

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-101

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 26, 2008

To: Donna Griebel, MD
Director, Division of Gastrointestinal Products

Thru: Kristina Arnwine, PharmD, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

From: Shary M. Jones, PharmD, MPH, Safety Evaluator
Division of Medication Errors and Technical Support

Subject: Labeling Review

Drug Name(s): Nexium Delayed Release Granules for Oral Suspension, 10 mg

Application Type/Number: NDA 22-101

Applicant/sponsor: AstraZeneca

OSE RCM #: 2008-119

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EXECUTIVE SUMMARY

Our analysis of container labels, carton and professional insert labeling noted vulnerabilities and improvements that could be made to the foil pouch label and package insert labeling to decrease the potential for selection errors, to minimize confusion with dosing, and to increase readability of information presented on the labeling. Such improvements include decreasing the prominence of the graphics displayed, changing the color of some text and relocating the proximity of the "Physician's Sample" statement.

The package insert labeling can also be improved by revising sections of the package insert containing the use of dangerous abbreviations, acronyms and symbols. For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to the Division of Gastrointestinal Products (DGP) to evaluate the Applicant's response to DMETS comments on the container labels, carton and package insert labeling for Nexium Delayed Release Granules for Oral Suspension, and identify any outstanding areas of concern from a medication errors perspective.

1.2 REGULATORY HISTORY

Nexium is currently supplied as delayed-release capsules and delayed-release granules for oral suspension, available in 20 mg and 40 mg strengths as indicated for treating Gastroesophageal Reflux Disease (GERD), risk reduction of Non Steroidal Anti-Inflammatory Disease (NSAID) associated gastric ulcer and eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence in adult patients. Nexium capsules were approved on February 20, 2001 and Nexium Delayed-release Granules for Oral Suspension was approved on October 20, 2006 for use in patients 12 years of age and older. This NDA provides for introduction of a 10 mg oral suspension strength and widening of the treatment population to include patients aged 1-11.

DMETS initially reviewed the foil pouch label, carton labeling, and package insert labeling and forwarded comments to DGP on November 16, 2006 (OSE Review 2006-765). Comments regarding the carton label and foil pouch label were forwarded to AstraZeneca on July 27, 2007 in the approvable letter. DMETS comments on the package insert labeling were not forwarded to the applicant.

1.3 PRODUCT INFORMATION

Nexium is a proton pump inhibitor approved for the healing and maintenance of erosive esophagitis, for symptomatic gastroesophageal reflux disease (GERD), and for use in combination with antibiotics to eradicate *Helicobacter pylori* (*H. pylori*) in patients with active or prior duodenal ulcer disease. The recommended dose of Nexium for patients ages 12 and above is 40 mg daily and up to 240 mg/day by mouth for Zollinger-Ellison syndrome. The recommended dose for patients aged 1-11 years of age is 10 to 20 mg once daily for up to 8 weeks. Nexium Delayed Release Oral Suspension will be supplied in 10 mg, 20 mg and 40 mg packets. The contents of a packet should be placed into a container with 1 tablespoon (15 ml) of water, stirred and left for 2-3 minutes to thicken. The mixture should be re-stirred before administration and administered within 30 minutes of preparation. Any residual drug left in container should be flushed with more water and administered immediately. Nexium should be

stored at room temperature (15° to 30°C) (59° to 86° F), and should be protected from exposure to light and moisture.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. DMETS defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because DMETS staff analyzes reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

On December 6, 2007, the Applicant submitted the following 20 mg and 40 mg labels for DMETS review (see Appendices A and B for images):

- Foil Pouch Label (Trade and Physician Sample)
- Carton Labeling (Trade and Physician Sample)
- Package Insert Labeling

On December 27, 2007, the Applicant submitted the revised 10 mg labels for DMETS review (see Appendices A and B for images):

- Foil Pouch Label (Trade and Physician Sample)
- Carton Labeling (Trade and Physician Sample)
- Package Insert Labeling

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

DMETS compared the approved 20 mg and 40 mg labels to the proposed 10 mg labels to identify any outstanding areas of concern from a medication errors perspective.

3 RESULTS

DMETS notes that the revised 10 mg labels are generally consistent with the requests and comments forwarded to the Applicant on July 27, 2007. However, some of the requested revisions were not implemented, and represent areas of concern from a medication errors perspective.

3.1 FOIL POUCH LABEL

The revised graphic on the bottom right hand corner of the principal display panel continues to have increased prominence.

The red text used for the “Physician’s Sample Not for Sale” statement on the physician sample label decreases the prominence of this statement, especially since it is located immediately following a large block of red text.

3.2 CARTON LABELING

No comments at this time.

3.3 PROFESSIONAL INSERT LABELING

Trailing zeroes and the abbreviation μg are used throughout the package insert.

4 DISCUSSION

Our analysis of the container labels noted the enlarged “bubble” graphic presented on the foil pouch labels. Although this is consistent with the approved product labeling of the 20 mg and 40 mg strengths, this may present a greater risk of distracting the focus of the practitioner or patient from other more critical information, such as the proprietary and established names. Being that the label is small, having the large and promotional “bubble” graphic on the label crowds the information on the label.

We also noted that the foil pouch labels have red lettering on the foil pouch. Foil labels are often difficult to read, especially when the color of the text does not provide a sufficient contrast to the foil. The information is often blurred or illegible. Thus, we are concerned about the continuous red font on the physician sample package, as it is difficult to differentiate the package as a physician sample. The “Physician’s Sample” statement appears at the bottom of the label in red text and is preceded by a large amount of information, also in red text, increasing the potential for the statement to be overlooked. This statement would have increased prominence if it appeared at the top of the label.

DMETS is specifically concerned with the use of the dangerous and error-prone abbreviation, “ μ ” and the use of trailing zeros throughout the insert. Both μg and trailing zeros appear on the Institute for Safe Medication Practices (ISMP) “List of Error-Prone Abbreviations, Symbols, and Dose Designations”. Furthermore our post-marketing experience shows, the abbreviation “ μ ” could resemble the letter “m” depending upon how it is scripted and result in misinterpretation of the units as milligram rather than microgram. Trailing zeros may lead to misinterpretation of the dose. The number 1.0 mg could be inadvertently read as 10 mg resulting in a 10- fold overdose.

Additionally in June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations such as “µg” and trailing zeros. As part of this campaign, FDA agreed not to approve such abbreviations in their labeling.

5 CONCLUSIONS AND RECOMMENDATIONS

Based upon our assessment of the labels and labeling, DMETS recommends the following areas be revised prior to approval.

1. The prominence of the bubble graphic on the foil pouch should be deleted or at a minimum decreased.
2. The color and location of the font on the physician sample foil pouch needs to be changed, in efforts to make the statement more prominent.
3. Delete the trailing zeros used throughout the package insert.
4. Eliminate the use of “µg”. Revise all reference to micrograms to read “mcg” throughout the package insert.

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 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Kristina Arnwine
2/26/2008 03:58:24 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Shary Jones

Denise Toyer
2/27/2008 08:20:53 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Predecisional Agency Information

Date: July 25, 2007

From: Michael Brony, Division of Drug Marketing, Advertising, and Communications (DDMAC)

To: Chantal Phillip, Division of Gastrointestinal and Coagulation Drug Products

RE: **NEXIUM**[®] (esomeprazole magnesium) DELAYED-RELEASE CAPSULES
NEXIUM[®] (esomeprazole magnesium) FOR DELAYED-RELEASE ORAL SUSPENSION

- Is there a clinical definition for the word “heal?” If so, we recommend referencing this definition.
- The Adverse Reactions section of the PI states:

In general, NEXIUM was well tolerated in both short and long-term clinical trials. (emphasis added)

DDMAC recommends deleting the phrase “well tolerated.” The term minimizes the risks associated with Nexium therapy and could be used promotionally.

We have no comments on the carton labels for this NDA.

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/s/

Michael Brony
7/25/2007 12:18:55 PM
DDMAC REVIEWER

**Study Endpoints and Label Development (SEALD) Team
Review of Physician Labeling Rule (PLR) Labeling**

Subject: Proposed Labeling Format Review

Application Number: NDA 22-101

Applicant: AstraZeneca

Drug Names: Nexium (esomeprazole magnesium)

Receipt Date: 9/27/06

SEALD Review Date: 12/14/06

Project Manager: Chantal Phillips

Review Division: Division of Gastrointestinal Products

SEALD Reviewer: Robin Anderson, RN, MBA

SEALD Director Concurrence: Laurie Burke, RPh, MPH

Executive Summary

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

SEALD Comments

Highlights:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(6) and (d)(8)]
- Add cross references to every statement. The preferred presentation of referencing in Highlights is the numerical identifier in parentheses following the summarized labeling information corresponding to the location of information in the FPI. For example, Under Indications and Usage, "Treatment of Gastroesophageal Reflux Disease (GERD) (1.1)."
[See <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.]

- List all dosage forms. Add Delayed-Release Granules for Oral Suspension to the drug name that follows the Highlights limitation statement. [See CFR 201.57 (a)(2)]
- Add a Recent Major Changes section to Highlights to contain any changes made to the following sections during the year before approval of this supplement: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions. [See CFR 201.57 (a)(5)]
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Delete capsule color and other descriptive attributes under Dosage Forms and Strengths in Highlights. This information belongs in the FPI only in 3 Dosage Forms and Strengths and 16 How Supplied/Storage and Handling.
- Regarding Contraindications, “theoretical” adverse reactions must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]
- Under Adverse Reactions, delete the “s” at the end of “nauseas” in the last statement.

FPI: Contents:

- The Contents must be limited in length to one-half page, in 8 point type, two-column format. [See <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.]
- Create subsection headings that identify the content. Avoid using the word “General.” See 5.1 Warnings and Precautions. This also applies to the FPI.
- The subsections for **14 CLINICAL STUDIES** are not listed and must be included. [See 21 CFR 201.57 (b)]

14.1 Healing of Erosive Esophagitis

14.2 Symptomatic Gastroesophageal Reflux Disease (GERD)

14.3 Risk Reduction of NSAID-Associated Gastric Ulcer

14.4 Helicobacter pylori (H. pylori) Eradication in Patients with Duodenal Ulcer Disease

- The required footnote “*Sections or subsections omitted from the full prescribing information are not listed.” should be right justified.
[See <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.]

FPI:

- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10), please use bold print sparingly. Use another method for emphasis such as italics or underline.
[See <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.]
- The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. For example, [*see Clinical Studies (14) and Dosage and Administration (2)*], not [See **Clinical Studies (14) and DOSAGE AND ADMINISTRATION. (2)**]. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. Please fix all cross-references throughout the labeling. [Implementation Guidance]
- Under Adverse Reactions, you refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance> and revise your Adverse Reactions section accordingly.
- Move the manufacturer’s information from the end of How Supplied/Storage and Handling to the last page of the labeling after the Patient Counseling Information.
- Delete “Revised: 09/2006” at the end of the labeling. The revision date at the end of Highlights replaces this information.

Recommendations

After the comments are conveyed to the applicant and revised labeling is submitted, please check to ensure that comments have been addressed and incorporated into the labeling. At the first labeling meeting, use the applicant’s updated (revised) draft labeling for review.

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 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Robin E Anderson
12/14/2006 03:09:11 PM
CSO

Laurie Burke
12/14/2006 07:48:19 PM
INTERDISCIPLINARY

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research

To: Brian Harvey, MD, PhD
Director, Division of Gastroenterology Products
HFD-180

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: November 16, 2006

Subject: OSE Review 2006-765, Nexium (Esomeprazole Magnesium for Oral Suspension)
10 mg; NDA 22-101

This memorandum is in response to a November 1, 2006 request from your Division for a review of the container label, carton and package insert labeling for Nexium for Oral Suspension 10 mg. Nexium for Oral Suspension 20 mg and 40 mg was approved on October 20, 2006. Subsequently, the sponsor is now submitting a new NDA supporting the use of the 10 mg strength in patients aged 1 to 11 years old.

The approval letter for the 20 mg and 40 mg strengths signed off October 24, 2006 (backdated to October 20, 2006) states the following:

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and labeling for immediate container and carton labels submitted on December 22, 2005. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

However, DMETS notes that the container labels and carton labeling submitted on December 22, 2005 do not reflect revisions negotiated between DMETS, the Division, and the sponsor made through e-mail correspondence throughout the month of October up until the approval date of the drug.

The 10 mg labels and labeling submitted to DMETS for review also did not reflect the revisions negotiated between DMETS, the Division, and the sponsor. Thus, DMETS requested that the labels and labeling for the 10 mg product strength be revised to reflect the revisions negotiated upon and resubmitted for review. The revised labels were submitted on December 6, 2006, and are the subject of this review. Furthermore, any reference to labels and labeling for the 20 mg and 40 mg strengths contained in this review are with regard to the labels and labeling which reflect the negotiated revisions, and not with regard to the labels and labeling submitted December 22, 2005.

In the review of the container labels, carton and insert labeling of Nexium for Oral Suspension, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement for the package insert labeling, which may minimize potential user error.

A. General Comments

1. DMETS refers the Division to DMETS' comments contained in an October 13, 2006 e-mail correspondence to the Division regarding the confusing nature of the expression of product strength with relation to the active moiety of the drug product and continues to recommend that Guirag Poochikian, Acting Chair of CDER's Labeling and Nomenclature Committee, be contacted for further guidance on this matter.
2. De-bold the font used to state the net quantity (e.g. 30 single dose packets).

B. Packet Label (Trade and Physician Sample)

1. See General Comments A-1 and A-3.
2. The graphic presented in the bottom right corner of the of the principal display panel is distracting and detracts attention from important information such as the proprietary name, established name, and product strength. Decrease the prominence of the graphic in order to allow for increased prominence of the proprietary and established names.

C. Carton Label (Trade and Physician Sample)

1. See General Comments A-1 and A-2.
2. The color schemes used for the 10 mg packets and 40 mg packets (purple background with white text) are identical, with exception to the background color used for the product strength (red background with white font for 10 mg vs. white background with purple font for 40 mg). A lack of distinct differentiation between the product strengths may lead to product selection errors. DMETS recommends increasing the size of the strength in order to increase it's prominence against the purple background which overwhelmingly causes the cartons to look similar. Additionally, we request a different background color be used for each strength to avert potential product selection errors.

D. Package Insert

1. See General Comment A-1.
2. The FDA in conjunction with the ISMP launched a campaign on June 14, 2006 to reduce medication errors and/or confusion caused by unclear medical abbreviations. Furthermore, the July 20, 2006 IOM Report titled "Preventing Medication Errors" recommends and urges FDA to standardize abbreviations, acronyms, and terms to the extent possible (i.e., recommendation #4 in the IOM report). Additionally, JCAHO discourages the use of dangerous abbreviations, acronyms, and symbols in their 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals. Therefore DMETS recommends the following.
 - a. Delete the trailing zeroes used throughout the package insert. The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol.
 - b. Use "mcg" instead of "µg" to denote micrograms. Based on our post-marketing experience, the abbreviation "µ" could resemble the letter "m" depending upon how it is scripted and result in misinterpretation of the units as milligram rather than microgram. Additionally, the symbol "µ" appears on the ISMP's (Institute for Safe Medication Practices) "List of Error-Prone Abbreviations, Symbols, and Dose Designations".

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/s/

Kristina Arnwine
12/22/2006 12:05:22 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/22/2006 12:29:23 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/22/2006 12:35:21 PM
DRUG SAFETY OFFICE REVIEWER