

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-957

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

MEMORANDUM

Date: October 20, 2006

To: NDA 21-957

Through: Moo-Jhong Rhee, Ph. D. , Branch Chief, Division of Pre-marketing Assessment 2

From: Milton J. Sloan, Ph. D. , Chemistry Reviewer, Division of Pre-marketing Assessment 2

Subject: Final Draft Printing of Label for Nexium® (esomeprazole magnesium) For Delayed Release Oral Suspension

The sponsor has revised their draft labeling as indicated in the attachments. The revisions have been reviewed and found acceptable.

Memorandum Prepared by

Milton J. Sloan, Ph. D. Chemist Reviewer

Date

for Concurrence:

Moo-Jhong Rhee, Ph. D. , Branch Chief,
Division of Pre-marketing Assessment 2

Date

ATTACHMENTS:

9 Page(s) Withheld

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✓ Draft Labeling

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/s/

Milton Sloan
10/20/2006 03:13:02 PM
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Moo-Jhong Rhee
10/20/2006 03:19:56 PM
CHEMIST
Chief, Branch III

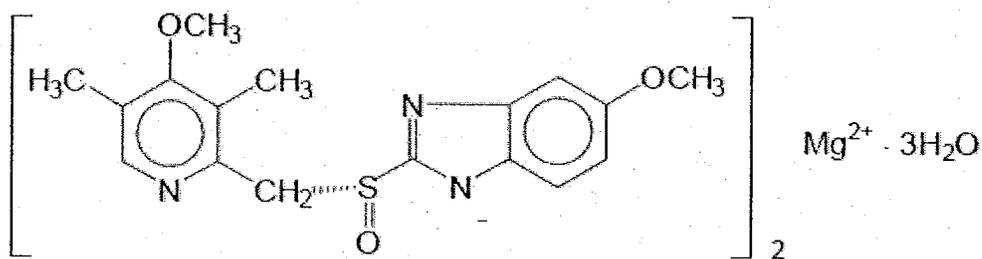
NDA 21-957**Nexium® (esomeprazole magnesium) For Delayed Release
Oral Suspension****Astra Zeneca, LP****Division of Gastroenterology Drug Products****Milton J. Sloan, Ph.D.****ONDQA Pre-Marketing Assessment Division II Branch IV**



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Chemistry Review Data Sheet

1. NDA: 21-957

2. REVIEW #: 1

3. REVIEW DATE: 13-October-2006:

4. REVIEWER: Milton J. Sloan, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

IND 53,733

18-July-1997

IND 54,599

21-November-1997

IND

17-October-2001

NDA 21-153

03-December-1999

NDA 21-154

28-February-2000

Original

22-December-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

22-December-2005

Amendment (BC)

11-July-2006

Amendment (BC)

13-July-2006

Amendment (BC)

07-September-2006

Amendment (BC)

12-September-2006

Amendment (BL)

13-October-2006



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Chemistry Review Data Sheet

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/# (ONDC only): H199/18
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Proton pump inhibitor

11. DOSAGE FORM: For Delayed-Release Oral Suspension

12. STRENGTH/POTENCY: 20mg, and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

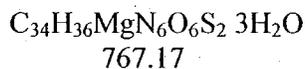
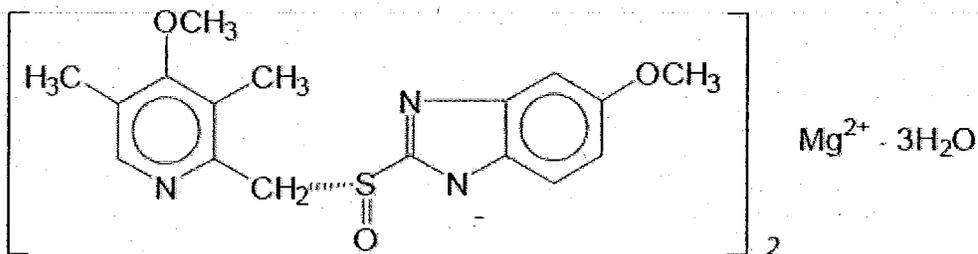
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	3	Adequate	04/27/2006	None

¹ 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")

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

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-153	Approved reference for Drug substance

18. STATUS:**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	12-Sept-2006	S. Adams
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	See review for recommendations	N/A	N/A
Methods Validation	N/A	N/A	N/A
DMETS	See review for recommendations	22-Sept-2006	K.C. Arnwine
EA	Categorical Exclusion claimed- Acceptable	N/A	N/A
Microbiology	N/A	N/A	N/A



The Chemistry Review for NDA 21-957

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.

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 esomeprazole pellets were 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, but has been taken from the cross-referenced capsules NDA mentioned above and included in this review. 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.

Esomeprazole (Nexium®) is the pure S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole (Losec/Prilosec®), and shares the same mechanism of action. Both omeprazole and esomeprazole work through an inhibition of the final step in gastric acid production (the H⁺/K⁺-ATPase, located in the secretory membranes of the parietal cells in the gastric oxyntic mucosa), resulting in a profound inhibition of gastric acid secretion. Omeprazole has an asymmetric center at the sulfur atom and can thus 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



Executive Summary Section

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*). This results in a better clinical efficacy and reduced inter-individual variation with esomeprazole compared to omeprazole, and is the rationale for the development of esomeprazole.

Drug Product

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). Although information has been included the NDA for [REDACTED] strengths ([REDACTED] 20 and 40 mg); in the original NDA submission, the currently proposed and approved indications and dosages of Nexium only encompass the 20 and 40 mg strengths which refers to the actual esomeprazole content. Esomeprazole (Nexium) has been on the market as a oral capsule formulation at the doses of 20 and 40 mg since the year 2000, and as an intravenous formulation at the same dosage since 2003. The three lower strengths are intended to facilitate administration to younger patients, and will be subject to future pediatric submissions.

Two drug product components (hereafter referred to as intermediates by the sponsor) are filled into each "sachet" during the manufacturing process. The first intermediate 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. [REDACTED]



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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. This newly proposed dosage form of esomeprazole is for an orally suspended drug product 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 recommended adult dosage is 20 or 40 mg once daily. 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 ([REDACTED] 15 mL for the higher strengths, [REDACTED] 20 and 40 mg esomeprazole) 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 30 months.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has demonstrated that the esomeprazole granules are the same as the enteric-coated esomeprazole pellets that are used in the approved capsule formulation. The bioequivalence study (see Clinical Study Report D9612C00032) between Esomeprazole "sachets" 40 mg and Nexium Capsules 40 mg was performed and it has been concluded that the two formulations are bioequivalent. A waiver of bioequivalence studies for the strengths lower than 40 mg is justified based on dose proportionality. *In vitro* dissolution profiles of the lower "sachet" strengths were compared to that of the 40 mg "sachet" and were statistically determined to be similar. Since the drug substance (esomeprazole magnesium) and the esomeprazole pellets in the "sachet" formulation are considered identical to those used in the currently approved Nexium Delayed-Release Capsules, the existing nonclinical documentation supporting the oral use of esomeprazole is considered to be relevant for both the formulations of Nexium. The drug substance, esomeprazole magnesium trihydrate, as well as the esomeprazole pellet composition were originally approved in the Nexium (esomeprazole magnesium) Delayed-Release Capsules NDA 21-153, in February 2001. No additional nonclinical studies were considered necessary to specifically support the use of the for oral suspension formulation. Since the finished dosage form differs, the analytical method was modified to accommodate this difference. The sponsor amended the NDA (12-Sept-2006) to revised the dissolution test acceptance criteria for the esomeprazole "pellets" and the esomeprazole "sachets". The sponsor has thus demonstrated explicitly, 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 not include testing for drug release in acid medium and is acceptable and is justified by the revised dissolution

**Executive Summary Section**

acceptance criterion of not less than ~~100%~~ (Q) of label claim of esomeprazole released at pH 6.8 buffer. The proposal for a tolerance of ~~100%~~ for the fill weight has been found acceptable. The commitment by the sponsor not to exceed the hold time of 6 months for the excipient granules and for the esomeprazole pellets (granules) is acceptable. The holding time was demonstrated from the results of the stability batches.

The nomenclature recommended is:

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

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

The term “sachet” is generally not consistent with CDER standards and not recommended. Recommended changes were made using “track changes” to the annotated draft label. The term “pellet” is not recommended for use with the delayed-release oral suspension dosage form. The recommended labeling changes have in principle been agreed to by the sponsor. There may be additional minor labeling comments communicated to the sponsor pending review of the final printed draft label. 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 30 months shelf life of the drug product. The manufacturing sites have all been found acceptable with the Office of Compliance. The EER has an acceptable overall recommendation (12-Sept-2006).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: September 15, 2006

Final Revision: October 16, 2006

Branch Chief: Moo Jong Rhee, Ph.D.

Date:

Project Manager:

Date

C. CC Block

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/s/

Milton Sloan

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Sponsor has agreed in principle to labeling recommendations. There
may be additional labeling comments communicated pending review
of final printed label.

Moo-Jhong Rhee

10/16/2006 03:40:15 PM

CHEMIST

Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 21-957
Applicant: AstraZeneca
Stamp Date: 12/21/05
Received by PAL: 1/10/06
Review Date: 3/27/06
PDUFA Date: 10/21/06
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

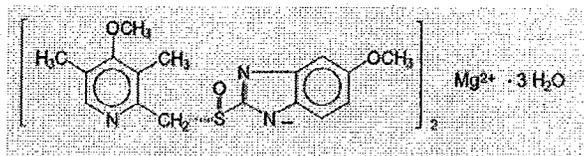
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	
Comments for 74-Day Letter		<input checked="" type="checkbox"/>

A. Summary

NEXIUM® Delayed Release Granules for Oral Suspension (esomeprazole magnesium) has been submitted in strengths in the present application, 20, and 40 mg. (The product is also referred to as Esomeprazole Sachet.)

The product, which is packaged in a single-use child resistant aluminum packet, is suspended in water prior to administration by spoon, drinking, or through enteric tubes.

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



The Esomeprazole Sachet formulation is a mixture of esomeprazole magnesium delayed release granules (also referred to as esomeprazole pellets in the submission and in this review) and excipient granules. For the purposes of this review esomeprazole pellets will be used exclusively in referring to

- Esomeprazole pellets contain: esomeprazole, glycerol monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polysorbate 80, sugar spheres, talc, and triethylcitrate. The esomeprazole pellets used in this product 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.

- Excipient granules contain: [REDACTED], xanthan gum, [REDACTED], citric acid, iron oxide [REDACTED], and hydroxypropyl cellulose. [REDACTED]

The different Esomeprazole Sachet product strengths are produced by varying the proportions of the esomeprazole pellets and the excipient granules,

Specifications

The specification for the esomeprazole pellets (as well as for the omeprazole drug substance) will be the same as approved in NDA 21-153, including assay, impurities, and dissolution.

Proposed impurity limits for individual and total impurities in the finished product are the same as approved for Nexium Capsules.

Stability and Expiration Dating

Although release testing is only based on testing of the esomeprazole pellets and excipient granules, the stability of the finished product is been evaluated for organic impurities, water, pH, viscosity, assay, and dissolution. Nine months of data are provided for primary stability batches stored at controlled room temperature and six months of data for samples stored at accelerated conditions. These studies included only [REDACTED] strengths, [REDACTED] 40 mg, in accord with the

agreement reached regarding the bracketing of stability data at a June 14, 2004 meeting between the firm and FDA. Additional eighteen months of supporting stability data are provided, in this case the bracketing approach included all product strengths. Lower levels of impurities were found in the primary stability batches than in the supporting batches.

Inspection requests for the two facilities involved in the manufacture of the drug substance and drug product have been entered into EES.

B. Critical issues for review

--Expiration dating for Esomeprazole Sachets

--Content Uniformity: A tolerance of _____ is specified for the fill weight. This would lead to an omeprazole content of _____ of label claim in the packets, which is not in accord with the $\pm 15\%$ content uniformity requirement in USP. This apparent discrepancy should be reconciled.

--The most critical issues requiring close evaluation relate to the applicant's proposal to base product release on the testing of the esomeprazole pellets and excipient granules which constitute the product, instead of testing the finished product. These include:

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/s/

Marie Kowblansky
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Moo-Jhong Rhee
4/13/2006 10:09:13 AM

CHEMIST
Chief, Branch III