CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204655Orig1s000

OTHER REVIEW(S)

Labeling Review for Nexium®24HR Delayed-Release Capsules *Draft Labeling*

SUBMISSION DATES:	May 30, 2013 September 27, 2013 October 18, 2013 November 18, 2013
NDA/SUBMISSION TYPE:	204-655
ACTIVE INGREDIENTS:	Esomeprazole magnesium, 22.3 mg
DOSAGE FORM	Delayed-release capsule
SPONSOR:	AstraZeneca LP Judy Firor Director, Regulatory Affairs 302-886-7539
REVIEWER:	Mary R. Vienna, RN, MHA, DNRD, ODE IV
TEAM LEADER:	Ruth E Scroggs, PharmD, DNRD, ODE IV
REGULATORY PROJECT MANAGER	Jeff Buchanan, Project Manager, DNCE, ODE IV

I. BACKGROUND

AstraZeneca LP (AstraZeneca) submitted on May 30, 2013, and as amended September 27, October 18, and November 18, 2013 an original new drug application (NDA) 204-655, under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act (FD&C Act). Under NDA 204-655, the sponsor proposes to change the proton pump inhibitor (PPI) esomeprazole magnesium 22.3 mg to over-the-counter (OTC) status by adding a new non-prescription indication. The proposed OTC indication is for the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of age and older.

AstraZeneca requested Agency approval of the proposed OTC proprietary trade name Nexium®24HR. The Division of Medication Error Prevention and Risk Management reviewed the proposed proprietary name and concluded that it was conditionally acceptable in their

September 16, 2013 communication to the sponsor. A pediatric waiver was requested by the firm and has been granted.

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
2-count immediate container (bottle)	N/A	October 18, 2013, replaces May 30, and September 27, 2013
2-count sample carton	N/A	October 18, 2013, replaces September 27, 2013
14-count immediate container (bottle)	N/A	May 30, 2013
14-count carton	N/A	May 30, 2013
14-count "club" carton with backer card	N/A	May 30, 2013
28-count carton	N/A	May 30, 2013
28-count "club" carton with backer card	N/A	May 30, 2013
42-count carton	N/A	May 30, 2013
42-count "club" carton with backer card	N/A	May 30, 2013
(b) (4)	N/A	May 30, 2013

II. REVIEWER'S COMMENTS

A. 2-, 14-, 28- and 42-count cartons

i. Outer Carton Label Outside Drug Facts

Primary Display Panel

a. The primary display panel's (PDP's) upper left corner has a blue oval, with the statement "New" in white font.
Comment: This is acceptable. Please remind the sponsor to delete the "New" graphic after six months of marketing.

b. Across the top center portion of the PDP is the statement "Treats Frequent Heartburn"
Comment: This statement is a true statement of the "Uses" section of the Drug Facts label and is acceptable.

c. The proposed proprietary name "Nexium® 24HR" is located on the large capsule graphic at the center of the PDP.
Comment: From an IDS perspective, the proposed proprietary name is acceptable. The proprietary name itself is conditionally acceptable (see Division of Medication Error Prevention and Analysis letter of September 16, 2013).

d. The PDP has a yellow background with purple edging in the lower left corners.
(b) (4)
[redacted]
Comment: This is not acceptable for the following reasons: (b) (4)
[redacted]

e. Below the "Nexium" section of the proprietary name and to the left of the "24HR" section of the proprietary name appears the statement "Esomeprazole Magnesium Delayed-release Capsules 22.3mg/Acid Reducer" (b) (4)
[redacted] It is important to note that the "24HR" part of the proprietary name (b) (4)
[redacted]
Comment: This is not acceptable. (b) (4)
[redacted]

(b) (4)

The determination of the correct established name and dose itself will be determined by CMC review.

f. Under the capsule graphic appears the statement "May take 1 to 4 days for full effect,

(b) (4)

Comment: This statement may not be acceptable.

(b) (4)

g. The declaration of net quantity of contents appears inside the dark purple edging of the lower right section of the PDP. The count and dosage form sections of the declaration

(b) (4)

Comment: This is not acceptable.

(b) (4)

h. For the 2-count sample carton, the statement "First two doses of a 14-day course of treatment" appears below the declaration of net quantity. The statement appears as the smallest font on the PDP.
Comment: The small type size of the statement is not acceptable. The 2-count product represents the first two days of a 14-day course of treatment, and as formatted, may be inadequate to communicate important treatment directions, that the consumer be aware of the need to continue treatment. It is for this reason that we recommend that the sponsor increase the prominence of this statement so that the consumer can be made aware of the need to follow up with more capsules. The sponsor may refer to Sec. 201.5 Drugs; adequate directions for use.

i. For the 14-count carton label, the statement "One 14-day course of treatment" appears underneath the declaration of net quantity. For the 28-count carton label, the statement "Two 14-day courses of treatment" appears underneath the declaration of

net quantity. For the 42-count carton label, the statement "Three 14-day courses of treatment" appears underneath the declaration of net quantity.
Comment: This is acceptable. The 2-count carton is discussed under section II.A.i.h.

j. The top flaps of the 14-, 28- and 42-count cartons display the proposed proprietary name "Nexium 24HR and the statement "Clinically Proven to **Treat Frequent Heartburn**" divided by two vertical graphic bars in the center. However, this is absent from the 2-count carton label.
Comment: This is acceptable.

k. Tamper-evident feature statement:
The right side panel's bottom margin displays the tamper-evident feature statement "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" or yellow band around the center of each capsule is broken or missing" (b) (4)
Comment: This is not acceptable. (b) (4)

l. The right side panels of the 14-, 28- and 42-count cartons display a graphic of the 14-count immediate container (bottle), with a statement of the net number of bottles (b) (4), the statement "ACTUAL SIZE" below the bottle graphic.
Comment: This is not acceptable. (b) (4)
Please refer to section II.A.d. for more detail.

m. Left side panel

The 14-, 28- and 42-count cartons' left side-panels (b) (4)
Comment: This is not acceptable. See comments for section II.A.i.d.

- The lower section of the left side-panel for all cartons displays the manufacturing information:

Marketed by:
Pfizer, Madison, NJ 07940 USA
©2014 Pfizer Inc.

Comment: This is acceptable.

- Below the manufacturing information is the country of origin statement: "Made in France"
  Comment: This is acceptable in accordance with 19 CFR 102, Rules of Origin. The content of the statement will rely on the findings of the CMC review.

- Below the country of origin statement appears the statements: "For most recent product information, visit www.Nexium24HR.com" and "Nexium and the colors purple and gold as applied to the capsule are registered trademarks of AstraZeneca AB and are used under license."
  Comment: This is acceptable.

n. Carton back :

- For the 14-, 28- and 42-count cartons, the boxed statement "KEEP (b) (4) CARTON (b) (4) IMPORTANT INFORMATION" is in bolded font above the Drug Facts label.
  Comment: This is acceptable.

- For the 2-count sample carton, the boxed statement "KEEP CARTON FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION" is in bold text above the Drug Facts label. (b) (4)

  Comment: This is not acceptable. (b) (4)

ii. Outer Carton Drug Facts Label

The Drug Facts on each label have identical content regardless of count size. The different sections include the following:

a. ***Active ingredient (in each capsule)***: "Esomeprazole magnesium (b) (4) mg (b) (4)

Comment: From an IDS perspective, this is acceptable, but the approved established name and dose will reflect the CMC review findings.

b. ***Purpose***: "Acid reducer"
Comment: This is acceptable as required under 21 CFR 201.66(d)(1).

c. ***Uses***:
- treats frequent heartburn (occurs **2 or more** days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Comment: This is acceptable.

d. ***Warnings***

1. Other warnings:
"**Allergy alert:** Do not use if you are allergic to esomeprazole"
Comment: This warning complies with 21CFR 201.66(c)(5)((ii)(B) and is acceptable.

2. "**Do not use**"
   - if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.

   Comment: From an IDS perspective, this warning is consistent with other OTC PPIs and is acceptable. However final wording of acceptability and wording will depend on clinical data and will be determined during labeling discussions.

3. "**Ask a doctor before use if you have**"
   - had heartburn over 3 months. This may be a sign of a more serious condition.
   - heartburn with **lightheadedness, sweating or dizziness**
   - chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
   - frequent **chest pain**
   - frequent wheezing, particularly with heartburn
   - unexplained weight loss
   - nausea or vomiting
   - stomach pain

   Comment: From an IDS perspective this is acceptable. However final wording of acceptability and wording will depend on clinical data and will be determined during labeling discussions.

4. "**Ask a doctor or pharmacist before use if you are** taking":

- warfarin, clopidogrel or cilostazole (blood-thinning medicines)
- prescription antifungal or anti-yeast medicines
- digoxin (heart medicine)
- diazepam (anxiety medicine)
- tacrolimus (immune system medicine)
- prescription antiretrovirals (medicines for HIV infection)

Comment: From an IDS perspective this is acceptable. However final wording of acceptability and wording will depend on clinical data and will be determined during labeling discussions.

5. "**Stop use and ask a doctor if**" :
   - your heartburn continues or worsens
   - you need to take this product for more than 14 days
   - you need to take more than 1 course of treatment every 4 months
   - you get diarrhea

   Comment: This is acceptable.

6. Pregnancy/breastfeeding :
   "**If pregnant or breast-feeding,** ask a health professional before use."
   Comment: This statement complies with 21CFR 201.63(a) and 201.66(c)(5)(ix), and is therefore acceptable.

7. Keep out of reach of children:
   "**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away."
   Comment: This statement complies with 21CFR 330.1(g) and 201.66(c)(5)(x), and is therefore acceptable.

e. ***Directions***

1. The first three bullets state:
   - adults 18 years of age and older
   - this product is to be used once a day (every 24 hours), every day for 14 days
   - (b) (4) may take 1 to 4 days for full effect, (b) (4)

   Comment: From an IDS perspective this is acceptable. However final wording of acceptability and wording will depend on clinical data and will be determined during labeling discussions. We recommend that "adults 18 years of age an older" be retained to reflect the approved PREA waiver.

2. Under the heading "**14-Day Course of Treatment**", the following bullets state:
   - swallow 1 capsule with a glass of water before eating in the morning
   - take every day for 14 days
   - do not take more than 1 capsule a day

- swallow whole. Do not crush or chew capsules.
- do not use for more than 14 days unless directed by your doctor

Under the heading "**Repeated 14-Day Courses (if needed)**, the following bullets state:

- you may repeat a 14-day course every 4 months
- **do not take for more than 14 days or more often than every 4 months unless directed by a doctor**

Comment: This is acceptable.

3. The last bullet in the Directions section states by proposing: "children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition". **Comment: On January 22, 2013, the Pediatric Review Committee (PeRC) recommended a full waiver to perform pediatric studies under the Pediatric Research Equity Act (PREA) based on the sponsor's request, because the product would be ineffective and/or unsafe for pediatric patients (a learned intermediary is needed). This direction is consistent with other OTC PPI labeling, therefore, we recommend retaining this statement.**

f. ***Other Information***

- read the directions and warnings before use
- keep the carton [redacted (b) (4)] contain important information.
- store at 20-25°C (68-77°F)

Comment on Storage statements: Defer to CMC for acceptability of storage temperature. Also, other OTC PPI products include additional storage statement information regarding product protection from moisture, high heat and humidity. Defer to ONDQA review as to acceptability of proposed storage statement and whether additional information should appear on this product label.

For the 2-count carton, the second bullet reads:

- keep the carton. It contains important information

Comment: [redacted (b) (4)] **this is not acceptable.** [redacted (b) (4)]

g. ***Inactive ingredients***

The inactive ingredients are listed in alphabetical order in compliance with 21 CFR 201.66(c)(8).

Comment: This is acceptable; however acceptability of the actual active ingredients is contingent with the CMC review.

h. ***Questions or comments?***
Call toll-free 1-866-226-1600
Comment: Recommend that the time that the toll-free number is in operation be included under this Drug Facts subheading.

i. **Other Sections/Issues**
For all carton sizes, the Drug Facts label specifications comply with 21CFR 201.66(d).
Comment: This is acceptable.

B. 14-, 28- and 42-count Club carton with backer card

This component is a card printed on both sides. The front card contains the PDP information the same as presented on the cartons. The front card has a front window, through which the principal display panel of the 14-count will appear. The back of this card will contain the Drug Facts and other back pane information.

i. Outer Carton Label Outside Drug Facts

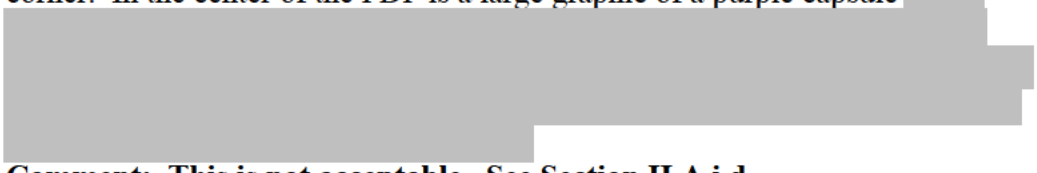
Primary Display Panel

a. The PDP's upper left corner has a blue oval, with the statement "New" in white letters.
Comment: This is acceptable. Please remind the sponsor to delete the "New" graphic after six months of marketing

b. Across the top center portion of the PDP is the statement "Treats Frequent Heartburn"
Comment: This is acceptable.

c. The proposed proprietary name "Nexium® 24HR" is located on the large capsule graphic at the center of the PDP.
Comment: From an IDS perspective, the proposed proprietary name is acceptable. The proprietary name itself is conditionally acceptable (see Division of Medication Error Prevention and Analysis letter of September 16, 2013).

d. PDP has yellow background with purple edging on upper right and lower left corner. In the center of the PDP is a large graphic of a purple capsule (b) (4)



Comment: This is not acceptable. See Section II.A.i.d.

e. Below the "Nexium" and to the left of the "24HR" section of the proprietary name appears the statement "Esomeprazole Magnesium Delayed-release Capsules 22.3mg/Acid Reducer" (b) (4)

Comment: This is not acceptable. See Section II.A.i.e.

f. Under the capsule graphic appears the statement "May take 1 to 4 days for full effect, (b) (4)
For the 14-count "Backer Card" label, this statement appears on the right side of the carton.
Comment: This may not be acceptable. See Section II.A.i.f.

g. The declaration of net quantity of contents appears inside the dark purple edging of the lower right section of the PDP. The number and dosage form sections of the declaration (b) (4)
Comment: This is not acceptable. See Section II.A.i.g.

h. For the 14-count card label, the statement "One 14-day course of treatment" appears underneath the declaration of net quantity. For the 28-count card label, the statement "Two 14-day courses of treatment" appears underneath the declaration of net quantity. For the 42-count card label, the statement "Three 14-day courses of treatment" appears underneath the declaration of net quantity.
Comment: This is acceptable.

i. Tamper-evident feature statement:

- The 14-count "club" carton with backer card label displays the tamper-evident feature statement "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" or yellow band around the center of each capsule is broken or missing" on the back side of the carton (backer card) immediately above the Drug Facts label and below the "Keep the carton" statement. (b) (4)

  Comment: This is not acceptable. (b) (4)

- The 28- and 42-count "club" carton with back card label displays the tamper-evident feature statement "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" or yellow band around the center of each capsule is broken or missing" (b) (4)
  and the background color of the text box is the same as the carton color, (b) (4)

  Comment: This is not acceptable. (b) (4)

j. The back of the card for all cartons displays the manufacturing information:
Marketed by:
Pfizer, Madison, NJ 07940 USA
©2014 Pfizer Inc.
Comment: This is acceptable.

Below the manufacturing information is the country of origin statement:
"Made in France"
Comment: This is acceptable in accordance with 19 CFR 102, Rules of Origin. The content of the statement will rely on the findings of the CMC review.

Below the country of origin statement appears the statements:
"For most recent product information, visit www.XXXXXXXXXX.com"
Comment: Recommend that the sponsor add correct website address to labels, as was done for the 14-, 28- and 42-count carton labels.

For the 28- and 42-count backer cards, the statement "Nexium and the colors purple and gold as applied to the capsule are registered trademarks of AstraZeneca AB and are used under license." appears under the country of origin statement.
Comment: This is acceptable.

k. Card back :

- For the 14-count "club" carton with backer card, the boxed statement "KEEP THE (b) (4) IMPORTANT INFORMATION" is in bold letters at the upper left corner of the backer card.
Comment: This is acceptable
- For the 28- and 42-count "club" carton with backer card, the boxed statement "KEEP (b) (4) (b) (4) (b) (4) IMPORTANT INFORMATION" is in bold letters against a white background immediately above the Drug Facts label.
Comment: This is acceptable
On the 28- and 42-count "club" carton with backer card, (b) (4)
Comment: This is not acceptable. See comments for section II.A.i.d.

ii. Outer Carton Drug Facts Label
See Section II.A.ii.

iii. Immediate Container (2- and 14-count bottle) Label
The immediate container label contains all of the Drug Facts label content except for the listing of inactive ingredients. It is also not consistent with format requirements for full Drug Facts labeling.

Comment: This is acceptable by regulation because the full Drug Facts label appears on all cartons and Club pack cards.

The "peel-back" type label is divided into three panels, identified by the firm as
a. Top – This is the panel visible to the consumer before the Top panel is peeled back and displays non-Drug Facts information
b. Release back – This is the backside of the top panel and displays part of the Drug Facts label content. It is hinged to connect directly to the "Base" panel so that the text continues onto the Base panel.
c. Base – This panel continues the Drug Facts content and is affixed directly to the bottle.

a. **Top panel**

- The statement "Treats Frequent Heartburn" appears at the top of the front side of the panel.
  Comment: This statement is a true statement of the "Uses" section of the Drug Facts label and is acceptable pending overall acceptability of the proposed claims for use.

- The top panel center has a yellow background with purple edging on upper right and lower left corner. In the center of the top panel is a large graphic of a purple capsule with the Nexium 24HR proprietary name (b) (4)
  Comment: This is not acceptable. See Section II.A.i.d.

- The statement of identity "Esomeprazole Magnesium Delayed-release Capsules 22.3mg/Acid Reducer appears on the capsule graphic.
  Comment: The statement of identity as configured is not acceptable. See section II.A.i.e

- Under the capsule graphic appears the statement "May take 1 to 4 days for full effect, (b) (4)
  Comment: This statement may not be acceptable. See Section II.A.i.f

- For the 2-count immediate container, the statement "SAMPLE-NOT FOR SALE" appears on the next line.
  Comment: This is acceptable.

- Below the statement described in A.II.e, is the declaration of net quantity of contents is located which reads: "2 capsules" or "14 capsules" for each respective immediate container count.
  Comment: This is acceptable as a true and accurate statement of the net contents contained in the bottles (2-count or 14-count).

- For the 14-count immediate container, the statement "One 14-day course of treatment" appears at the bottom margin of the top panel's front side.

Comment: This is acceptable.

- For the 2-count immediate container, that statement "first two doses of a 14-day course of treatment" appears.
  Comment: As presented, it is unacceptable. See Section II.A.i.h.

- In the top panel's upper right corner is the boxed statement "KEEP CARTON FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION".
  Comment: This is not acceptable. See Section II.A.i.n, second bullet. Revise the statement to read "KEEP THE CARTON AND (b) (4) FOR IMPORTANT INFORMATION".

- In the top panel's lower right corner is the direction to "Lift here for more (b) (4) " followed by an arrow.
  Comment: This is not acceptable. (b) (4) We recommend that the sponsor revise the statement "LIFT HERE For More (b) (4)" located in the top panel's lower right corner by deleting "(b) (4)" entirely or revising the direction to read "LIFT HERE For More Information".

- The tamper-evident feature statement "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" or yellow band around the center of each capsule is broken or missing" appears on the upper left side of the top panel label.
  Comment: This statement is acceptable.

- The manufacturer's address information, country of origin statement, and website for product information appears (b) (4).
  Comment: The manufacturer's address information is acceptable. The country of origin statement acceptability is pending with the CMC review. Adding a website Nexium24HR.com to the 2-count label is acceptable, however the 14-count is missing the website address; therefore, please remind the sponsor to fill in the website address for the 14-count immediate container label.

b. **Release-back panel**

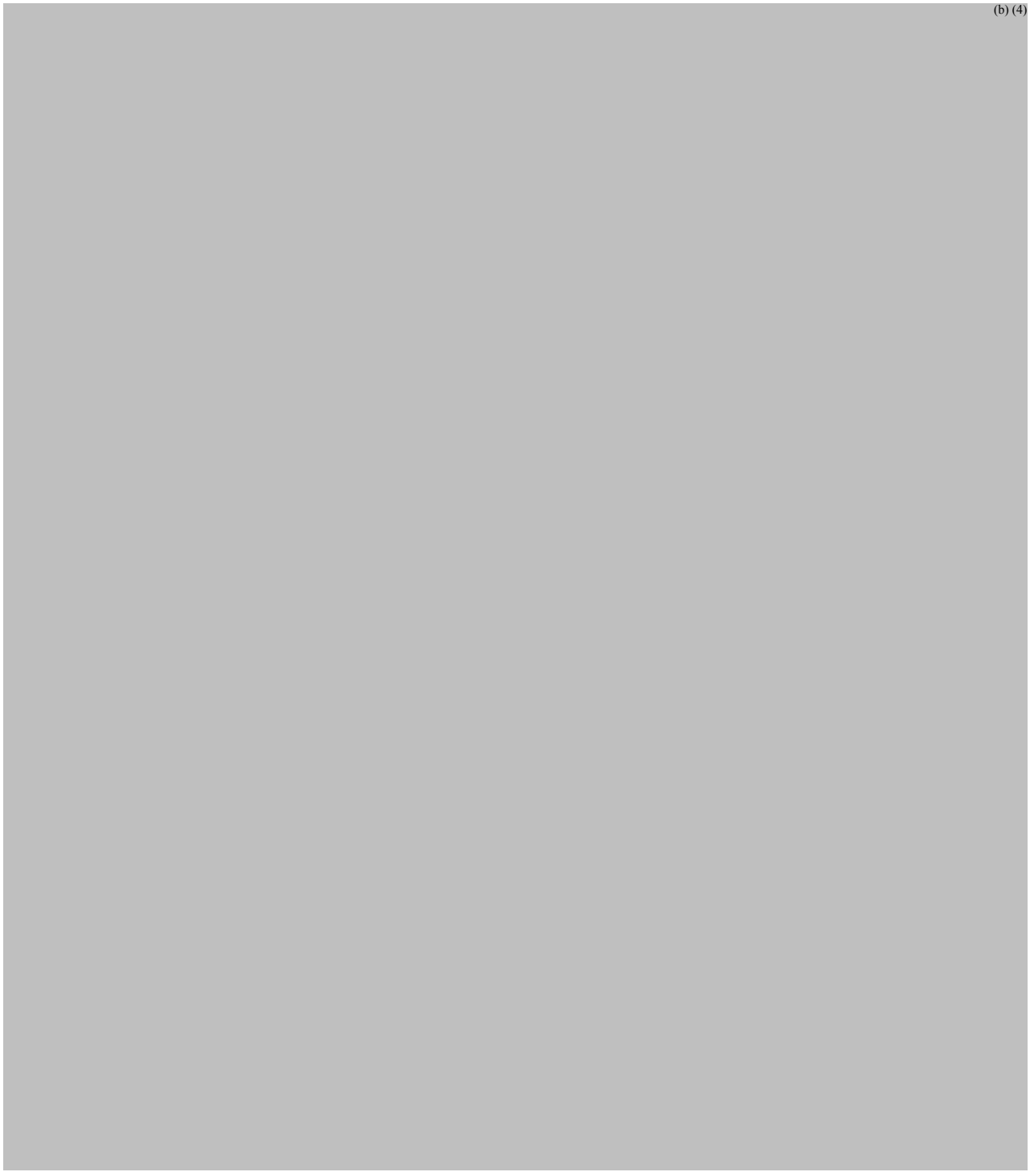
The unformatted Drug Facts label content found under the Active ingredient, Purpose, Uses headings, and through the Warnings drug-drug interactions subheading is found on the Release-back panel (i.e., backside of the top panel). A directional arrow leads the reader to the adjacent base panel.
Comment: Drug Facts label is to be revised based on clinical findings and label negotiations.

c. **Base panel**

The base panel continues the unformatted Drug Facts label content from the Release back panel starting with the Warnings subheading “Stop use and ask a doctor if, pregnancy breast-feeding and Keep out of reach of children warnings. It includes Directions and Other Information (storage statement), “Keep the carton…” and Questions and comments. The inactive ingredients are not listed on the immediate container labels and are not required to be as they are listed on the cartons.

Comment: This is acceptable pending CMC for the storage statement.

(b) (4)



(b) (4)

III. RECOMMENDATIONS

Please communicate the following to the sponsor:

A. The following revisions are to be made by the sponsor:

i. Non Drug Facts Labeling

a. Remove or modify the graphic of the purple capsule behind the product name on the PDP, or change to an accurate representation of the OTC drug product wherever it appears on the carton labels, immediate container labels and consumer information leaflet (CIL).

b. Move the statement of identity to follow the proprietary name and increase its prominence wherever it appears on the carton labels, immediate container labels and the CIL.

c. Modify the established name and dose in accordance with the CMC review wherever it appears on the carton labels, immediate container labels and the CIL.

d. Revise the statement "May take 1 to 4 days for full effect, (b) (4)

e. Move the capsule graphic that divides the declaration of net quantity of contents on the carton labels.

f. Increase the visibility of the statement "First two doses of a 14-day course of treatment" on the 2-count carton and 2-count immediate container labels.

g. Increase the visibility of the tamper-evident feature statement on all carton labels.

h. Change the boxed statement to read "KEEP (b) (4) CARTON (b) (4) (b) (4) IMPORTANT INFORMATION" on the back of the 2-count carton and on the immediate container labels,

i. (b) (4)

j. For the 14-, 28- and 42-count backer cartons, the immediate container labels and the CIL, replace "www.XXXXXXXXXX.com" with the appropriate website information.

k. Remove the (b) (4) phrase after the 24-hour period statement on the CIL.

ii. Drug Facts Label

a. ***Active ingredient(in each capsule)***: revise statement to reflect the findings of the CMC review.

b. ***Directions*** section, third bullet: revise the statement "May take 1 to 4 days for full effect, (b) (4) to reflect the DGIEP review findings.

c. ***Other Information*** section, second bullet: for the 2-ct carton, revise the bullet to read "keep the carton and (b) (4). They contain important information."

d. ***Other Information*** section, third bullet: revise the storage statement to reflect the recommendations of the CMC review.

e. ***Inactive ingredients*** section: revise to reflect CMC review comments.

B. We also recommend that the sponsor make the following revisions:

i. Non-Drug Facts labeling:

a. For the 2-count and 14-count immediate container labels, revise the direction to "Lift here for more (b) (4)" by deleting (b) (4)" entirely or revising the direction to read "LIFT HERE For More Information".

ii. Drug Facts label:

a. ***Questions or comments*** section: include the time that the toll-free number is in operation.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

10 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.

/s/

MARY R VIENNA
02/27/2014

RUTH E SCROGGS
02/27/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	January 7, 2014
Acting Team Leader:	Chi-Ming Tu, PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Nexium 24HR (Esomeprazole) Delayed-release Capsules, 20 mg
Application Type/Number:	NDA 204655
Submission Number:	3
Applicant:	AstraZeneca
OSE RCM #:	2013-1563

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label and carton labeling for Nexium 24HR NDA 204655 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

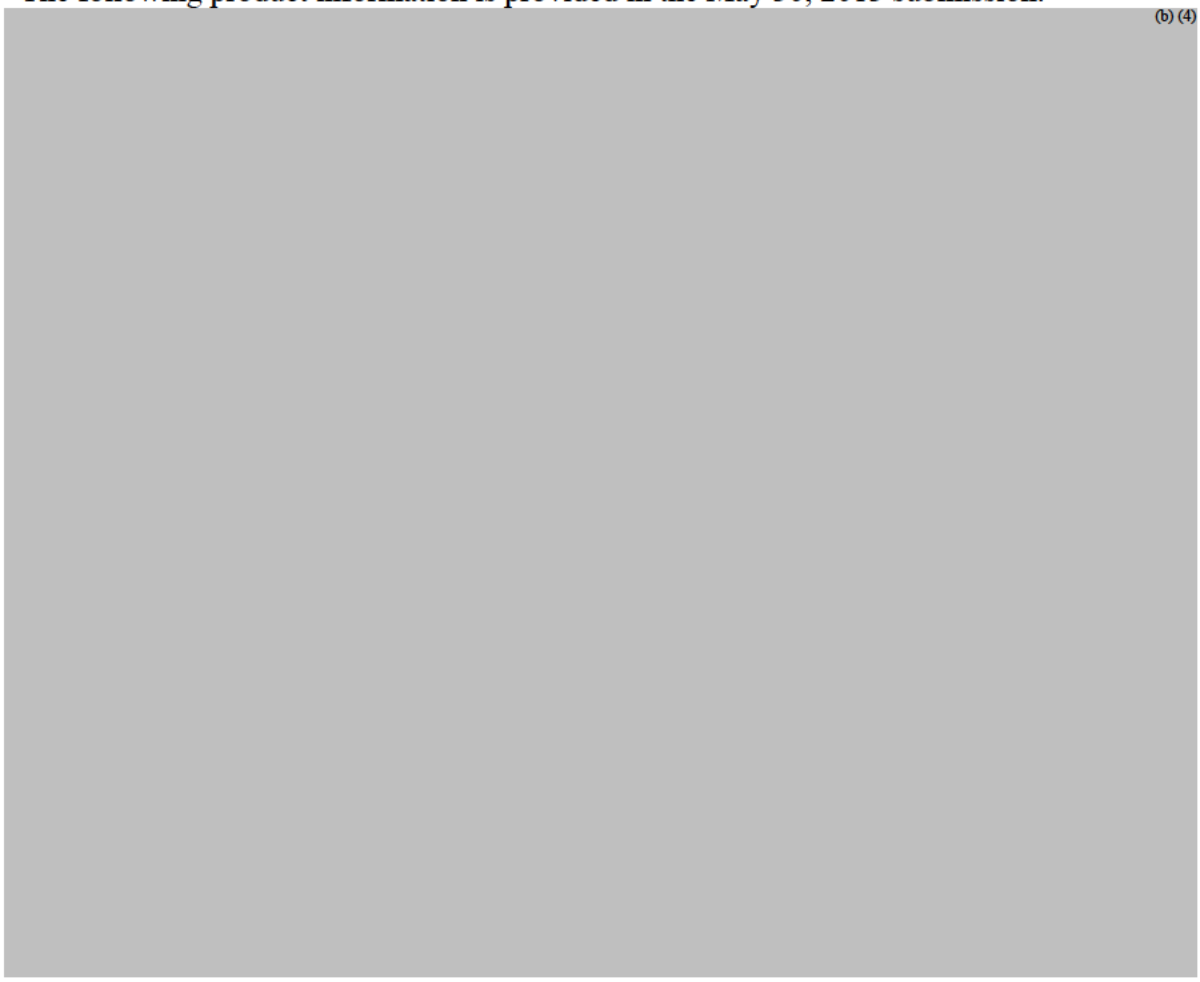
Nexium (Esomeprazole Magnesium) Delayed-Release Capsules, 20 mg and 40 mg, were approved as prescription (Rx) drug products on February 20, 2001 (NDA 021153). In addition to the capsules formulation, Nexium Delayed-release Suspension, dosage packets containing 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg, was approved as a prescription product on October 20, 2006 (NDA 021957). Nexium IV (Esomeprazole Sodium) Injection, 20 mg and 40 mg per vial, were approved on March 31, 2005 (NDA 021689).

On May 30, 2013, the Applicant filed NDA 204655 seeking over-the-counter (OTC) marketing approval for the 20 mg strength under the proposed new indication heartburn. The Applicant also plans to continue to market the 20 mg strength for Rx indications if OTC marketing is approved.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 30, 2013 submission.

(b) (4)



- How supplied: Bottle containing 14 capsules. Outer carton will contain 1, 2, or 3 bottles for a total of 14, 28, or 42 capsules (1, 2 or 3 courses of treatment, respectively).
- Container and Closure System: The drug product is packed in 45 mL square shaped bottles made of white high density polyethylene with a (b) (4) closure made of (b) (4). Inside the screw closure are a liner and a seal. The liner is made of (b) (4) and the seal is an aluminum foil (b) (4). The (b) (4) is in contact with the product. The seal is induction welded to the bottle for tamper evidence. The (b) (4) (b) (4). A desiccant containing (b) (4) is placed inside the bottle.

2 METHODS AND MATERIALS REVIEWED

We reviewed the Nexium 24HR labels and labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted May 30, 2013 (Appendix B)
- Carton Labeling submitted May 30, 2013 (Appendix C)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the labels and labeling of the (b) (4) We looked at the review to ensure applicable recommendations are considered for the proposed Nexium 24HR labels and labeling.

3 CONCLUSIONS

DMEPA concludes that the proposed Nexium 24HR labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Division

1. DMEPA notes the established name on container labels and carton labeling is "Esomeprazole magnesium Delayed-Release Capsules, 22.3 mg". This presentation differs from the strength presentation of the prescription Nexium Capsules, 20 mg. We defer to the Division and CMC as to whether the established name should be revised to "Esomeprazole Delayed-Release Capsules, 20 mg" on all container labels and carton labeling.

B. Comments to the Applicant

1. Container Label and Carton Labeling

   i. Remove the large purple capsule graphic that surrounds the proprietary and established names because it competes with the prominence of the proprietary name. Additionally, the large purple

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

capsule graphic is not an accurate depiction of the actual capsules of the proposed Nexium 24HR product.

ii. Ensure adequate color contrast between the proprietary and established names and the background color after removing the large purple capsule graphic [redacted (b) (4)] The color contrast between the text and the background color should be chosen to afford adequate legibility of the text.

iii. Relocate the established name, strength and the pharmacological category to immediately below the full proprietary name, Nexium 24HR, such that the established name, strength and the pharmacological category do not interrupt the proprietary name.

2. Carton Labeling

i. Relocate the capsule image to below or to the right of the phrase "# capsules" such as "42 capsules" instead of "[redacted (b) (4)]".

If you have further questions or need clarifications, please contact Abiola Olagundoye, project manager, at 301-796-3982.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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.

/s/

CHI-MING TU
01/07/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204655	NDA Supplement #:S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Nexium 24HR Established/Proper Name: esomeprazole magnesium Dosage Form: delayed-release capsule Strengths: 20 mg		
Applicant: AstraZeneca Agent for Applicant (if applicable): N/A		
Date of Application: 05/30/13 Date of Receipt: 05/30/13 Date clock started after UN: N/A		
PDUFA Goal Date: 03/30/14	Action Goal Date (if different): 03/28/14	
Filing Date: 07/29/13	Date of Filing Meeting: 07/11/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 8		
Proposed indication(s)/Proposed change(s): frequent heartburn		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: Rx-to-OTC, new indication	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): DGIEP (Sohrabi/Fiorentino)

List referenced IND Number(s): NDA 021153; IND 053733; IND 111185

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: Three (3) ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X			

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :			**X**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	X			A PeRC date has been requested, but has not been provided to DNCE at the time of this RPM filing review.

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL				

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?			X	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☒ Consumer Information Leaflet (CIL) ☐ Physician sample ☒ Consumer sample ☒ Other (specify) Backer Card			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***		X		Labeling from one SKU is missing. Will be requested in 74-day letter.
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?		X		
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			Only EA consult required-06/20/13

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		Sponsor submitted a Pre-NDA mtg request, but subsequently canceled the mtg following receipt of FDA preliminary responses.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 11, 2013

NDA #: 204655

PROPRIETARY NAME: Nexium 24HR

ESTABLISHED/PROPER NAME: esomeprazole magnesium delayed-release capsules

DOSAGE FORM/STRENGTH: 20 mg

APPLICANT: AstraZeneca

PROPOSED INDICATION: Proposed new indication: frequent heartburn

BACKGROUND: Rx-to-OTC switch (proposed new indication)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeffrey Buchanan	Y
	CPMS/TL:	Dan Brum	N
Cross-Discipline Team Leader (CDTL)	Lesley Furlong		Y
Clinical	Reviewer:	Lolita Lopez, DNCE Farrokh Sohrabi, DGIEP	Y Y
	TL:	Lesley Furlong, DNCE Robert Fiorentino, DGIEP	Y Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Mary Vienna	Y
	TL:	Betsy Scroggs	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:	Wen Jen Chen	Y
	TL:	Stephen Wilson	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Robert Dorsam	Y
	TL:	Paul Brown	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sheldon Markofsky	N
	TL:	Swapan De	Y
Quality Microbiology **This is a non-sterile product**	Reviewer:	Stephen Langille	Y-tcon
	TL:	John Metcalfe	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Alice Tu	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
BioPharm (ONDQA)	Tien Mien (Albert) Chen Angelica Dorantes		Y N
Other attendees	Joseph Tonning - DPV		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**: Neither DNCE nor DGIEP have 74-day letter comments.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No inspections required per DGIEP	☐ YES ☒ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: BioPharm will have 74-day letter comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: No formal consult was made of CMC Micro. ONDQA decided internally to review the NDA. This is a non-sterile product being reviewed for microbial limits.	☐ Not Applicable ☐ YES ☒ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Theresa Michele, MD, Acting Division Director (DNCE)

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

JEFFREY A BUCHANAN
07/24/2013

Filing Review for Nexium® 24HR

SUBMISSION DATES:	May 30, 2013
NDA/SUBMISSION TYPE:	NDA 204655
ACTIVE INGREDIENTS:	Esomeprazole magnesium, 20 mg
DOSAGE FORMS:	Delayed release capsule
SPONSOR:	AstraZeneca LP Judy Firor Director, Regulatory Affairs 302-886-7539
REVIEWER:	Mary R. Vienna, RN, MHA
TEAM LEADER:	Ruth E. Scroggs, PharmD, RPh

Submitted Labeling	Representative of Following SKUs
2-count immediate container (bottle)	N/A
14-count immediate container (bottle)	N/A
14-count carton	N/A
14-count ”club” carton with backer card	N/A
28-count carton	N/A
28-count “club” carton with backer card	N/A
42-count carton	N/A
42-count “club” carton with backer card	N/A
(b) (4)	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is a new NDA.
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	2-count bottle does not contain complete Drug Facts and no 2-count carton label was submitted
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	No	Drug Facts title not visible on submitted 2-count label
Do any of the labels include "prescription strength" or similar statements?	No	
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes; No multiple trade names	New OTC trade name Nexium 24HR proposed, Proprietary name request submitted under IND 111,185, found conditionally acceptable in April 19, 2013 letter from DMEPA.
Does a medical officer need to review any clinical issues?	Yes	New OTC NDA with clinical studies
If SLR, should ONDQA also review?	N/A	

Information Request:
Information request is necessary. Request that the sponsor submit a label for the 2-count sample that complies with 21 CFR 201.66 and address how the consumer information leaflet will be included with the 2-count sample.

Reviewer's Comment:

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

/s/

MARY R VIENNA
07/12/2013

RUTH E SCROGGS
07/12/2013