

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**

	DOCUMENT	CDER	ASSIGNED
Amendment BC	20-Dec-2000	22-Dec-2000	29-Dec-2000

**PREVIOUS DOCUMENTS:**

DOCUMENT	DOCUMENT DATE
Original	03-Dec-1999
Amendment AZ	03-Apr-2000
Amendment BC	01-Jun-2000
Amendment BC	23-Jun-2000
Amendment BC	17-Jul-2000
Amendment BL	02-Aug-2000
Amendment BC	25-Aug-2000
Chem. Review #1	22-Sep-2000
DR Letter	30-Sep-2000
AE Letter	03-Oct-2000
OPDRA Review of October 16 amendment	24-Oct-2000
IR Letter	15-Nov-2000
Amendment BZ	06-Oct-2000
Amendment BC	13-Oct-2000
Amendment AL, MR	16-Oct-2000
OPDRA Review of October 16 amendment	24-Oct-2000
IR Letter	15-Nov-2000
Amendment BC	19-Oct-2000
Chem. Review #2	28-Nov-2000
DR Letter	29-Nov-2000
BL Amendment	20-Nov-2000
Chem. Review #3 (Review of BL Amendment only)	07-Dec-2000

**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

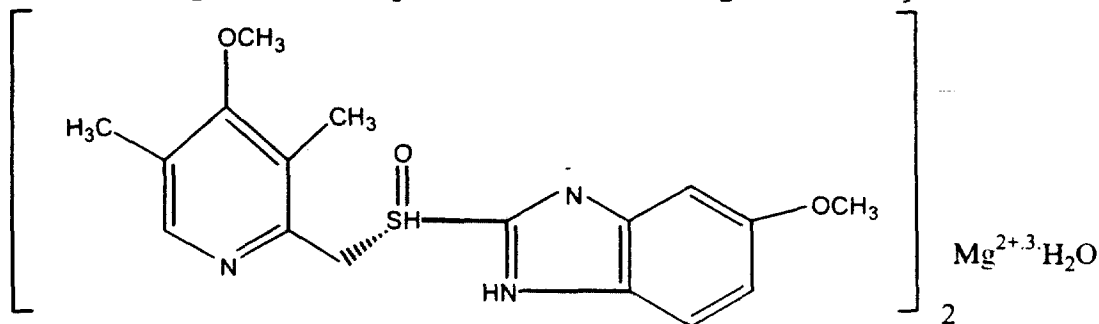
13. **CHEMICAL IDENTIFICATION:**

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

(C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</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:**

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

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

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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

/s/

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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**

	DOCUMENT	CDER	ASSIGNED
Amendment BL	20-Nov-2000	21-Nov-2000	28-Nov-2000

**PREVIOUS DOCUMENTS:**

DOCUMENT	DOCUMENT DATE
Original	03-Dec-1999
Amendment AZ	03-Apr-2000
Amendment BC	01-Jun-2000
Amendment BC	23-Jun-2000
Amendment BC	17-Jul-2000
Amendment BL	02-Aug-2000
Amendment BC	25-Aug-2000
Chem. Review #1	22-Sep-2000
DR Letter	30-Sep-2000
AE Letter	03-Oct-2000
OPDRA Review of October 16 amendment	24-Oct-2000
IR Letter	15-Nov-2000
Amendment BZ	06-Oct-2000
Amendment BC	13-Oct-2000
Amendment AL, MR	16-Oct-2000
Amendment BC	19-Oct-2000
Chem. Review #2	28-Nov-2000
DR Letter	28-Nov-2000

**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

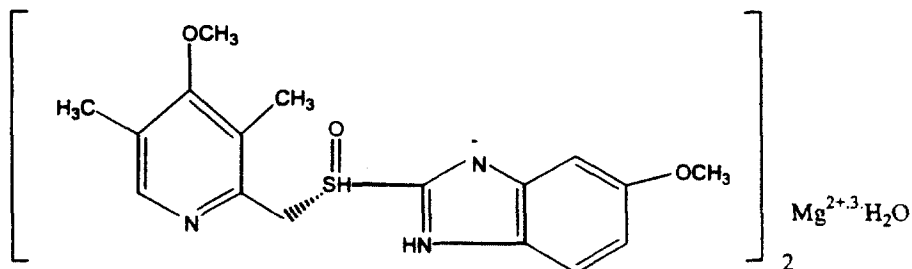
13. CHEMICAL IDENTIFICATION:

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>3</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.  
**ACCEPTABLE**

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.

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

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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/

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Art Shaw

12/7/00 01:09:13 PM

CHEMIST

Laebing 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

1. NDA: # 21-153 2. CHEM REVIEW # 2 3. REVIEW DATE: 18-Oct-2000

**4. APPLICATION HISTORY**

**SUBMISSIONS REVIEWED**

	<b>DOCUMENT</b>	<b>CDER</b>	<b>ASSIGNED</b>
Amendment BZ	06-Oct-2000	10-Oct-2000	11-Oct-2000
Amendment BC	13-Oct-2000	16-Oct-2000	17-Oct-2000
Amendment AL, MR	16-Oct-2000	17-Oct-2000	18-Oct-2000
Amendment BC	19-Oct-2000	20-Oct-2000	24-Oct-2000

**PREVIOUS DOCUMENTS:**

<b>DOCUMENT</b>	<b>DOCUMENT DATE</b>
Original	03-Dec-1999
Amendment AZ	03-Apr-2000
Amendment BC	01-Jun-2000
Amendment BC	23-Jun-2000
Amendment BC	17-Jul-2000
Amendment BL	02-Aug-2000
Amendment BC	25-Aug-2000
Chem. Review #1	22-Sep-2000
DR Letter	30-Sep-2000
AE Letter	03-Oct-2000
OPDRA Review of October 16 amendment	24-Oct-2000
IR Letter	15-Nov-2000

**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

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:**  Rx  OTC

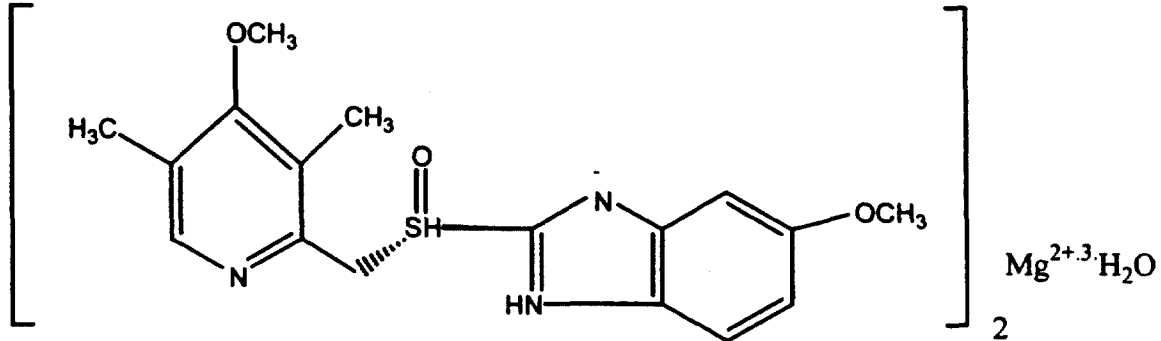
13. **CHEMICAL IDENTIFICATION:**

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

$(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$ .

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/

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

11/27/00

APPEARS THIS WAY  
ON ORIGINAL

/S/

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

11/27/00

**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**

	<b>DOCUMENT</b>	<b>CDER</b>	<b>ASSIGNED</b>
Original	03-Dec-1999	06-Dec-1999	07-Dec-1999
Amendment AZ	03-Apr-2000	03-Apr-2000	10-Apr-2000
Amendment BC	01-Jun-2000	02-Jun-2000	09-Jun-2000
Amendment BC	23-Jun-2000	26-Jun-2000	03-Jul-2000
Amendment BC	17-Jul-2000	18-Jul-2000	20-Jul-2000
Amendment BL	02-Aug-2000	03-Aug-2000	08-Aug-2000
Amendment BC	25-Aug-2000	28-Aug-2000	29-Aug-2000

**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:  Rx  OTC

13. CHEMICAL IDENTIFICATION:

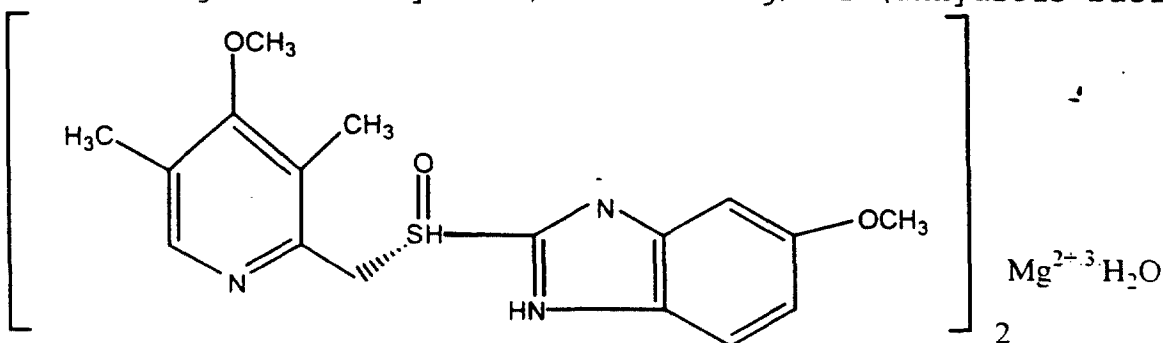
N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl]-),magnesium salt, trihydrate

$C_{34}H_{36}N_6O_6S_2Mg \times 3H_2O$

The molecular formula should be  $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$ . 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/*

*Sept 21, 2000*

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

APPEARS THIS WAY  
ON ORIGINAL

*/S/* *9/22/00*

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

**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**

<b>SUBMISSION:</b>	<b>DOCUMENT DATE:</b>	<b>CDER DATE:</b>	<b>ASSIGNED DATE:</b>
Original	28-FEB-2000	29-FEB-2000	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

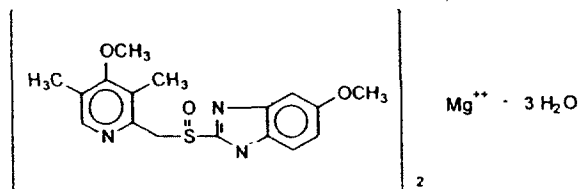
**INDICATION:** Eradication of *Helicobacter Pylori*

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

**ROUTE OF ADMINISTRATION:** Oral

**CHEMICAL NAME/STRUCTURAL FORMULA:**

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



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



**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**

<b>SUBMISSION:</b>	<b>DOCUMENT DATE:</b>	<b>CDER DATE:</b>	<b>ASSIGNED DATE:</b>
Original	28-FEB-2000	29-FEB-2000	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

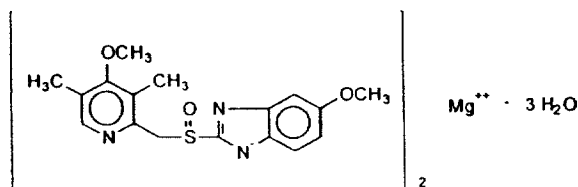
**INDICATION:** Eradication of *Helicobacter Pylori*

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

**ROUTE OF ADMINISTRATION:** Oral

**CHEMICAL NAME/STRUCTURAL FORMULA:**

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



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

