

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-957

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop Room 4447)**

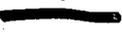
DATE RECEIVED: February 27, 2006	DESIRED COMPLETION DATE: May 27, 2006	OSE REVIEW #: 06-0054
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TO: Brian Harvey, MD, PhD
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HFD-180

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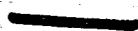
PRODUCT NAME:

Nexium
(Esomeprazole Magnesium Delayed-release  Oral Suspension)
20 mg and 40 mg

NDA#: 21-957

NDA SPONSOR: AstraZeneca

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Nexium. This is considered a final decision. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section IV of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Nexium Delayed-release  Oral Suspension, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
White Oak Bldg 22, Mail Stop Room 4447
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

PROPRIETARY NAME AND LABEL/LABELING REVIEW

DATE OF REVIEW: April 6, 2006
NDA#: 21-957
NAME OF DRUG: Nexium
(Esomeprazole Magnesium Delayed-release [REDACTED] Oral Suspension)
20 mg and 40 mg
NDA HOLDER: AstraZeneca

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastroenterology Products (HFD-180), for assessment of the proprietary name, Nexium, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

The sponsor, AstraZeneca, currently markets Nexium Delayed-release Capsules (21-153) which were approved February 20, 2001 and Nexium IV injection (NDA 21-689) which was approved March 31, 2005. Nexium Delayed-release [REDACTED] Oral Suspension is an extension of the Nexium product line.

PRODUCT INFORMATION

Nexium Delayed-release [REDACTED] Oral Suspension is a proton-pump inhibitor indicated for the treatment of gastroesophageal reflux disease, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and risk reduction of NSAID-associated gastric ulcers. The usual dose of Nexium Delayed-release [REDACTED] Oral Suspension is 20 mg or 40 mg by mouth once daily. The granules should be mixed with one tablespoon of water; left for a few minutes to thicken, stirred, and drank within 30 minutes. The granules may also be mixed with water and administered via nasogastric or gastric tube. Nexium Delayed-release [REDACTED] Oral Suspension are supplied in unit-dose packets, containing either 20 mg or 40 mg per packet. Thirty packets will be contained in each carton.

II. SEARCH OF FDA ADVERSE EVENT REPORTING SYSTEM (AERS):

Since the proprietary name, Nexium, has been used in the marketplace since February 2001, DMETS conducted a search of the Adverse Event Reporting System (AERS) for medication errors associated with the product Nexium. The search was conducted using the high group level term "medication errors," and the preferred terms "medication error", "pharmaceutical product complaint", "accidental overdose", and "overdose," and "circumstance or information capable of leading to medication error," as well as the active ingredient "esomeprazole," the trade name "Nexium," and the verbatim substance

name "Nexium%." The search identified eleven medication errors (n=11) associated with Nexium. The errors can be divided into the following categories, wrong strength, wrong drug, and inappropriate dose. See Appendix A for a table containing summaries of all eleven reports.

A. Wrong Drug (n=4)

In total, four cases of postmarketing name confusion were reported between Nexium and other drug products [Prilosec (1), Neurontin (2), and Flexium (1)]. The case involving confusion between Nexium and Prilosec reports the patient was ordered Prilosec 40 mg but was dispensed Nexium 40 mg. The patient took one or two capsules of Nexium 40 mg and experienced severe bruising on the back of her legs as well as thrombocytopenia. The reporter did not identify any contributing factors which may have led to the errors. However, upon further review, DMETS notes that there were three AERS reports (see section II-C below) which discussed similar looking capsules between Nexium and Prilosec which may have contributed to the error described above. Nexium capsules and Prilosec capsules are both purple. Additionally, the reporter in one of those cases indicated that the generic names of Nexium and Prilosec (esomeprazole and omeprazole) are similar and that the stock bottles of both products look similar. In summary, the reported cases of confusion between Nexium and Prilosec may have been related to the similar capsule appearance, similar established names, and/or similar looking stock bottles, rather than proprietary name confusion. Since the confusion to this point does not warrant a change to the established name of either product, consideration may need to be given to revising the color of these capsules and differentiating the labeling of each product.

In both cases concerning Nexium and Neurontin confusion, the patient was ordered Neurontin but Nexium was dispensed and administered in error. In both cases, the patient was hospitalized. The first case describes hospitalization after taking Nexium three times daily for one week. The patient experienced congestive heart failure, shortness of breath, weight gain, and increased hypertension within one week of taking the Nexium. In the second case, the patient took three to five capsules of Nexium daily for fifty-one days when the error was discovered. The patient was hospitalized and experienced abdominal cramping, felt tired, and had more headaches. The cases of confusion between Nexium and Neurontin occurred as a result of similar looking proprietary names. These errors occurred in 2003 and 2004. We have not seen additional errors, thus, DMETS will continue to monitor errors due to confusion between Nexium and Neurontin, but does not believe that any regulatory action is required at this time.

The final case (n=1) of reported name confusion was a complaint that Nexium and Flexium could be confused. With respect to Nexium and Flexium, DMETS will continue to monitor errors due to confusion, but does not believe that any regulatory action is required at this time.

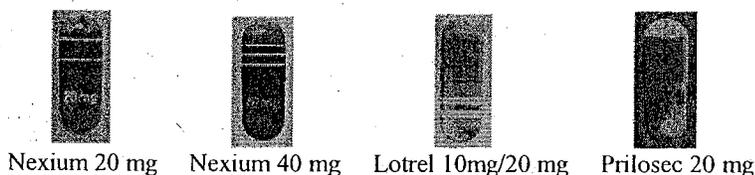
B. Improper Dose (n=3)

Three medication error cases involve administration of an improper dose of Nexium. The first case involved a patient that took an overdose of Nexium. The patient was prescribed 40 mg daily but she ingested all seven Nexium 40 mg capsules in one day. The patient experienced loose stools, nausea, and weakness. The second case involved a patient who was prescribed Nexium 40 mg daily. However, he took three Nexium 40 mg capsules within an eight-hour period. The patient had also consumed alcohol. The patient experienced confusion, insomnia, and was not himself. The last case involved a patient that took Nexium 40 mg three times daily for five days instead of once daily as prescribed. The patient was hospitalized with what was believed to be a transient ischemic attack. The three reports described above did not identify any contributing factors which may have led to the

medication errors. Thus, we cannot determine the main cause of confusion. We cannot assess if the directions on the bottle were correct or if the patient was instructed to take these improper doses by a healthcare practitioner or if the patients were confused with regard to the dosing directions.

C. Look-Alike Capsules (n=4)

Overall there were four potential medication errors which described concerns about similar capsule appearance among Nexium's various strengths as well as Nexium when compared to other drug products. In two error cases (n=2) the reporter states concerns about the similar appearance of Nexium 20 mg capsules and 40 mg capsules. DMETS notes that both Nexium 20 mg and Nexium 40 mg are purple capsules with yellow font and yellow lines. The only difference between the capsules is that the 40 mg capsule has three yellow stripes and the 20 mg capsule only has two yellow stripes (see below). Additionally, there was one case (n=1) in which the reporter noted the similar appearance of the Nexium 20 mg, Nexium 40 mg, and Prilosec capsules. DMETS notes that as mentioned above, the Nexium capsules are both purple capsules, which is similar to the Prilosec 20 mg capsule which is purple as well. However, the Prilosec capsule does not have any yellow writing or stripes on the capsule (see below). Lastly, there was one case (n=1) that noted the similar appearance of Nexium and Lotrel capsules. DMETS notes that the Lotrel 10 mg/20 mg capsule looks similar to the Nexium capsule since the Lotrel capsule is purple with stripes as well (see below). DMETS does not believe that any regulatory action is required at this time. DMETS will continue to monitor errors due to confusion between Nexium, Prilosec, and Lotrel.



III. SAFETY EVALUATOR RISK ASSESSMENT

The AERS search identified existing confusion with Nexium capsules' similar color and appearance to Lotrel and Prilosec. Additionally, name confusion was noted with Nexium and Neurontin. Following assessment of the medication errors identified in the AERS search, DMETS believes that the introduction of delayed-release granules for oral suspension dosage form of Nexium should not exacerbate current confusion with Nexium. Since the proposed product is supplied as granules for oral suspension it should not add to the confusion caused by similar product appearance. With respect to the name confusion of Neurontin and Nexium, we note Neurontin is available as an oral solution as well, but the prescribed and dispensed dosage form is different (granules vs. oral solution) which should help to prevent confusion. Additionally, the usual dose of Nexium is 20 mg to 40 mg taken once daily unlike Neurontin, whose usual dose is 300 mg to 800 mg three times daily.

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

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

A. General Comments

1. DMETS notes that the strength is based on the active moiety. Thus, we suggest revising the labels and labeling in one of the three following formats. Please note that DMETS prefers choice 'a' because this nomenclature is consistent with USP recommendations on "amount of ingredient per dosage unit".

a. Nexium
(Esomeprazole Delayed-release Granules for Oral Suspension)
XX mg

b. Nexium
(Esomeprazole Magnesium Delayed-release Granules for Oral Suspension)
XX mg*

*Each packet contains esomeprazole magnesium equivalent to XX mg of esomeprazole

c. Nexium
(Esomeprazole Magnesium Delayed-release Granules for Oral Suspension)
equivalent to XX mg esomeprazole

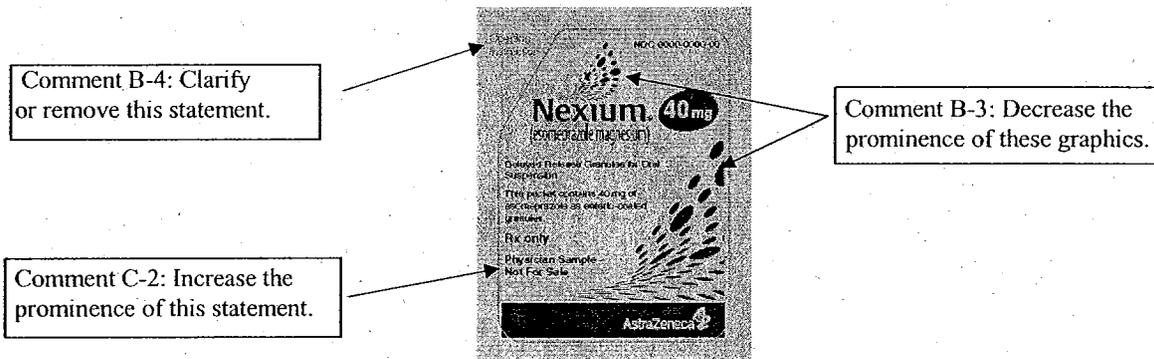
2. Indicate specifically how long "a few minutes" is with regard to how long a patient must wait for the suspension to thicken.

B. Packet Label (20 mg and 40 mg, trade packet)

1. See General Comments A-1 and A-2.
2. The color schemes used for the 20 mg and 40 mg capsules are identical (gray background with black text). A lack of distinct differentiation between the product strengths may lead to selection errors, especially if the packets are not stored in the cartons. Revise so that the strengths are differentiated using methods such as boxing, differing color schemes, etc.
3. The graphic presented immediately above the proprietary name and in the bottom right corner of the packet distracts from and decreases the readability and prominence of important information such as the proprietary and established names, as well as the product strengths (see page 6). Decrease the prominence of these graphics.
4. Clarify or remove the statement, "Opening Instruction." As currently presented there are no instructions regarding the opening of the packet (see page 6). If the intent of this statement is to clue patients in on how to open the packet, the language should be revised so that it provides instructions to the patient such as "cut here" or "open here".

C. Packet Label (20 mg and 40 mg, Physician's Sample)

1. See General Comments A-1 and A-2 and comments B-2 through B-4.
2. Increase the prominence of the statement, "Physician's Sample – Not For Sale."



D. Carton Labeling (20 mg and 40 mg, 30 count)

1. See General Comments A-1 and A-2.
2. The color schemes used for the 20 mg capsules and 40 mg capsules (purple background with white text) are identical, with exception to the background color used for the product strength (blue background with white font for 20 mg vs. white background with purple font for 40 mg). A lack of distinct differentiation between the product strengths may lead to selection errors. DMETS recommends increasing the size of the strength in order to increase its 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.

E. Carton Labeling (20 mg and 40 mg, Physician's Sample)

See General Comments A-1 and A-2 and comments C-2 and D-2.

F. Insert Labeling

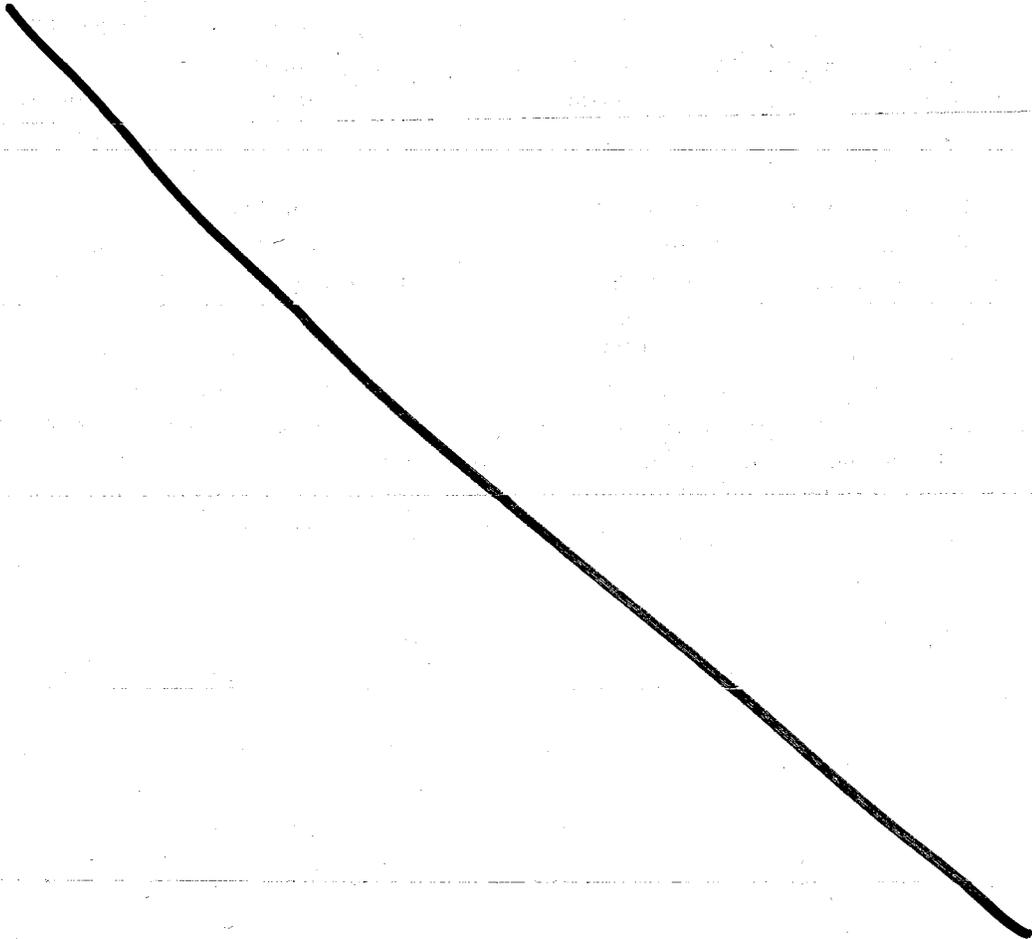
1. See General Comment A-1.
2. Remove the trailing zeroes used throughout the package insert (e.g. Precautions Section, Carcinogenesis, Mutagenesis, Impairment of Fertility Subsection and Pregnancy Subsection). The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. The FDA in conjunction with the ISMP launched a campaign on June 14, 2006 to reduce medication mistakes and/or confusion caused by unclear medical abbreviations. Thus in order to comply with these recommendations, we request all trailing zeroes be removed from the insert.
3. Precautions, Information for Patients Sub-Section

See comment A-2.

4. Dosage and Administration Section, Administration Options Subsection

a. See General Comment A-2.

b. Nexium Delayed-Release Capsules Subsection



1 Page(s) Withheld

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Draft Labeling

Deliberative Process

**This is a representation of an electronic record that was signed electronically and
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/s/

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