

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 207920/S-002

Trade Name: Nexium® 24HR

Generic or Proper Name: Esomeprazole magnesium delayed-release tablet, 20 mg

Sponsor: Pfizer, Inc.

Approval Date: December 18, 2017

This “Changes Being Effected” (CBE-0) supplemental new drug application, submitted in response to the Agency’s April 6, 2017, CBE-0 Supplement Request Letter, adds a new warning to the Drug Facts labeling to instruct consumers to stop use and ask a doctor if “you develop a rash or joint pain.”

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 207920/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 207920/S-002

APPROVAL LETTER



NDA 207920/S-002

SUPPLEMENT APPROVAL

Pfizer Inc.
Attention: Nicola Romano
Director, Regulatory Affairs NA
Worldwide Regulatory Strategy
One Giralda Farms
Madison, NJ 07940

Dear Mr. Romano:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 23, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nexium[®] 24HR (esomeprazole magnesium) delayed-release tablet, 20 mg.

This “Changes Being Effected” (CBE-0) supplemental new drug application, submitted in response to the Agency’s April 6, 2017 CBE-0 Supplement Request Letter, adds a new warning to the Drug Facts labeling to instruct consumers to stop use and ask a doctor if “you develop a rash or joint pain.”

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We remind you to remove the “See new warning” flag 6 months after the marketing start date.

LABELING

Submit final printed labeling, as soon as they are available, but no more than 30 days after they are printed. The final printed labeling must be identical to the table below. The final printed labeling must also be in the “Drug Facts” format (21 CFR 201.66), where applicable.

Submitted Labeling	Submission Date
2-count sample bottle carton with peel back label	June 23, 2017
2-count immediate container (bottle)	June 23, 2017
14-count outer carton	June 23, 2017
14-count immediate container (bottle)	June 23, 2017
28-count (2x14-count) outer carton	June 23, 2017
42-count (3x14-count) outer carton	June 23, 2017

42-count (3x14-count) club outer carton, Clear Shell-Pack	June 23, 2017
---	---------------

The final printed labeling should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Labeling for approved NDA 207920/S-002.**” Approval of this submission by FDA is not required before the labeling is used.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REPORTING REQUIREMENTS

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

If you have any questions, call CAPT Janice Adams-King, Safety Regulatory Project Manager, at (301) 796-3713.

Sincerely,

{See appended electronic signature page}

Valerie Pratt, MD
Deputy Director for Safety
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURES:

Carton and Container Labeling

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

/s/

VALERIE S PRATT
12/18/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 207920/S-002

LABELING



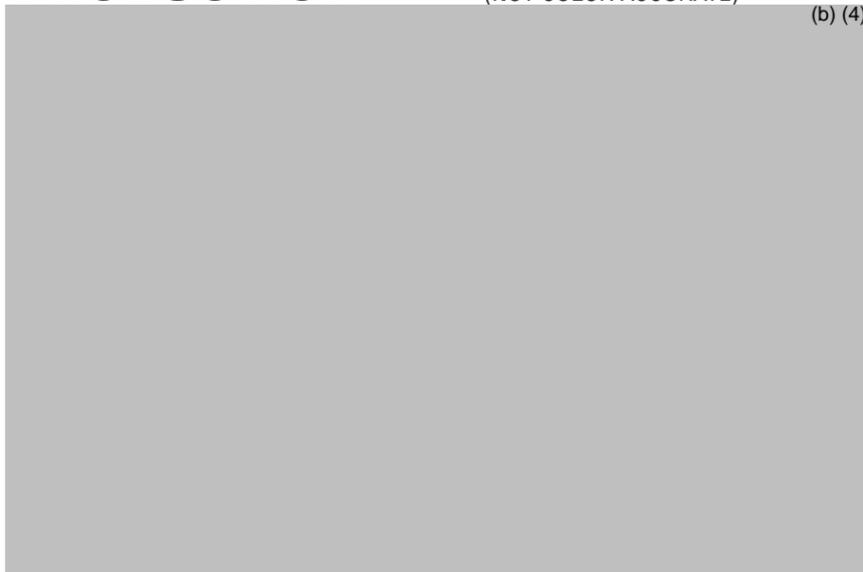
128 CODE AREA - SUBSET C 10 MIL DENSITY WITH 4 OR 6 DIGITS (CODE TO EXTEND TO EDGE OF FLAP - UNVARNISHED) PRINTED SIDE OF CARTON 128 CODE = 090862

DRUG FACTS TEXT DEFINED	TYPE SIZE
• DRUG FACTS TITLE	9 pt
• DRUG FACTS CONTINUED	8 pt
• HEADINGS	8 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

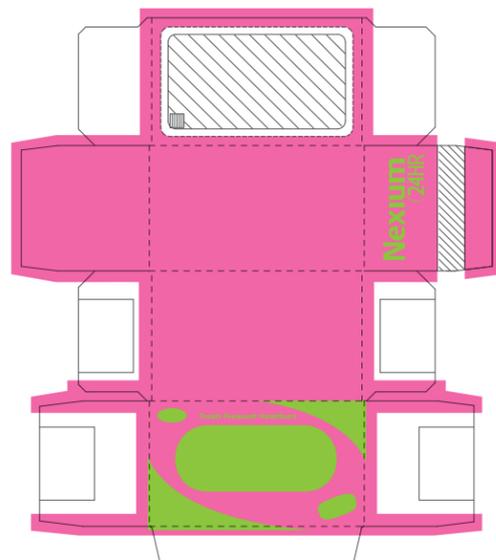
PRODUCTION

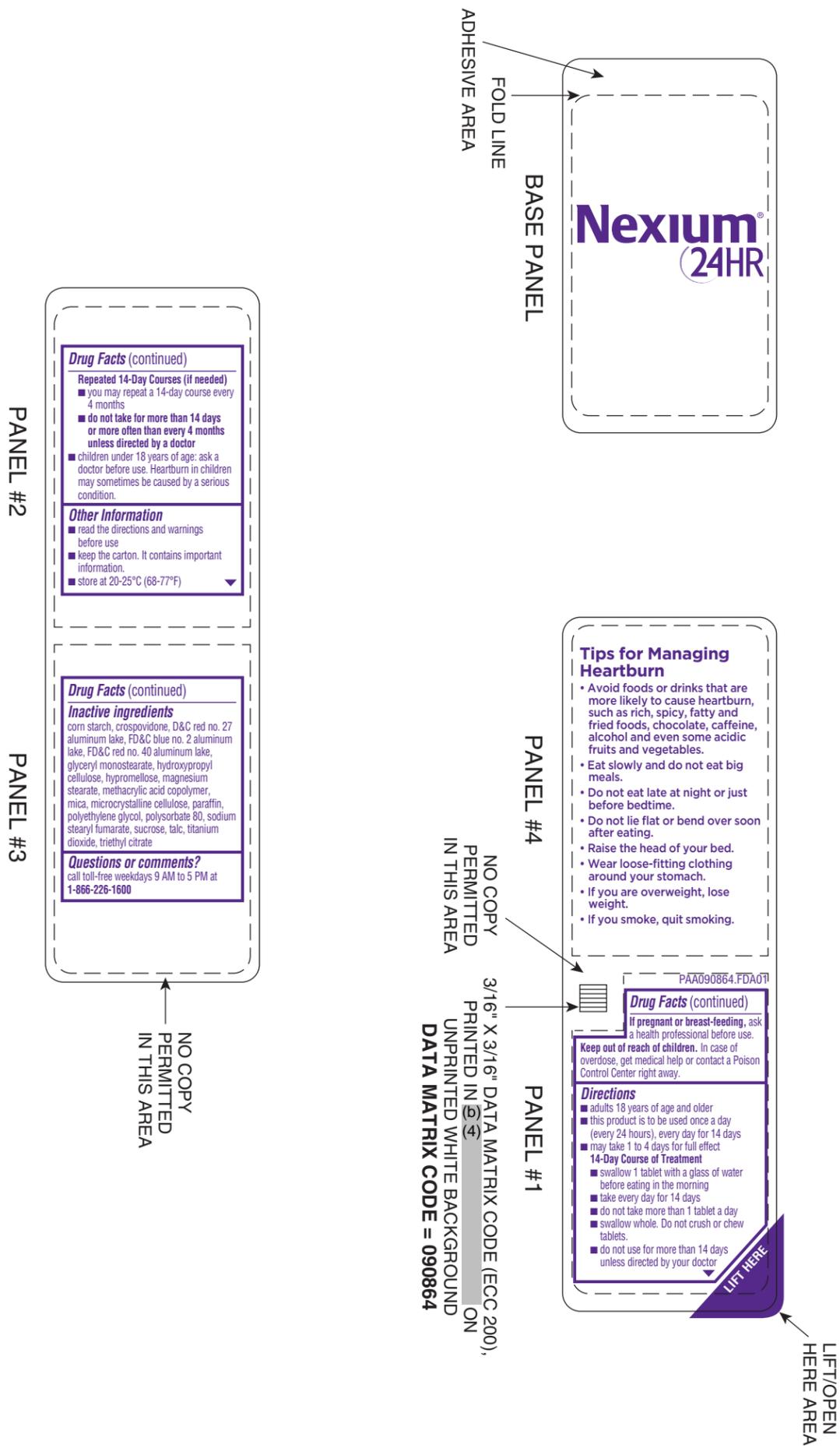
(NOT COLOR ACCURATE)

(b) (4)



Gloss and Matte Varnish - Full size file on Varnish layer





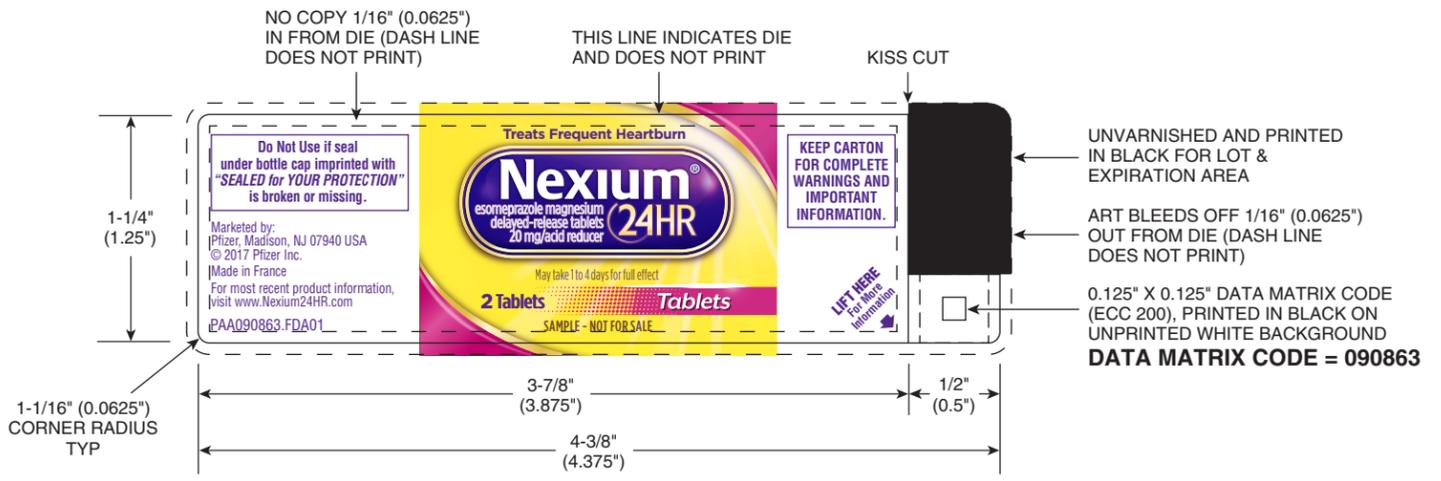
PRODUCTION

(NOT COLOR ACCURATE)

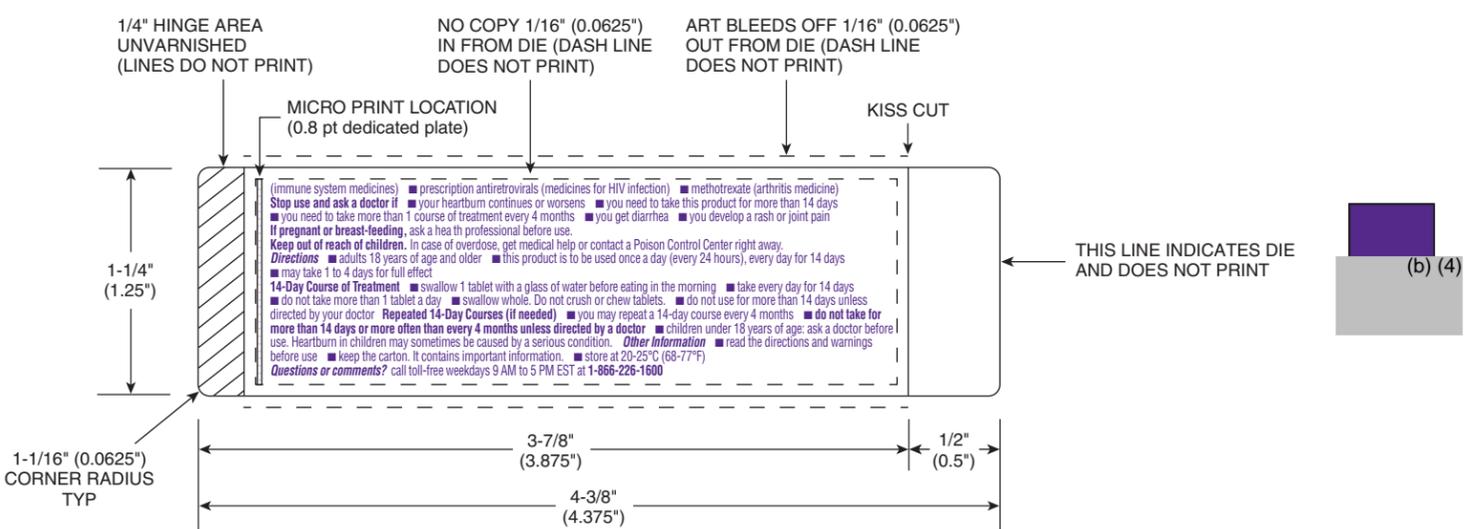
Job Information	Color Legend
(b) (4)	

DRUG FACTS TEXT DEFINED	TYPE SIZE
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• DRUG FACTS CONTINUED	8 pt
• HEADINGS	8 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

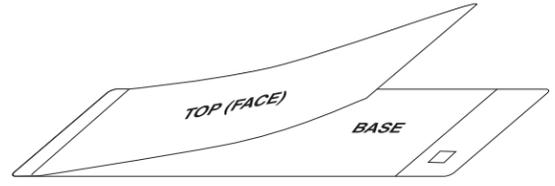
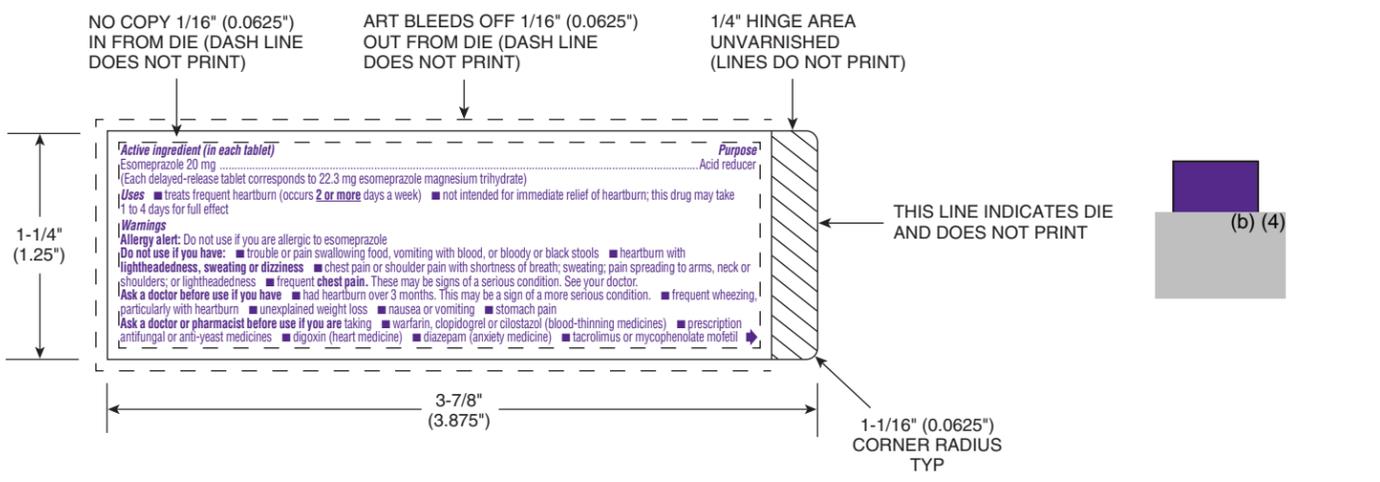
**TOP (FACE)
PANEL 1**



**BASE
PANEL 3**



**TOP (BACK)
PANEL 2**

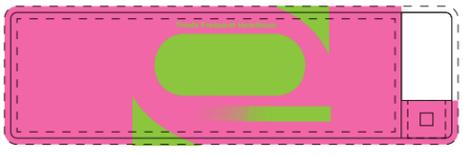


PRODUCTION

(NOT COLOR ACCURATE)

Job Information	Color Legend
(b) (4)	

Gloss and Matte Varnish - Full size file on Varnish layer



DRUG FACTS TEXT DEFINED	TYPE SIZE
• HEADINGS	5.5 pt
• SUBHEADINGS/BODY TEXT	5.5 pt
• LEADING	5.5 pt
• BULLETS	4.5 pt
• SPACE BEFORE BULLET	2 ems
• WARNING BOX LINE, HAIRLINES	.5 pt

UNCOATED
NO COPY
NO PRINT 128 Code: 090868



128 CODE AREA - SUBSET C 10 MIL DENSITY WITH 4 OR 6 DIGITS (CODE TO EXTEND TO EDGE OF FLAP - UNVARNISHED) PRINTED SIDE OF CARTON
128 Code: 090868

MICRO PRINT LOCATION

LOT & EXP AREA. DARK COLOR FOR LASER PRINTING.
3/16" DATA MATRIX CODE WITH 1/8" QUIET ZONE ON ALL SIDES
DATA MATRIX CODE= 090868

Specific Rule Legend

- Cut _____
- Crease - - - - -
- 1/8 1/8 perf - - - - -
- 1/2 x 3/16 Cut Land _____

PRODUCTION

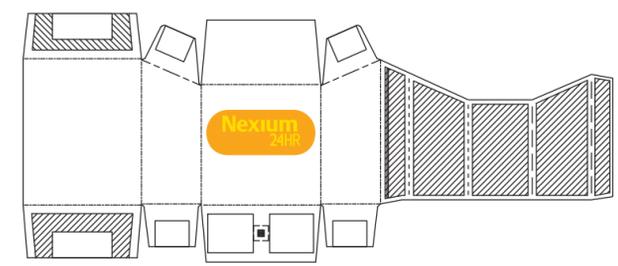
(NOT COLOR ACCURATE)

Job Information	Color Legend
(b) (4)	

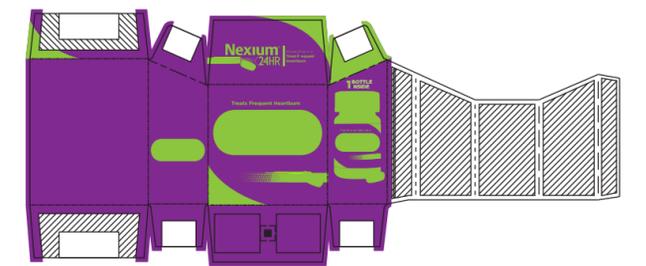
DRUG FACTS TEXT DEFINED	TYPE SIZE
• DRUG FACTS TITLE	9.0 pt
• DRUG FACTS CONTINUED	8.0 pt
• HEADINGS	8.0 pt
• SUBHEADINGS/BODY TEXT	6.0 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5.0 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

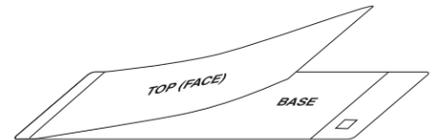
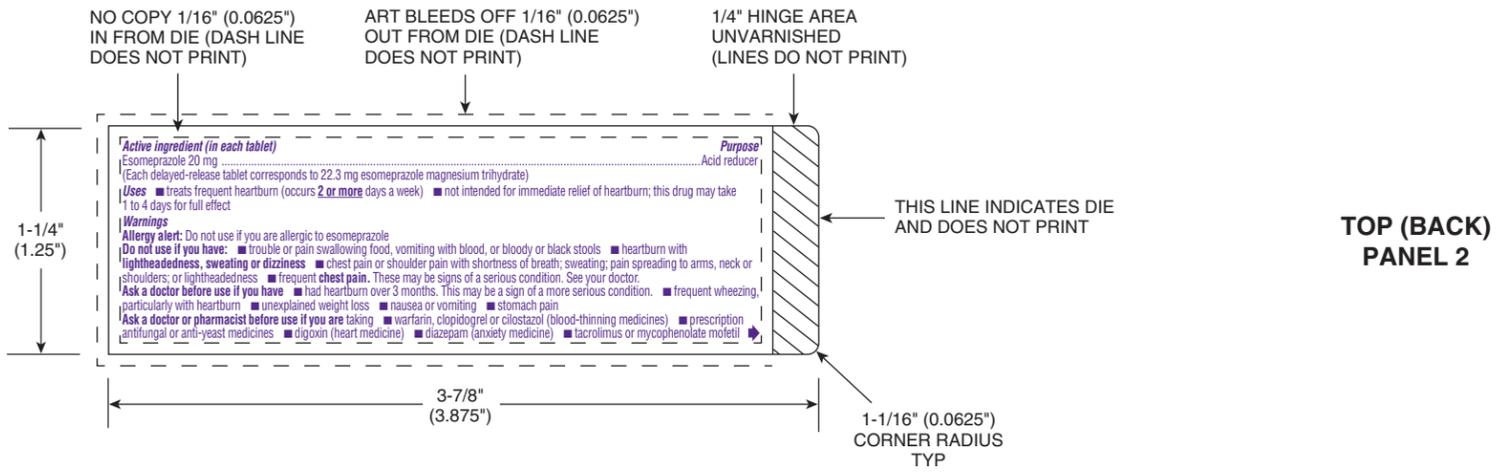
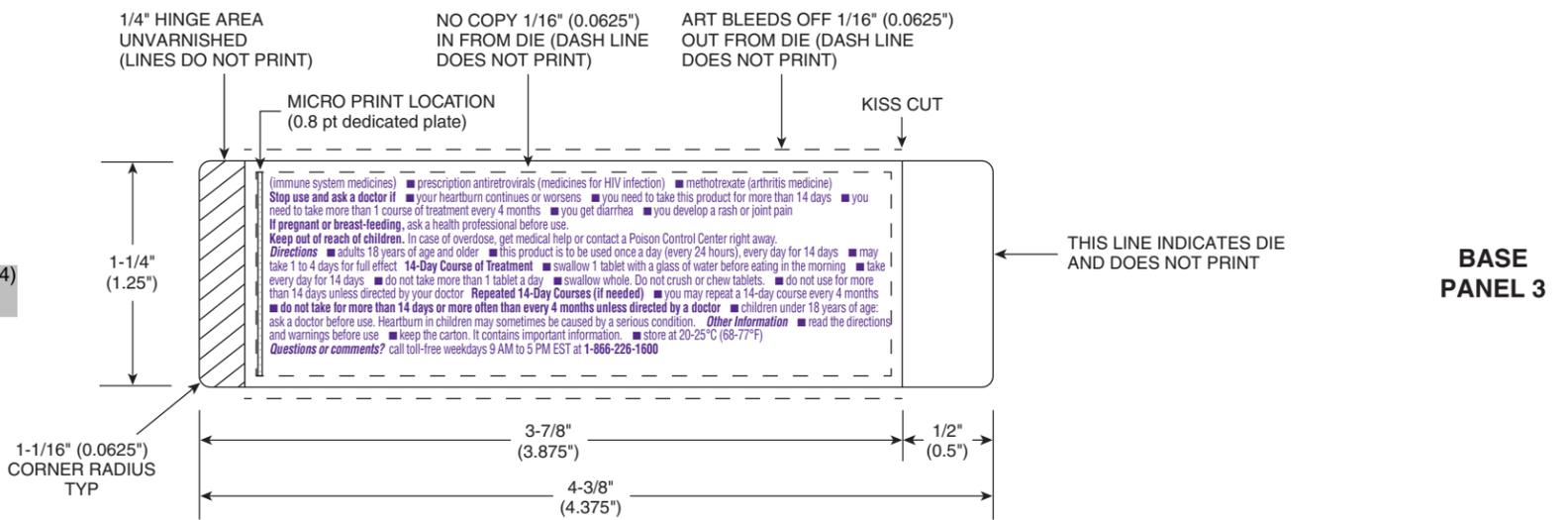
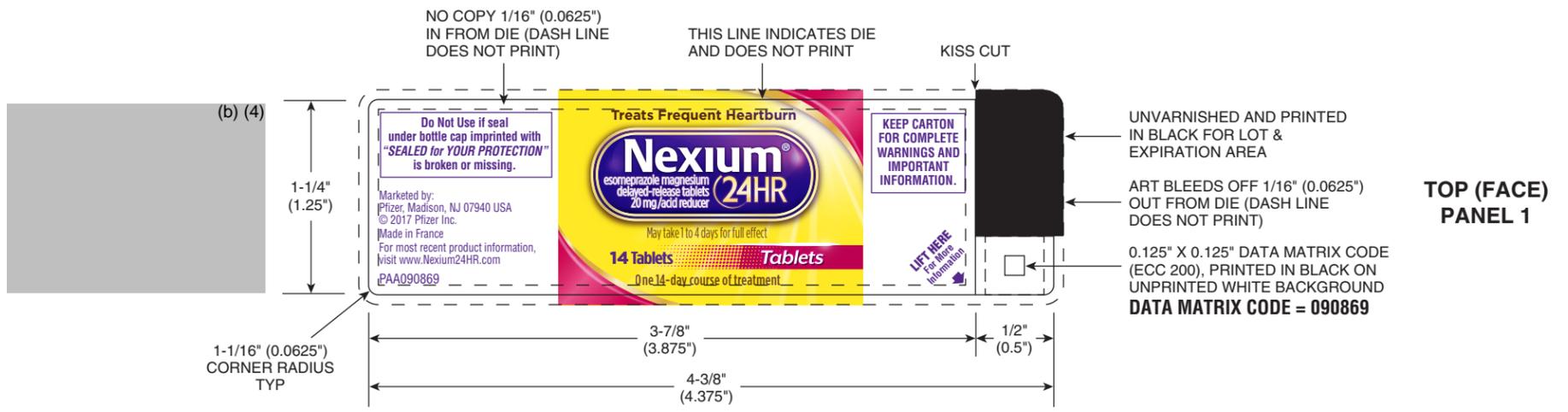


Emboss - Full size file on Emboss layer*
* There are two levels of Embossing.



High Gloss Varnish and Matte Coating - Full size file on Coating layers





PRODUCTION

(NOT COLOR ACCURATE)

Job Information	Color Legend
(b) (4)	

Gloss Varnish - Full size file on Varnish layer



DRUG FACTS TEXT DEFINED	TYPE SIZE
• HEADINGS	5.5 pt
• SUBHEADINGS/BODY TEXT	5.5 pt
• LEADING	5.5 pt
• BULLETS	4.5 pt
• HAIRLINES	.5 pt

NDC 0573-2451-43

See new warning

Treats Frequent Heartburn

Nexium[®]

esomeprazole magnesium
delayed-release tablets 20 mg/acid reducer

May take 1 to 4 days for full effect

3 Pack

Tablets



42 TABLETS

Three 14-day courses of treatment

REMOVE VARNISH IN THIS AREA ONLY

WHITE HOLDOUT QUIET AREA

DATA MATRIX CODE 59124

REMOVE VARNISH
LOT/EXP
WHITE HOLDOUT

Marketed by: Pfizer, Madison, NJ 07940 USA
© 2017 Pfizer Inc.
Made in France
For most recent product information, visit
www.Nexium24hr.com
Nexium is a registered trademark of AstraZeneca
Ad and is used under license.



Drug Facts
Active ingredient (in each tablet): Esomeprazole 20 mg (Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate) Acid reducer

Uses
Treats frequent heartburn (occurs 2 or more days a week) and provides for immediate relief of heartburn; this drug may take 1 to 4 days for full effect.

Warnings
Do not use if you have:
- chest pain or shoulder pain with shortness of breath, sweating, black stools
- heartburn with lightheadedness, sweating or dizziness
- pain spreading to arms, neck or shoulders, or lightheadedness
- frequent heartburn
- frequent chest pain
These may be signs of a serious condition. See your doctor.
Ask a doctor before use if you have:
- had heartburn over 3 months. This may be a sign of a more serious condition.
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are taking:
- warfarin, digoxin or clobazam (blood-thinning medicines)
- prescription antifungal or anti-yeast medicines
- dexamethasone (steroid medicine)
- diazepam (anxiety medicine)
- tacrolimus or mycophenolate mofetil (immune system medicines)
- methotrexate (arthritis medicine)
- prescription antiretrovirals (medicines for HIV infection)

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
- you develop a rash or joint pain

Other information
- read the directions and warnings before use
- keep the card. It contains important information.
- store at 20-25°C (68-77°F)

Inactive ingredients
- D, E, and G: 27 aluminum lake, FD&C blue 2, aluminum lake, FD&C red no. 40 aluminum lake, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, mica, microcrystalline cellulose, paraffin, polyethylene glycol, polyisobutyl fumarate, sucrose, talc, titanium dioxide, triethyl citrate

Questions or comments? call toll-free weekdays 9 AM to 5 PM EST at 1-866-226-1600

KEEP CARD FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION.

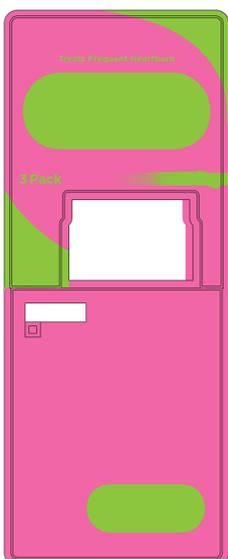
Tips for Managing Heartburn

- Avoid foods or drinks that are more likely to cause heartburn such as rich, spicy, fatty and fried foods, chocolate, caffeine, alcohol and even some acidic fruits and vegetables.
- Eat slowly and do not eat big meals.
- Do not eat late at night or just before bedtime.
- Do not lie flat or bend over soon after eating.
- Raise the head of your bed.
- Wear loose-fitting clothing around your stomach.
- If you are overweight, lose weight.
- If you smoke, quit smoking.



Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Gloss and Matt Varnish - Full size file on Varnish layers



PRODUCTION

(NOT COLOR ACCURATE)

Job Information	Color Legend
(b) (4)	

DRUG FACTS TEXT DEFINED	TYPE SIZE
• DRUG FACTS TITLE	10 pt
• DRUG FACTS CONTINUED	9 pt
• HEADINGS	9 pt
• SUBHEADINGS/BODY TEXT	7 pt
• LEADING	7.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	6 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 207920/S-002

OTHER REVIEW(S)

Labeling Review for Nexium[®] 24HR *Draft Labeling*

SUBMISSION DATES: June 23, 2017

NDA/SUBMISSION TYPE: NDA 207920/supplement-002/CBE

ACTIVE INGREDIENTS: Esomeprazole magnesium, 20 mg

DOSAGE FORMS: Delayed-release tablets

SPONSOR: Pfizer, Inc.
Nicola Romano
Director, Regulatory Affairs, NA
(973) 660-5858

REVIEWER: Yoon Kong, PharmD, OND/ODEIV/DNDP

TEAM LEADER: Kevin L. Lorick, PhD, RAC, OND/ODEIV/DNDP

PROJECT MANAGER: Janice Adams-King, MSN, CPHN, CRNP,
OND/ODEIV/DNDP

I. Background:

NDA 207-920 for Nexium[®] 24HR (esomeprazole magnesium, 20 mg) delayed-release tablets was approved as an OTC proton pump inhibitor on November 23, 2015, for the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of age and older. This application includes a 2-count immediate container (bottle), a 2-count sample carton with peel-back label, a 14-count immediate container (bottle), 14-, 28- (2x14 count) and 42-count (3x14 count) cartons and a 42-count (3x14) Clear Shell-Pack. Supplement 001, approved on February 3, 2017, is the most recently approved labeling for this product.

Supplement 002, submitted June 23, 2017, is a changes being effected (CBE-0) supplement in response to the Agency's April 6, 2017 CBE supplement request letter. This letter notified the Sponsor of a mandatory safety related labeling change to inform consumers of risks of cutaneous and systemic lupus erythematosus events associated with the use of Proton Pump Inhibitors (PPIs). FDA requested that the Drug Facts labeling (DFL) be revised as described below.

“Warnings” section of the Drug Facts labeling:

Following the subheading, “**Stop use and ask a doctor if,**” add the following bullet after the bullet that reads “you get diarrhea”:

- you develop a rash or joint pain

The labeling reviewed is the draft labeling submitted on June 23, 2017, and is compared to the labeling approved with supplement-001, approved on February 3, 2017.

Submitted Labeling	Representative of Following SKUs	Submission Date(s)
2-count sample bottle carton with peel back label	N/A	June 23, 2017
2-count immediate container (bottle)	N/A	June 23, 2017
14-count carton	N/A	June 23, 2017
14-count immediate container (bottle)	N/A	June 23, 2017
28-count (2x14-count) carton	N/A	June 23, 2017
42-count (3x14-count) carton	N/A	June 23, 2017
42-count (3x14-count) club carton, Clear Shell-Pack	N/A	June 23, 2017

II. Reviewer’s Comments

A. 2-count sample, 14-, 28- (2x14-count), 42-count cartons (3x14-count) and 42-count (3-14-count) “Club” Clear-Shell Pack

i. Outer Carton Label Outside Drug Facts

- For all cartons, except the 2-count sample bottle carton, a “See new warning” flag is added on the top left corner of the principal display panel (PDP).

Comment: This is acceptable as it is truthful and not misleading. This statement is helpful to alert consumers of the new warning and does not interfere with other required information on the principal display panel.

- For the 42-count club carton, clear-shell pack, the “call toll free weekdays 9 AM to 5 PM EST at 1-866-226-1600” statement is moved from immediately below the “Questions or comments?” heading to immediately next to it.

Approved label



Proposed label



Comment: This is acceptable as permitted in 21 CFR 201.66(d).

- c. The copyright date on the “Marketed by: Pfizer, Madison, NJ 07940 USA” statement is changed from 2016 to 2017.

Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

- a. In the “**Warnings**” section, under the “Stop use and ask a doctor if” subsection, the following bulleted statement: “you develop a rash or joint pain” is added following the “you get diarrhea” statement.

Comment: This change is acceptable per the Agency’s CBE request letter on April 6, 2017.

- b. For the 2-count sample bottle carton, the statement “**If pregnant or breast-feeding, ask a health professional before use**” is moved from the “**Drug Facts (continued)**” section to the peel back carton label immediately before the “**Keep out of reach of children.**” statement.

Comment: This is acceptable.

iii. Immediate Container (2- and 14-count bottle) labels

- a. The copyright date in the “Marketed by: Pfizer, Madison, NJ 07940 USA” statement is changed from 2016 to 2017.

Comment: This is acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Nexium 24HR delayed-release tablet labeling and request final printed labeling. The final printed labeling (FPL) must be identical to the following labeling:

Submitted Labeling	Submission Date(s)
2-count sample bottle carton with peel back label	June 23, 2017
2-count immediate container (bottle)	June 23, 2017
14-count carton	June 23, 2017
14-count immediate container (bottle)	June 23, 2017
28-count (2x14-count) carton	June 23, 2017
42-count (3x14-count) carton	June 23, 2017
42-count (3x14-count) club carton, Clear Shell-Pack	June 23, 2017

IV. SUBMITTED LABELING

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

Following this page, 8 pages withheld in full - duplicate approved labeling

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

/s/

YOON KONG
12/06/2017

KEVIN L LORICK
12/06/2017

I concur with the review and recommendations.

Filing Review for Nexium® 24HR

SUBMISSION DATES: June 23, 2017

NDA/SUBMISSION TYPE: NDA 207920/supplement-002/CBE

ACTIVE INGREDIENTS: Esomeprazole magnesium, 20 mg

DOSAGE FORMS: Delayed-release tablets

SPONSOR: Pfizer, Inc.
Nicola Romano
Director, Regulatory Affairs, North America
(973) 660-5858

REVIEWER: Yoon Kong, Pharm.D., OND/ODEIV/DNDP

TEAM LEADER: Kevin L. Lorick, PhD, RAC, OND/ODEIV/DNDP

PROJECT MANAGER: Janice Adams-King, MSN, CPHN, CRNP,
OND/ODEIV/DNDP

Background:

Appears this way on original.

Nexium 24HR (esomeprazole magnesium 20 mg) delayed-release tablets, was approved as an OTC proton pump inhibitor on November 23, 2015, for the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of age and older. New drug application (NDA) approved labeling includes a 2-count immediate container (bottle), a 2-count sample carton with peel-back label, a 14-count immediate container (bottle), 14-, 28- (2x14 count) and 42-count (3x14 count) cartons and a 42-count (3x14) Clear Shell-Pack. Supplement 001, approved on February 3, 2017, is the most recently approved labeling and Drug Facts label for this product.

Submitted Labeling	Representative of Following SKUs
2-count sample bottle carton with peel-back label	N/A
2-count immediate container (bottle)	N/A
14-count carton	N/A
14-count immediate container (bottle)	N/A
28-count (2x14 count) Carton	N/A
42-count (3x14 count) Carton	N/A
42-count (3x14 count) Club carton with backer card	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	CBE-0
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	None were submitted.
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?	Yes	
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?	No	

Issues	Yes/No	Comments
Does a medical officer need to review any clinical issues?	No	
If SLR, should ONDQA also review?	No	

Reviewer's Comments: No issues are identified and no information requests are necessary at this time.

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

/s/

YOON KONG
08/10/2017

KEVIN L LORICK
08/14/2017

I concur with the review and recommendations