

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

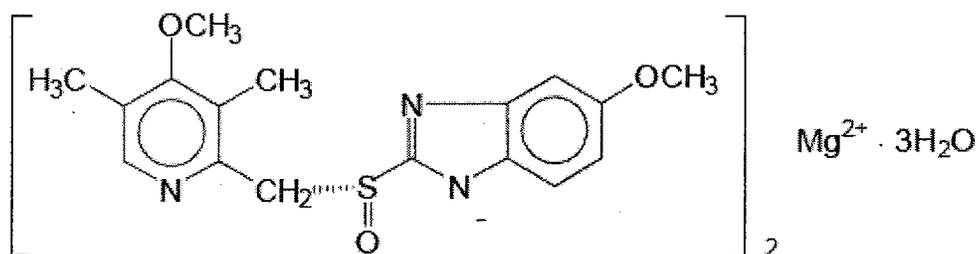
**22-101**

**CHEMISTRY REVIEW(S)**



## NDA 22-101

### Nexium<sup>®</sup> (esomeprazole magnesium) For Delayed Release Oral Suspension



Astra Zeneca, LP

Division of Gastroenterology Drug Products

Milton J. Sloan, Ph.D.  
ONDQA Pre-Marketing Assessment Division II Branch IV

For  
Branch III



# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>6</b>
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability .....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s) .....	6
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block .....	9
<b>Chemistry Assessment.....</b>	<b>10</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Name, Manufacturer] .....	10
P DRUG PRODUCT [Name, Dosage form].....	11
A APPENDICES .....	45
R REGIONAL INFORMATION .....	45
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	46
A. Labeling & Package Insert .....	46
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	48
III. List Of Deficiencies To Be Communicated.....	48



# Chemistry Review Data Sheet

1. NDA: 22-101
2. REVIEW #: 1
3. REVIEW DATE: 01-June-2007:
4. REVIEWER: Milton J. Sloan, Ph. D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

27-September-2006

Amendment (BL)

06-December-2006

Amendment (BC)

25-April-2007

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca LP

1800 Concord Pike

Address: P.O. Box 8355  
Wilmington, DE 19803-8355

Representative: N/A

Telephone: (800) 456-3669

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NEXIUM

b) Non-Proprietary Name (USAN): esomeprazole magnesium

c) Code Name/# (ONDQA only): H199/18

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: Standard Review



## CHEMISTRY REVIEW

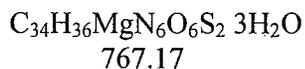
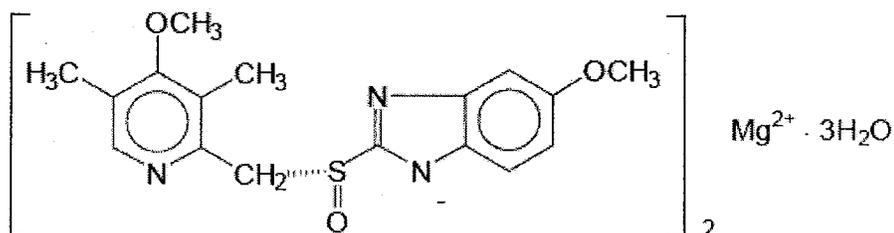


### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Proton Pump Inhibitor
11. DOSAGE FORM: For Delayed-Release Oral Suspension
12. STRENGTH/POTENCY: 10 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

bis(5-methoxy-2-((S)[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl] sulfinyl)-1H benzimidazol-1-yl) magnesium trihydrate



17. RELATED/SUPPORTING DOCUMENTS:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
_____	III	_____	_____	3, 4	Adequate	07/31/2006	Shulin Ding

b(4)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-153	Approved reference for Drug substance
NDA	21-957	Approved reference for 20 and 40 mg for delayed release oral suspension

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	12-Nov-2006	S. Adams
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	To be done per ONDQA policy	N/A	N/A
DMETS	Acceptable pending update of comments	16-Nov-2006	K.C. Arnwine Pharm.D.
EA	Acceptable	09-Feb-2007	Raanan A. Bloom, Ph.D.
Microbiology	N/A	N/A	N/A



# The Chemistry Review for NDA 22-101

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended for approval (AP) from the Chemistry, Manufacturing, and Controls perspective, pending minor labeling revisions.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Substance

The drug substance, esomeprazole magnesium trihydrate, as well as the enteric coated esomeprazole pellets was originally approved for the Nexium (esomeprazole magnesium) Delayed-Release Capsules NDA 21-153. The information on the drug substance is not included in this NDA. Esomeprazole is acid labile and is therefore formulated as a multitude of enteric-coated pellets of esomeprazole magnesium trihydrate. The chemical name is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. The esomeprazole magnesium trihydrate is formulated in the form of enteric-coated pellets (granules) containing the following excipients: glyceryl 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate.

b(4)

Esomeprazole (Nexium®) is the pure S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole (Losec/Prilosec®), and shares the same mechanism of action. Omeprazole has an asymmetric center at the sulfur atom that can be resolved into the S-enantiomer esomeprazole (H 199/18) and the R-enantiomer H 199/19. The pharmacodynamic effects of the enantiomers do not differ from each other or from the racemate *in vitro*, since both enantiomers are chemically converted to the same active molecule (the achiral sulfenamide), in the gastric parietal cell. However, the pharmacokinetic properties of esomeprazole have been found preferable to those of both H 199/19 and omeprazole in humans (*in vivo*). Hence, the rationale for the development of esomeprazole is the better clinical efficacy and reduced inter-individual variation with esomeprazole compared to omeprazole.

## Executive Summary Section

Drug Product

The current proposed dosage of Nexium is a 10 mg strength which refers to the actual esomeprazole content. Information has been included in the NDA for — strengths — 10, 20 and 40 mg), as in NDA 21-957 previously submitted and approved (20-Oct-2006) for the 20 and 40 mg of the same oral suspension. Esomeprazole (Nexium) has been on the market as an oral capsule formulation also at the doses of 20 and 40 mg since the year 2000, and as an intravenous formulation at the same dosage since 2003. **b(4)**

The Esomeprazole “sachet” contains esomeprazole pellets and excipient granules, which are both filled into single-use, child resistant, aluminum packet (denoted as a “sachet” by the sponsor). Two drug product components are filled into each “sachet” during the manufacturing process. The first drug component consists of esomeprazole delayed-release granules (also denoted as esomeprazole pellets). The esomeprazole pellets are the same enteric-coated esomeprazole pellets that are used in the approved capsule formulation. **b(4)**

The approved nomenclature recommended remains as:

Nexium® (esomeprazole magnesium\*) for Delayed-release Oral Suspension.

Since the strength is expressed in terms of the base esomeprazole, an asterisk (\*) to the labeling statement to indicate: “contains 22.3 mg of esomeprazole magnesium trihydrate which is equivalent to 20 mg of esomeprazole as enteric coated granules” remains the recommended and agreed upon approach.

The term “sachet” is not consistent with CDER standards and remains not recommended. The term “pellet” has been replaced for use with the delayed-release oral suspension dosage form. Additional minor labeling comments may not be captured in this review but will be communicated to the sponsor for review of the final printed draft label.



## Executive Summary Section

**B. Description of How the Drug Product is Intended to be Used**

The proposed clinical use is as an alternative “Sachet formulation” to Nexium® Delayed-Release Capsules. The proposed dosage form of esomeprazole is an oral suspension that is suitable for administration by spoon, drinking or through an enteric tube. Esomeprazole is currently approved for the treatment of gastroesophageal reflux disease (GERD), the treatment, prevention and/or risk reduction of ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and in combination with appropriate antibacterial therapeutic regimens, for the eradication of *H. pylori*. The proposed dosage of 10 mg once daily for 1 to 11 years old population group (and 20 mg) is proposed for this NDA. Depending on the indication, Nexium may be taken from 10 days or up to 6 months (refer to dosing and administration in labeling). Prior to administration, the full contents of a single “sachet” are added to water 15 mL for the 10 mg strength to form a viscous suspension, which can be left for up to 30 minutes before administration. The drug product has been found to be stable when stored at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature]. The recommended expiry date for this drug product is 36 months.

**C. Basis for Approvability or Not-Approval Recommendation**

The sponsor has demonstrated that the esomeprazole granules are stable and are the same as the enteric-coated esomeprazole pellets that are approved in the capsule and oral suspension formulations. The bioequivalence study between Esomeprazole “sachets” and Nexium Capsules concluded that the two formulations are bioequivalent. The drug substance, esomeprazole magnesium trihydrate and the enteric-coated esomeprazole pellets in the “sachet” formulation are identical to those used in the currently approved Nexium (esomeprazole magnesium) Delayed-Release Capsules NDA 21-153.

The dissolution test acceptance criteria for the esomeprazole “pellets” and the esomeprazole “sachets” is the same specification that has been approved and is acceptable for the 10 mg strength. The sponsor has demonstrated that the finished oral suspension dosage form conforms to USP <724> article for delayed release (enteric coated) dosage forms. The sponsor’s rationale for the modified analytical method for dissolution to not include testing for drug release in acid medium is acceptable. It is justified by the revised dissolution acceptance criterion of not less than — (Q) of label claim of esomeprazole released at pH 6.8 buffer.

b(4)

The proposed specifications have been found adequate and suitable for a quality drug product. The applicant has demonstrated via CMC data submitted in the application that this new formulation is stable throughout the proposed 36 months shelf life of the drug product. The manufacturing sites have all been found “Acceptable” by the Office of Compliance (16-Nov-2006). All comments have been communicated to the sponsor and satisfactorily resolved.



**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: October 15, 2006

Revised Draft: June 01, 2007

Final Draft: June 22, 2007

Branch Chief: Moo Jhong Rhee, Ph.D.

Date:

**C. CC Block**

# 41 Page(s) Withheld

  X   Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

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Milton Sloan  
7/13/2007 10:50:35 AM  
CHEMIST

Moo-Jhong Rhee  
7/13/2007 11:04:42 AM  
CHEMIST  
Chief, Branch III

**Initial Quality Assessment**  
**Branch 3**  
**Pre-Marketing Assessment Division 2**

**OND Division:** Division of Gastroenterology Products  
**NDA:** 22-101  
**Applicant:** AstraZeneca  
**Stamp Date:** 9/27/06  
**Received by PAL:** 10/2/06  
**Review Date:** 12/15/06  
**PDUFA Date:** 7/27/07  
**Trademark:** Nexium®  
**Established Name:** esomeprazole magnesium  
**Dosage Form:** Delayed Release Granules for Oral Suspension  
**Route of Administration:** oral  
**Indication:** Proton pump inhibitor

**PAL:** Marie Kowblansky, PhD

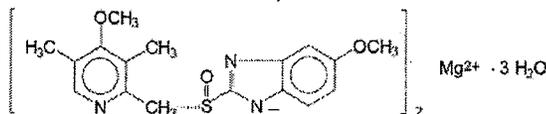
	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

### A. Summary

The current application for NEXIUM® for Delayed Release Oral Suspension (esomeprazole magnesium) has been submitted for use in the 1 to 11 year old population. The product is packaged in single-use child resistant aluminum packets containing 10 mg of omeprazole per packet. It is suspended in water prior to administration by spoon, drinking, or through enteric tubes. The identical product, but containing 20 and 40 mg of omeprazole per packet, was recently approved under NDA 21-957. That NDA was originally filed with CMC information for — strengths — 10, 20, and 40 mg), but the Agency informed AstraZeneca that the acceptability of the 10. — mg dosages would not be reviewed under NDA 21-957, since these strengths had no relevance to the proposed labeling. The current application is a complete re-presentation of the quality information submitted to NDA 21-957 for the purpose of supporting the approval of the 10 mg (and 20 mg) product for administration once daily in the 1-11 year old population.

b(4)

The active drug substance is the magnesium salt of the S enantiomer of omeprazole:



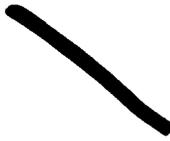
The drug product consists of two drug product intermediates, esomeprazole delayed release granules (also referred to as esomeprazole pellets) and excipient granules. It is prepared by

b(4)

two types of granules is given as:

The composition of these

- Esomeprazole delayed release granules contain: esomeprazole, glycerol monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polysorbate 80, sugar spheres, talc, and triethylcitrate. These esomeprazole granules are the same as the esomeprazole enteric coated pellets approved in NDA 21-153 for use in Nexium Delayed- Release Capsules; Consequently, most of the information regarding the drug substance and the esomeprazole pellets is cross-referenced to NDA 21-153. b(4)
- Excipient granules contain: glucose, xanthan gum, crosslinked polyvinylpyrrolidone, citric acid, iron oxide \_\_\_\_\_, and hydroxypropyl cellulose. According to the applicant, \_\_\_\_\_ Therefore, the amount of xanthan has been kept to a minimum. b(4)



b(4)

Specification acceptance criteria and testing procedures are as approved under NDA 21-957 for the 20 mg and 40 mg product.

Inspection requests for the two facilities involved in the manufacture of the drug substance and drug product have been entered into EES and on November 16, 2006 the facilities were classified as Acceptable by the Office of Compliance.

An Environmental Assessment has been submitted with the NDA. It has been consulted to the Office of Pharmaceutical Sciences for evaluation.

**B. Critical issues for review**

Since the product that is the subject of this NDA is identical to the product that was recently approved in NDA 21-957, with the exception of strength, it should conform to the same specifications as approved in NDA 21-957. The full review of NDA 22-101 should ensure that the revisions that were made to NDA 21-915 as a consequence of our evaluation (e.g. revised dissolution specification, labeling) have been incorporated into the current NDA.

**C. Comments for 74-Day Letter -- None**

Marie Kowblansky, PhD  
Pharmaceutical Assessment Lead

12/15/2006  
Date

Moo-Jhong Rhee, PhD  
Branch Chief

12/15/2006  
Date

## **MANUFACTURING FACILITIES**

The manufacture, quality control testing, and release of the drug substance is performed at:

AstraZeneca Dunkerque Production (AZDP)  
224 Avenue de la Dordogne  
Dunkerque, France  
FEI: #3003814870

The manufacture, quality control testing, packaging, labeling and release of the product and esomeprazole pellets and excipient granules are performed at:

AstraZeneca AB  
Gartunavagen SE-151 85  
Sodertalje, Sweden  
FEI: #3002806411

The AstraZeneca contact for the above manufacturing facilities is John Grazal, Senior Director AstraZeneca Global Compliance Management Group (302) 886-3527

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Marie Kowblansky  
1/30/2007 11:50:47 AM  
CHEMIST

This document will be replacing an earlier version that  
was placed into DFS with the wrong NDA  
number

Moo-Jhong Rhee  
1/30/2007 04:57:45 PM  
CHEMIST  
Chief, Branch III