortly thereafter.

Regarding methotrexate, Rx labeling has recently been updated to include cautionary language that use of PPIs with methotrexate, primarily high dose methotrexate, may elevate levels of methotrexate. Although the prescriber of methotrexate should be aware of all the medicines a patient is using, an OTC drug that is used intermittently can sometimes be missed during a medical history. Adding methotrexate to the list may be helpful to some consumers who are taking methotrexate.

Regarding moving the symptoms of cardiac ischemia, Dr. Filie notes that this is consistent with the labeling regulations in 21CFR 201.66(c)(5)(iii). The two serious cardiac events observed in the run-in phase of the clinical trials for the heartburn indication were a reminder that chest pain that is cardiac in origin needs medical attention.

The applicant will likely want to know that both of Dr. Filie’s proposed changes will be requested of all OTC PPIs as class labeling changes.

I concur with Dr. Sohrabi that the esomeprazole data do not adequately support the labeling claim (b) (4) I recommend removing this phrase.

The applicant may object as removal could result in a marketing disadvantage. There may be data from PK/PD studies to support the language; if, for example, the applicant provides PK data showing highly similar PK of the common active metabolite of the esomeprazole and omeprazole, this would be reasonable support to allow the claim that (b) (4)

There may be CMC recommendations regarding certain elements of labeling when the CMC review is finalized.

## 13. Recommendations/Risk Benefit Assessment

### 13.1 Recommended Regulatory Action

I recommend an approval action contingent on satisfactory labeling negotiations and recommendations of approval from FDA's CMC and biostatistics reviewers, whose reviews were pending when this review was finalized.

### 13.2 Risk Benefit Assessment

The risk/benefit profile of Nexium 24HR is comparable to the risk/benefit profiles of already approved OTC PPIs, omeprazole and lansoprazole.

The benefit of Nexium 24HR for the treatment of frequent heartburn was demonstrated by two clinical trials. The benefit is comparable to the benefit shown for lansoprazole in two similarly designed clinical trials for the same indication. Benefit for omeprazole was shown in trials of different design; however, the benefit of omeprazole and esomeprazole should be very similar, as both are pro-drugs for the same active metabolite.

The risks identified for esomeprazole also appear comparable to the risks identified for omeprazole and lansoprazole. No new unique safety signals for esomeprazole were identified in the clinical trials or postmarketing databases.

### 13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

Routine postmarketing pharmacovigilance is appropriate.

### 13.4 Recommendation for other Postmarketing Requirements and Commitments

None

### 13.5 Recommended Comments to Applicant

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 to PPIs and childhood asthma. Study results will be available in the fourth quarter of 2014. The following minor comment may be conveyed in the NDA action letter:

(b) (4)

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## Appendix

### CDTL Recommendations for Edits of the Drug Facts Label and Package Insert:

(b) (4)

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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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LESLEYANNE FURLONG  
03/02/2014