DDI Webinar Series:  May 2, 2017

Labeling on Drugs@FDA vs. DailyMed

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Learning Objectives

At the conclusion of this webinar, participants should be able to:

- Discuss the types of prescription drug labeling
- Discuss the types of labeling on Drugs@FDA and DailyMed
- Identify the differences between labeling on Drugs@FDA and DailyMed
Labels vs. Labeling

- **Labels**: a display of written, printed, or graphic matter upon the immediate container of any article. For example:
  - e.g., container label

- **Labeling**: all labels and other written, printed, or graphic matters upon any article (or its containers or wrappers) or accompanying the article. Examples include:
  - FDA-approved patient labeling
  - Carton and container labeling
  - Prescribing information

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1 See Section 201, Chapter II, (k) and (m) of Food Drug and Cosmetic Act (FD&C Act)
Prescription Drug Labeling
# Prescription Drug Labeling

<table>
<thead>
<tr>
<th>Type of Prescription Drug Labeling</th>
<th>Audience</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FDA-approved patient labeling:</td>
<td>Patients and/or caregivers</td>
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<tr>
<td>➢ Medication Guides</td>
<td></td>
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<td>➢ Patient Package Inserts</td>
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<td>➢ Instructions for Use</td>
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<tr>
<td>2. Prescribing Information</td>
<td>Healthcare providers</td>
</tr>
<tr>
<td>3. Carton and container labeling</td>
<td>➢ Healthcare providers (physician, pharmacist, nurse, pharmacy technician)</td>
</tr>
<tr>
<td></td>
<td>➢ Sometimes for patients or caregivers</td>
</tr>
</tbody>
</table>
Patient Labeling: Medication Guide

MEDICATION GUIDE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

injection

Read the Medication Guide that comes with HUMIRA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about HUMIRA?

HUMIRA is a medicine that affects your immune system. HUMIRA can lower the ability of your immune system to fight infections. Serious infections have happened in people taking HUMIRA. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some people have died from these infections.

- Your doctor should test you for TB before starting HUMIRA.
Patient Labeling: Patient Package Insert

Patient Information

Patient Information
femhrt (fē’mērt)
(norethindrone acetate/ethinyl estradiol)
Tablets

Read this Patient Information before you start taking femhrt and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about femhrt (a combination of estrogen and progestin)?

- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia (decline of brain function).
- Using estrogens with progestins may increase your chances of getting a heart attack, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with femhrt.
Patient Labeling: Instructions for Use

INSTRUCTIONS FOR USE
HUMIRA® (Hu-MARE-ah)
(adalimumab)
40 MG/0.8 ML
SINGLE-USE PEN

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

IMPORTANT:
• Do not use HUMIRA if frozen, even if it has been thawed.
• The HUMIRA Pen contains glass. Do not drop or crush the Pen because the glass inside may break.
• Do not remove the gray cap or the plum-colored cap until right before your injection.
• When the plum-colored button on the HUMIRA Pen is pressed to give your dose of HUMIRA, you will hear a loud “click” sound.
  • You must practice injecting HUMIRA with your doctor or nurse so that you are not startled by this click when you start giving yourself the injections at home.
  • The loud click sound means the start of the injection.
  • You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.
Patient Labeling: Instructions for Use

Injectable Areas
Carton and Container Labeling

2 SINGLE-USE PREFILLED PENS
HUMIRA® PEN
adalimumab
40 mg / 0.8 mL
FOR SUBCUTANEOUS USE ONLY

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.
Needle Cover for Syringe Contains Dry Natural Rubber.
The entire carton is to be dispensed as a unit.
Return to pharmacy if dose tray seal is broken or missing.

www.HUMIRA.com
abbvie

This carton contains:
• 2 dose trays (each containing 1 single-use prefilled pen with 27 gauge 1/2 inch length fixed needle)
• 2 alcohol preps
• 1 Medication Guide
• 1 package insert
• 1 Instructions for Use

Rx only
Prescribing Information (PI) (1 of 2)

Written for healthcare providers and must:¹

- Contain a summary of essential scientific information needed for safe and effective use of the human prescription drug or biological product
- Be informative and accurate and neither promotional in tone nor false or misleading
- Be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading

¹ 21 CFR 201.56(a)(1) and (2)
Also known as “package insert”; however, FDA recommends using term “prescribing information”

PI has two formats:
- Physician Labeling Rule (PLR) format
- Non-PLR “old” format

Brand drugs PI:
- ~ 61% of PI for brand drugs are in PLR format

Generic drug PI
- ~ 35% of PI for generic drugs are in PLR format
Non-PLR Labeling Format\textsuperscript{1}

- Limited format requirements

- **Not** included:
  - Concise summary of important information
  - Table of Contents
  - Numbered sections or subsections

- Information **not** ordered according to clinical relevance

\textsuperscript{1} See 44 FR 37434 (June 26, 1979); 21 CFR 201.80
Physician Labeling Rule (PLR)¹

January 2006 PLR amended regulations about format and content of PI

Rationale:

- Ensure PI contains necessary information for safe and effective use of product
- Make information easier for healthcare providers to access, read, and use
- Reduce medication errors

¹ Final Rule (PLR) “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products” 71 FR 3922 (January 24, 2006)
PLR Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

• Text (4)
• Text (5.x)

RECENT MAJOR CHANGES
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION
• Text (2.x)
• Text (2.x)

DOSAGE FORMS AND STRENGTHS
Dosage form(s): strength(s) (3)

CONTRAINDICATIONS
• Text (4)
• Text (4)

WARNINGS AND PRECAUTIONS
• Text (5.x)
• Text (5.x)

ADVERSE REACTIONS
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Text (7.x)
• Text (7.x)

USE IN SPECIFIC POPULATIONS
• Text (8.x)
• Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y
PLR Highlights – Product Title

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PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

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- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y
PLR Highlights – Recent Major Changes

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PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

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- Text (5.1

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- Text (2.1

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- Text (7.1

-------------------USE IN SPECIFIC POPULATIONS-------------------
- Text (8.1
- Text (8.1

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y
PLR Highlights: Indication Statement

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PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

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• Text (4)
• Text (5.x)

RECENT MAJOR CHANGES
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• Text (8.x)
• Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y
PLR Highlights: Adverse Reactions Reporting Contact Statement

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYYY

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- Text (4)
- Text (5.x)

**RECENT MAJOR CHANGES**
Section Title, Subsection Title (x.x)  M/201Y
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**USE IN SPECIFIC POPULATIONS**
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See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y
PLR Highlights: Revision Date

HIGHLIGHTS OF PRESCRIBING INFORMATION
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PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYYY

WARNING: TITLE OF WARNING
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- Text (4)
- Text (5.x)

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Dosage form(s): strength(s) (3)

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- Text (4)
- Text (4)

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- Text (7.x)

-------------------------------USE IN SPECIFIC POPULATIONS---------------------------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.
FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
   2.1 Subsection Title
   2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
   5.1 Subsection Title
   5.2 Subsection Title
6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Immunogenicity
   6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
   7.1 Subsection Title
   7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
   8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
   8.4 Pediatric Use
   8.5 Geriatric Use
   8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.2 Abuse
   9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
   12.4 Microbiology
   12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
   14.1 Subsection Title
   14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
* Sections or subsections omitted from the full prescribing information are not listed.
PLR Full Prescribing Information

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<tr>
<td>BOXED WARNING</td>
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<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
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<td>4 CONTRAINDICATIONS</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
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<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>
Drugs@FDA: FDA Approved Drug Products

Search by Drug Name, Active Ingredient, or Application Number

[Search Box]

www.fda.gov/DrugsatFDA
Includes information about FDA-approved products for human use:¹

- **Brand and generic prescription drugs (NDAs and ANDAs, respectively)**
  - e.g., LIPITOR, atorvastatin calcium

- **Brand prescription biological products² (BLAs)**
  - e.g., ENBREL, BOTOX

- **Brand and generic OTC drugs (NDAs and ANDAs)**
  - e.g., ADVIL, ibuprofen

NDAs = New Drug Applications; ANDAs = Abbreviated New Drug Applications; BLAs = Biologics License Applications; OTC = over-the-counter

¹ Products approved by Center for Drug Evaluation and Research (CDER) at FDA
² Biological products are made with or from live cells or organisms (includes biosimilar products)
Types of Products that Drugs@FDA Does NOT Include

- **FDA-approved products not included:**
  - Blood, vaccine, allergenic, or cellular/tissue products (e.g., albumin, GARDASIL, FLUMIST)
  - FDA-approved drugs for animals

- **FDA-regulated products not included:**
  - OTC drugs approved under monograph system (e.g., TYLENOL, hydrocortisone, bacitracin zinc, diphenhydramine hydrochloride)
  - Dietary supplements (e.g., st. john's wort, vitamin E)

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1 Biological products approved by Center of Biologics Evaluation and Research (CBER) at FDA
Drugs@FDA: Includes

- Application type (e.g., NDA, ANDA, BLA) and number
- Information about product (drug name, active ingredient, dosage form, route of administration strength)
- Last approved labeling (e.g., prescribing information) and historical labeling
- Approval letters
- Scientific reviews
- Safety information
- Therapeutic equivalents for drug products
Drugs@FDA: What Gets Posted?

- Action packages include scientific reviews, approval letters, safety information, and prescription drug labeling

- Action packages:
  - New molecular entities (NMEs) and new biological products: must be posted within 30 days of approval
  - Other NDAs approved since 1998: are being posted

- Additional labeling (e.g., PI and Medication Guides) are posted for new NDAs/BLAs, efficacy supplements, labeling supplements
Drugs@FDA: How to Search Labeling

Step #1: Type in drug name

Drugs@FDA: FDA Approved Drug Products

Search by Drug Name, Active Ingredient, or Application Number

nexium
Step #2: After clicking on “NEXIUM”, choose dosage form
Drugs@FDA: How to Review Labeling

Step #3: After clicking on “Labels for NDA 021153”, click on **most recent** labeling

### Approval Date(s) and History, Letters, Labels, Reviews for NDA 021153

#### Labels for NDA 021153

<table>
<thead>
<tr>
<th>Action Date</th>
<th>Submission</th>
<th>Submission Classification or Approval Type</th>
<th>Letters, Reviews, Labels, Patient Package Insert</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/20/2016</td>
<td>SUPPL-51</td>
<td>Labeling</td>
<td>Label (PDF)</td>
</tr>
<tr>
<td>10/24/2016</td>
<td>SUPPL-52</td>
<td>Labeling</td>
<td>Label (PDF)</td>
</tr>
<tr>
<td>12/19/2014</td>
<td>SUPPL-50</td>
<td>Labeling-Package Insert</td>
<td>Label (PDF)</td>
</tr>
</tbody>
</table>

www.fda.gov
Drugs@FDA: Review Labeling

Labeling is in PDF format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXIUM safely and effectively. See full prescribing information for NEXIUM.

**NEXIUM** (esomeprazole magnesium) delayed-release capsules, for oral use

**NEXIUM** (esomeprazole magnesium) for delayed-release oral suspension

Initial U.S. Approval: 1989 (omeprazole)

------------------------ RECENT MAJOR CHANGES ------------------------

- Warnings and Precautions, Atrophic Gastritis removed 10/2016
- Warnings and Precautions, Cutaneous and Systemic Lupus Erythematosus 10/2016

---------------------- INDICATIONS AND USAGE ----------------------

NEXIUM is a proton pump inhibitor indicated for the following:

- Treatment of gastroesophageal reflux disease (GERD). (1.1)
- Risk reduction of NSAID-associated gastric ulcer. (1.2)
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence. (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome. (1.4)

--------------------- DOSAGE AND ADMINISTRATION ---------------------

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal Reflux Disease (GERD)</td>
<td></td>
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</tr>
<tr>
<td>Adults</td>
<td>20 mg or 40 mg</td>
<td>Once daily for 4 to 8 weeks</td>
</tr>
<tr>
<td>12 to 17 years</td>
<td>20 mg or 40 mg</td>
<td>Once daily for up to 8 weeks</td>
</tr>
<tr>
<td>1 to 11 years</td>
<td>10 mg or 20 mg</td>
<td>Once daily for up to 8 weeks</td>
</tr>
</tbody>
</table>

---------------------- ADVERSE REACTIONS ----------------------

Most common adverse reactions (6.1):

- Adults (≥ 18 years) (incidence ≥1%): headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth.
- Pediatric (1 to 17 years) (incidence ≥2%): headache, diarrhea, abdominal pain, nausea, and somnolence.

- *Clostridium difficile-Associated Diarrhea*: PPI therapy may be associated with increased risk. (5.3)
- *Bone Fracture*: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- *Cutaneous and Systemic Lupus Erythematosus*: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue NEXIUM and refer to specialist for evaluation. (5.5)
- *Interaction with Clopidogrel*: Avoid concomitant use of NEXIUM. (5.6)
- *Cyanocobalamin (Vitamin B-12) Deficiency*: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.7)
- *Hypomagnesemia*: Reported rarely with prolonged treatment with PPIs. (5.8)
- *Interaction with St. John’s Wort or Rifampin*: Avoid concomitant use of NEXIUM. (5.9, 7.3)
- *Interactions with Diagnostic Investigations for Neuroendocrine Tumors*: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors, temporarily stop NEXIUM at least 14 days before assessing CgA levels. (5.10, 12.2)
- *Interaction with Methotrexate*: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider temporary withdrawal of NEXIUM. (5.11, 7.7)
After following Steps #1 and #2, click on “Approval Date(s) and History, Letters, Labels, Reviews for NDA 021153”
Then click on “Review”
Medical officer review contains detailed review of efficacy and safety of product.
How do you find generic drugs for a brand drug?

After following Steps #1 and #2, click on “Therapeutic Equivalents for NDA 020702”
DailyMed
This website contains 89957 drug listings as submitted to the Food and Drug Administration (FDA).
At the present time, this Web site does not contain a complete listing of labels for approved prescription drugs.
DailyMed

- Contains > 90,000 product labeling
- Includes most-recently labeling submitted to FDA
- Labeling may be different than FDA-approved labeling:
  - Pending CBE-0 labeling supplements
    - Labeling supplements to add safety information under FDA review
    - Labeling changes have not been approved by FDA
  - Annual reportable changes
    - Changes have minimal potential to adversely affect product (e.g., change in inactive ingredient or how supplied information)
Drugs for humans
- Brand and generic prescription drugs (NDAs and ANDAs, respectively)
- Biological products\(^1\) (BLAs)
  - Therapeutic biologics and monoclonal antibodies
  - Blood, vaccine, allergenic, and cellular/tissue products
- Brand and generic OTC drugs (NDAs and ANDAs; and monograph system)

Other products for humans
- Dietary supplements
- Homeopathic products

Animal prescription and OTC drugs

---
\(^1\) Includes biosimilar products
DailyMed: How to Search Labeling

Step #1: Type in drug name

Nexium
DailyMed: How to Review Labeling

Step #2: Choose dosage form

SEARCH RESULTS FOR: Nexium (25 results)

NEXIUM (esomeprazole magnesium) capsule, delayed release
NEXIUM (esomeprazole magnesium) granule, delayed release

NDC Code(s): 0186-4010-01, 0186-4020-01, 0186-4025-01, 0186-4025-02
Packager: AstraZeneca Pharmaceuticals LP
Step #3: Choose method to view labeling (i.e., webpage, PDF, or SPL)

SPL (Structured Product Labeling) is based on extensible markup language (XML)
DailyMed: How to Review Labeling

SPL Labeling Format

NEXIUM® – esomeprazole magnesium capsule, delayed release
NEXIUM® – esomeprazole magnesium granule, delayed release
AstraZeneca Pharmaceuticals LP

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEXIUM safely and effectively. See full prescribing information for NEXIUM.
NEXIUM® (esomeprazole magnesium) delayed-release capsules, for oral use
NEXIUM® (esomeprazole magnesium) for delayed-release oral suspension
Initial U.S. Approval: 1989 (omeprazole)

--- RECENT MAJOR CHANGES ---

Warnings and Precautions, Atrophic Gastritis (5.2) removed 10/2016
Warnings and Precautions, Cutaneous and Systemic 10/2016
Lupus Erythematosus (5.5)

--- INDICATIONS AND USAGE ---

NEXIUM is a proton pump inhibitor indicated for the following:
- Treatment of gastroesophageal reflux disease (GERD). (1.1)
- Risk reduction of NSAID-associated gastric ulcer. (1.2)
- H. pylori eradication to reduce the risk of duodenal ulcer recurrence. (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome. (1.4)

--- DOSAGE AND ADMINISTRATION ---

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal Reflux Disease (GERD)</td>
<td>20 mg or 40 mg</td>
<td>Once daily for 4 to 8 weeks</td>
</tr>
</tbody>
</table>

--- ADVERSE REACTIONS ---

Most common adverse reactions (6.1):
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
- Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk. (5.3)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue NEXIUM and refer to specialist for evaluation. (5.5)
- Interaction with Clopidogrel: Avoid concomitant use of NEXIUM. (5.6)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.7)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.8)
- Interaction with St. John’s Wort or Rifampin: Avoid concomitant use of NEXIUM. (5.9,7.3)
- Interactions with Diagnostic Investigations for Neuroendocrine Tumor: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors, temporarily stop NEXIUM at least 14 days before assessing CgA levels. (5.10,12.2)
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider temporary withdrawal of NEXIUM. (5.11,7.7)
Drugs@FDA vs. DailyMed Labeling (1 of 2)

<table>
<thead>
<tr>
<th></th>
<th>Drugs@FDA</th>
<th>DailyMed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who posts/submits labeling?</td>
<td>FDA posts labeling</td>
<td>Firms submit labeling</td>
</tr>
<tr>
<td>FDA reviews labeling</td>
<td>Always</td>
<td>Generally no</td>
</tr>
<tr>
<td>Format</td>
<td>PDF</td>
<td>1. View on webpage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. PDF</td>
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<tr>
<td></td>
<td></td>
<td>3. SPL</td>
</tr>
<tr>
<td></td>
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<td>• Hyperlinks</td>
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<td></td>
<td></td>
<td>• Allows for indexing</td>
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<tr>
<td>PI</td>
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<td>Most recent PI submitted to FDA</td>
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<tr>
<td>Includes recent PI updates:</td>
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<td>Yes</td>
</tr>
<tr>
<td>• Annual reportable changes</td>
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<td></td>
</tr>
<tr>
<td>• Pending CBE-0 labeling supplements</td>
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</tbody>
</table>

PDF = Portable Document Format; SPL = Structured Product Labeling
CBE = Changes Being Effected
<table>
<thead>
<tr>
<th></th>
<th>Drugs@FDA</th>
<th>DailyMed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient labeling</td>
<td>Last approved patient labeling</td>
<td>Most recent patient labeling submitted to FDA</td>
</tr>
<tr>
<td>Carton/container labeling</td>
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</tr>
<tr>
<td>Generic product labeling</td>
<td>Rarely present</td>
<td>Present</td>
</tr>
<tr>
<td>Includes regulatory history and FDA reviews</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Includes historical approved labeling</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Labeling Resources
PLR Requirements for Prescribing Information


On January 24, 2006, the U.S. Food and Drug Administration (FDA) issued final regulations governing the content and format of prescribing information (PI) for human drug and biological products. The rule is commonly referred to as the "Physician Labeling Rule" (PLR) because it addresses prescription drug labeling that is used by prescribers and other health care providers.

The goal of the PLR content and format requirements as described at 21 CFR 201.56 and 201.57 is to enhance the safe and effective use of prescription drug products by providing health care providers with clear and concise PI that is easier to access, read, and use. The PLR format also makes PI more accessible for use with electronic prescribing tools and other electronic information resources.

PI submitted with new drug applications (NDAs), biologic license applications (BLAs), and efficacy supplements must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. The Labeling Development Team works with review divisions to ensure PI conforms with the PLR. This page includes links to the Final Rule, regulations, related guidance documents, and additional labeling resources.

On December 3, 2014, the FDA published the Pregnancy and Lactation Labeling Rule (PLL R). The goal of the PLLR is to enhance the safe and effective use of prescription drug products in pregnant women, lactating women, and females and males of reproductive potential.

PLR Final Rule and Labeling Requirements

- **Physician Labeling Rule**
  - Requirements on content and format of labeling for human prescription drug and biological products, January 24, 2006 (Federal Register Notice)
  - 21 CFR 201.56
    - Requirements on content and format of labeling for human prescription drug and biological products
  - 21 CFR 201.57
    - PLR Labeling: Specific requirements on content and format of PLR labeling for human prescription drug and biological products described in § 201.56(b)(1)
  - 21 CFR 201.80
    - Older drugs: Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1)
http://labels.fda.gov/

FDA Online Label Repository

IMPORTANT DISCLAIMER

Please be aware of the following when using information from this Web site:

The drug labels and other drug-specific information on this Web site represent the most recent drug listing information companies have submitted to the Food and Drug Administration (FDA). (See 21 CFR part 207.) The drug labeling and other information has been reformatted to make it easier to read but its content has neither been altered nor verified by FDA. The drug labeling on this Web site may not be the labeling on currently distributed products or identical to the labeling that is approved. Most OTC drugs are not reviewed and approved by FDA, however they may be marketed if they comply with applicable regulations and policies described in monographs. Drugs marked "OTC monograph final" or "OTC monograph not final" are not checked for conformance to the monograph. Drugs marked "unapproved medical gas", "unapproved homeopathic" or "unapproved drug other" on this Web site have not been evaluated by FDA for safety and efficacy and their labeling has not been approved. In addition, FDA is not aware of scientific evidence to support homeopathy as effective.

The device labeling and other device-specific information on this website have been voluntarily submitted to the FDA by device manufacturers. FDA has not reviewed this information prior to posting on this website. The device labeling has been reformatted to make it easier to read but its content has not been altered nor verified by FDA. The device labeling on this website may not be the labeling on currently distributed products.

Proprietary Name Search      NDC Number Search
Active Ingredient Search    Application Number or Regulatory Citation Search
Company Search              Proprietary Name and Company Search

Search for Labels on DailyMed

The labels are also available on the National Library of Medicine's DailyMed web site. You can search for labels by drug name and link to the Library’s information resources about marketed drugs.
References

- Drugs@FDA:  www.fda.gov/DrugsAtFDA
- DailyMed:  
- http://labels.fda.gov/
- PLR Requirements for Prescribing Information:  
Thank you!

U.S. FOOD & DRUG ADMINISTRATION
Extra Slides
How FDA Reviews PI

- In response to application holder questions, FDA provides comments about draft PI before NDA/BLA submission.
- Application holder submits an NDA/BLA that includes a draft PI that meets labeling regulatory requirements and is consistent with guidance recommendations.
- FDA reviews PI upon submission and throughout review cycle.
- FDA and application holder develop final PI:
  - Iterative process of communications/discussions with both parties.
- Final PI (PDF format) is approved by FDA and attached to approval letter (PI is posted on Drugs@FDA).