CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/ 21-154

CHEMISTRY REVIEW(S)
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls
1. NDA: # 21-153 2. CHEM REVIEW #: 4 3. REVIEW DATE: 02-Jan-2001
4. APPLICATION HISTORY

SUBMISSIONS REVIEWED

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5. NAME & ADDRESS OF APPLICANT:
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington DE 19803-8355

6. DRUG PRODUCT NAME:
Proprietary: Nexium
Nonproprietary/USAN: esomeprazole magnesium
Chem.Type/Ther.Class: 1S
Code names: H 199/18

7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor

8. INDICATION: acute healing of erosive esophagitis,
maintenance of healing of erosive esophagitis, and treatment
of symptomatic gastroesophageal reflux disease (SGERD)

9. DOSAGE FORM: delayed release pellets
10. **STRENGTH:** — 20, and 40 mg. Approval only for 20 and 40 mg strengths
11. **ROUTE OF ADMINISTRATION:** oral
12. **HOW DISPENSED:** X Rx OTC
13. **CHEMICAL IDENTIFICATION:**
   N Bis (1H-Benzimidazole, 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfanyl] ), magnesium salt, trihydrate
   \((C_{13}H_{14}N_{3}O_{5}S)_{2}Mg \times 3H_{2}O\).
   CAS Number 217087-09-7
   MW = 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

14. **SUPPORTING DOCUMENTS:**
15. **RELATED DOCUMENTS** NDA 19-810
16. **CONSULTS:** Biometrics and Biopharm complete
17. **REMARKS/COMMENTS:** The MV package needs updating. Send DR Letter. Specifications for—— should be amended.
18. **CONCLUSIONS & RECOMMENDATIONS:** Approvable

Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

CC:
NDA 21-153
HFD-180/Division File/NDA 21-153
HFD-181/CSO
HFD-180/LTalarico
HFD-180/LZhou
HFD-180/HGallo-Torres
HFD-180/ASHaw
R/D Init by: 09-Jan-2001
f/t/ABS 09-Jan-2001
Art Shaw  
1/9/01 05:48:33 PM  
CHEMIST

Liang Zhou  
1/10/01 12:30:38 PM  
CHEMIST

APPEARS THIS WAY  
ON ORIGINAL
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls
1. NDA: #21-153 2. CHEM REVIEW # 3 3. REVIEW DATE: 06-Dec-2000
4. APPLICATION HISTORY
SUBMISSIONS REVIEWED

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5. NAME & ADDRESS OF APPLICANT:
AstraZeneca LP
725 Chesterbrook Blvd
Wayne PA 19087-5677

6. DRUG PRODUCT NAME:
Proprietary: Nexium
Nonproprietary/USAN: esomeprazole magnesium
Chem.Type/Ther.Class: 1S
Code names: H 199/18

7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor

8. INDICATION: acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic gastroesophageal reflux disease (sGERD)

9. DOSAGE FORM: delayed release pellets

10. STRENGTH: 20, and 40 mg. Approval only for 20 and 40 mg strengths
11. ROUTE OF ADMINISTRATION: oral

12. HOW DISPENSED: ___ X Rx ___ OTC

13. CHEMICAL IDENTIFICATION:
N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-
dimethyl-2-pyridinyl)methyl]sulfinyl]-), magnesium salt, trihydrate
(C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>O<sub>5</sub>S)<sub>2</sub>Mg x 3H<sub>2</sub>O.
CAS Number 217087-09-7
MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

14. SUPPORTING DOCUMENTS: N/A

15. RELATED DOCUMENTS NDA 19-810, IND

16. CONSULTS: Biometrics and Biopharm ACCEPTABLE

17. REMARKS/COMMENTS: Labeling changes. The applicant has made commitments to change certain aspects of the labeling of the blister, carton, and bottles at the next printing.

18. CONCLUSIONS & RECOMMENDATIONS: The application may be approved from a CMC point of view with a 24 month expiration date for 20 and 40 mg capsules packaged in ~100 and 1000 count bottles and Hospital Unit Dose blister packages.

---

Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

CC:
NDA 21-153
HFD-180/Division File/NDA 21-153
HFD-181/CSO
HFD-180/LTalarico
HFD-180/LZhou
HFD-180/HGallo-Torres
HFD-180/AShaw
R/D Init by: LZhou 06-Dec-2000
f/t/ABS 06-Dec-2000
/s/
----------------
Art Shaw
12/7/00 01:09:13 PM
CHEMIST
Labelling changes will be made at next printing

Liang Zhou
12/7/00 01:13:57 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls


4. APPLICATION HISTORY

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AstraZeneca LP
725 Chesterbrook Blvd
Wayne PA 19087-5677

6. DRUG PRODUCT NAME:
Proprietary: Nexium
Nonproprietary/USAN: esomeprazole magnesium
Chem.Type/Ther.Class: 1S
Code names: H 199/18
See discussion below concerning the nomenclature

7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor

8. INDICATION: acute healing of erosive esophagitis,
maintenance of healing of erosive esophagitis, and treatment
of symptomatic gastroesophageal reflux disease (sGERD)

9. DOSAGE FORM: delayed release pellets

10. STRENGTH: 20, and 40 mg. Approval only for 20 and 40
mg strengths

11. **ROUTE OF ADMINISTRATION:** oral

12. **HOW DISPENSED:** X Rx  OTC

13. **CHEMICAL IDENTIFICATION:**

N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl]-), magnesium salt, trihydrate

$$(C_{12}H_{18}N_{3}O_{5}S)_{2}Mg \times 3H_{2}O.$$  

CAS Number 217087-09-7

MW = 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

14. **SUPPORTING DOCUMENTS:** All are Type III. See Container Closure Section

15. **RELATED DOCUMENTS** NDA 19-810

16. **CONSULTS:** Biometrics and Biopharm complete

17. **REMARKS/COMMENTS:** The application is approvable with a 24 month expiration date. However, there is some information that should be provided either in an amendment to the NDA or as a post-approval commitment. There are some labeling comments that need to be discussed further with OPDRA.

18. **CONCLUSIONS & RECOMMENDATIONS:** Approvable. The applicant should be sent a Discipline Review Letter.

/S/  11/27/00

Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

Appears this way on original

/S/  11/27/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

1. NDA #: 21-153  2. CHEM REVIEW #: 1  3. REVIEW DATE: 20-Sep-2000

4. SUBMISSIONS REVIEWED

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5. NAME & ADDRESS OF APPLICANT:
AstraZeneca LP
725 Chesterbrook Blvd
Wayne PA 19087-5677

6. DRUG PRODUCT NAME:

Proprietary: Nexium
Nonproprietary/USAN: esomeprazole magnesium
Chem.Type/Ther.Class: 1S
Code names: H 199/18

There is some confusion in the application. Sometimes H199/18 refers to the S-enantiomer of omeprazole. (Description of Drug substance, Page 004-002-012 of original submission Vol. 1.6) Sometimes it refers to “esomeprazole magnesium” (Cover letter to original submission)

COMMENT0: The applicant should clarify the use of the name “H199/18”. Sometimes H199/18 refers to the S-enantiomer of omeprazole, e.g. in the “Description” of Drug substance, Page 004-002-012 of original submission, Vol. 1.6. Sometimes it refers to “esomeprazole magnesium”, e.g. cover letter to original submission.

In this review, “H199/18” refers to esomeprazole, while “esomeprazole magnesium” refers to the drug substance, esomeprazole magnesium trihydrate.

7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor

8. INDICATION: acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic gastroesophageal reflux disease (sGERD)

9. DOSAGE FORM: delayed release pellets

10. STRENGTH: 20, and 40 mg. Approval only for 20 and 40 mg strengths
11. **ROUTE OF ADMINISTRATION:** oral

12. **HOW DISPENSED:** _X_ Rx ___OTC

13. **CHEMICAL IDENTIFICATION:**

N Bis (1H-Benzimidazole, 5-methoxy-2-[(S)-[4-methoxy-3,5-
dimethyl-2-pyridinyl)methyl)sulfinyl]-), magnesium salt,
trihydrate  
C₃₄H₃₇N₆O₆S₂Mg x 3H₂O

The molecular formula should be (C₁₁₁₇H₁₉N₃O₃S)₂Mg x 3H₂O. See discussion under "Labeling" below

CAS Number 217087-09-7

MW = 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

14. **SUPPORTING DOCUMENTS:** All are Type III. See Container Closure Section

15. **RELATED DOCUMENTS** NDA 19-810

16. **CONSULTS:** Biometrics Pending.

17. **REMARKS/COMMENTS:** There are a number of relatively minor issues. One major concern is the lack of testing for ___ in the drug substance.

17. **CONCLUSIONS & RECOMMENDATIONS:** Approvable. The applicant should be sent a Discipline Review Letter.

/S/ Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

/S/ Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-150
DIVISION OF SPECIAL PATHOGEN
AND IMMUNOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: 21-154

CHEMISTRY REVIEW #: 1   DATE REVIEWED: 03-OCT-2000

SUBMISSION: DOCUMENT DATE: CDER DATE: ASSIGNED DATE:

NAME & ADDRESS OF SPONSOR: AstraZeneca LP
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

REPRESENTATIVE: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs

DRUG PRODUCT NAME:
Proprietary: Nexium™
Nonproprietary: esomeprazole magnesium
Code Name/#: H-199/18

PHARMACOLOGICAL CATEGORY: Antiulcerative

INDICATION: Eradication of Helicobacter Pylori

DOSAGE FORM/STRENGTH: Delayed release capsules, 20 and 40 mg.

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

\[
\text{Bis-(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate}
\]

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

Mol. Formula: C\(_{34}\)H\(_{36}\)N\(_6\)O\(_6\)S\(_2\)Mg \cdot 3 \text{H}_2\text{O} \quad \text{Mol. Weight: 767.2} \quad \text{CAS: 217087-09-7}
SUPPORTING DOCUMENTS:

IND
NDA 19-810 and 21-153
DMF

RELATED DOCUMENTS:

REMARKS/COMMENTS: Nexium™ (esomeprazole) Delayed Release Capsules was originally submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) for the treatment of gastric esophageal reflux disease (GERD) on December 3, 1999. Subsequently, it was submitted to this Division on February 28, 2000 for eradication of Helicobacter pylori infections in conjunction with amoxicillin and clarithromycin in patients with duodenal ulcer disease or a history thereof.

NDA 21-154 incorporates by reference all Chemistry, Manufacturing and Controls information contained in NDA 21-153. Accordingly, CMC information is found in the chemist’ review(s) of NDA 21-153 and is incorporated in this review by cross-reference. Summarized information is included here as a convenient reference. A copy of the list of chemistry deficiencies and comments is also included in this review.

DGCDP has taken an Approvable action on NDA 21-153 in part due to the CMC issues noted. The division also found the data did not support the companies claim of superiority to omeprazole.

CONCLUSIONS & RECOMMENDATIONS: Approvable. The HFD-180 chemistry team has sent a Discipline Review Letter to the sponsor.

/G/  
Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590: N. Schmuff /S/ 12/1/00

cc:
HFD-590: N. Schmuff  HFD-590: G. Holbert  HFD-590: Biopharm
HFD-590: Micro  HFD-590: S. Hundley  File:  

File:
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: 21-154

CHEMISTRY REVIEW #: 2                     DATE REVIEWED: 15-DEC-2000

SUBMISSION: Original                      DOCUMENT DATE: 28-FEB-2000
CDER DATE: 29-FEB-2000
ASSIGNED DATE: 01-MAR-2000

NAME & ADDRESS OF SPONSOR: AstraZeneca LP
725 Chesterbrook Blvd:
Wayne, PA 19087-5677

REPRESENTATIVE: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs

DRUG PRODUCT NAME:
Proprietary: Nexium™
Nonproprietary: esomeprazole magnesium
Code Name/#: H-199/18

PHARMACOLOGICAL CATEGORY: Antiulcerative

INDICATION: Eradication of Helicobacter Pylori

DOSAGE FORM/STRENGTH: Delayed release capsules, 20 and 40 mg.

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

\[
\text{Bis-(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate}
\]

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

Mol. Formula: C_{34}H_{36}N_{6}O_{6}S_{2}Mg \cdot 3 \text{H}_2\text{O}   Mol. Weight: 767.2   CAS: 217087-09-7
SUPPORTING DOCUMENTS:  IND
NDA 19-810 and 21-153
DMF

RELATED DOCUMENTS:

REMARKS/COMMENTS: AstraZeneca has responded to the Discipline Review Letter sent by the HFD-180 chemistry team. Their response has been reviewed and found acceptable (Arthur B. Shaw, NDA 21-153 Chemistry Reviews Nos. 2 and 3, dated 18 October and 06 December-2000, respectively). The chemistry reviewer states that the application may be approved from a CMC perspective.

CONCLUSIONS & RECOMMENDATIONS: This NDA may be approved with respect to CMC.

/S/  
Gene W. Holbert, Ph.D., Review Chemist

Concurrence:  
HFD-590: N. Schmuff

cc:
Original: NDA 21-154
HFD-590: N. Schmuff
HFD-590: Micro
HFD-590: J. Meyer
HFD-590: G. Holbert
HFD-590: S. Hundley
HFD-590: J. Fritsch
HFD-590: Biopharm
File:  

APPEARS THIS WAY ON ORIGINAL