CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-101

CHEMISTRY REVIEW(S)
NDA 22-101

Nexium\textsuperscript{©} (esomeprazole magnesium) For Delayed Release Oral Suspension

\[
\text{Mg}^{2+} \cdot 3\text{H}_2\text{O}
\]

Astra Zeneca, LP

Division of Gastroenterology Drug Products

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

For
Branch III
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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:

<table>
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<tr>
<th>Previous Documents</th>
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6. SUBMISSION(S) BEING REVIEWED:

<table>
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<th>Submission(s) Reviewed</th>
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<tbody>
<tr>
<td>Original</td>
<td>27-September-2006</td>
</tr>
<tr>
<td>Amendment (BL)</td>
<td>06-December-2006</td>
</tr>
<tr>
<td>Amendment (BC)</td>
<td>25-April-2007</td>
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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

Page 3 of 50
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:  X_ Rx   ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   ____ SPOTS product – Form Completed
   X____ 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

   \[
   \begin{array}{c}
   \text{Mg}^{2+} \cdot 3\text{H}_2\text{O} \\
   \end{array}
   \]

   \[\text{C}_{34}\text{H}_{36}\text{MgN}_6\text{O}_{15}\text{S}_2 \cdot 3\text{H}_2\text{O} \quad 767.17\]

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

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<th>STATUS 2</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
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<td>3, 4</td>
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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)

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tr>
<td>NDA</td>
<td>21-153</td>
<td>Approved reference for Drug substance</td>
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<td>NDA</td>
<td>21-957</td>
<td>Approved reference for 20 and 40 mg for delayed release oral suspension</td>
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18. STATUS:

ONDQA:

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<td>S. Adams</td>
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<td>Methods Validation</td>
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<td>K.C. Arnwine Pharm.D.</td>
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<td>Raanan A. Bloom, Ph.D.</td>
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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]sulfonyl]-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. 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.
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.

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.

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.
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 that — (Q) of label claim of esomeprazole released at pH 6.8 buffer.

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)

Withheld Track Number: Chemistry-1
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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

ONDQA Fileability: YES NO

Comments for 74-Day Letter

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.

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

\[
\text{H}_2\text{C} \quad \text{OCH}_3 \quad \text{OCH}_3 \\
\text{N} \quad \text{S} \\
\text{H}_2\text{C} \quad \text{OCH}_3
\]

\[\text{Mg}^{2+} \cdot 3 \text{H}_2\text{O}\]

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

The composition of these two types of granules is given as:
- **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.

- **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.

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

<table>
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<tr>
<th>Name</th>
<th>Date</th>
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<tbody>
<tr>
<td>Marie Kowblansky, PhD</td>
<td>12/15/2006</td>
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<tr>
<td>Pharmaceutical Assessment Lead</td>
<td>Date</td>
</tr>
<tr>
<td>Moo-Jhong Rhee, PhD</td>
<td>12/15/2006</td>
</tr>
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<td>Branch Chief</td>
<td>Date</td>
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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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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