

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-101**

**ENVIRONMENTAL ASSESSMENT**

**ENVIRONMENTAL ASSESSMENT**

**AND**

**FINDING OF NO SIGNIFICANT IMPACT**

**FOR**

**Nexium® (esomeprazole magnesium)  
Delayed-Release Granules for Oral Suspension, 10 mg**

**NDA 22-101**

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Office of New Drug Quality Assessment**

**February 9, 2007**

**REVIEW**  
**OF**  
**ENVIRONMENTAL ASSESSMENT**  
**FOR**

**Nexium® (esomeprazole magnesium)**  
**Delayed-Release Granules for Oral Suspension, 10 mg**

**NDA 22-101**

**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Office of New Drug Quality Assessment**

**February 9, 2007**

**REVIEW**  
**OF**  
**ENVIRONMENTAL ASSESSMENT**  
**FOR**  
**Nexium® (esomeprazole magnesium)**  
**Delayed-Release Granules for Oral Suspension, 10 mg**

**NDA 22-101**

**EXECUTIVE SUMMARY**

This environmental assessment (EA), dated September 1, 2006, supports the new drug application for Nexium Delayed-Release Granules for Oral Suspension 10 mg for treatment of Gastroesophageal Reflux Disease (GERD) in the 1-11 year old pediatric population. Nexium is currently approved for treatment of Gastroesophageal Reflux Disease (GERD): Healing of Erosive Esophagitis, Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease; Risk Reduction of NSAID-Associated Gastric Ulcer; *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence; and Pathological Hypersecretory conditions, including Zollinger-Ellison Syndrome (NDAs 21-153, 21-957). The EA was prepared in accordance with 21 CFR Part 25 by AstraZeneca Pharmaceuticals.

Esomeprazole is the S-enantiomer of the racemate omeprazole. Due to the similarities between esomeprazole and omeprazole, omeprazole is included in evaluating the environmental characteristics of esomeprazole.

Esomeprazole is extensively metabolized by humans. Esomeprazole and its metabolites are predicted to partition to the aqueous environment. Since the activity of many of the metabolites is unknown, the firm assumed the metabolites exhibit the same ecotoxicity as the parent compound. This is the worst case scenario, as the two studied metabolites showed activity 100 fold less than the parent compound, and the other known metabolites would be predicted to have a similarly low activity.

Environmental effects data submitted included ecotoxicological studies of fish, daphnia, and algae, and showed that the most sensitive species tested is the zebrafish. The EC<sub>50</sub>/EIC ratio for the zebrafish is 18217, which is significantly greater than 100 (the tier 2 assessment factor). In addition, there are no observed effects at the MEEC (in this case the EIC). This assessment indicates that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

As reported in this EA, the total quantity of esomeprazole and omeprazole required for all products manufactured by AstraZeneca in any of the next 5 years is expected to be —  
— The calculated EIC is 2.3 µg/L (ppb). These are the same values as provided in the EA for NDA 21-153 S-023 (Nexium Delayed-Release Capsules) also dated September 1, 2006. Accordingly, the environmental fate and effects information provided in the present EA is identical to that provided under NDA 21-153 S-023. For a review of the EA, refer to the review conducted under NDA 21-153 S-023.

b(4)

A FONSI is recommended.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY:

Raanan A. Bloom, Ph.D.  
Senior Environmental Officer  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

CONCURRED BY:

Jon Clark, M.S.  
Associate Director for Policy  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

CONCURRED BY:

Moheb Nasr, Ph.D.  
Director, Office of New Drug Quality Assessment  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

Attachment:

Environmental Assessment  
Appended Electronic Signature Page



---

**NDA 22-101**

NEXIUM<sup>®</sup> (esomeprazole magnesium)

Delayed-Release Granules for Oral Suspension

New Drug Application

---

---

### **1.12.14 Environmental Assessment**

---

---

**Environmental Assessment**

Drug Substance	Esomeprazole
Document No.	GI.000-105-152
Date	1 September 2006

---

---

**Environmental Assessment of Esomeprazole**

---

**Author:** Gisela Holm, PhD  
Ecotoxicologist  
Global SHE Operations

<b>TABLE OF CONTENTS</b>	<b>PAGE</b>
1. DATE .....	4
2. NAME OF APPLICANT/PETITIONER .....	4
3. ADDRESS .....	4
4. DESCRIPTION OF PROPOSED ACTION .....	4
4.1 Requested approval .....	4
4.2 Need for action .....	4
4.3 Locations of use .....	4
4.4 Disposal sites .....	4
5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION .....	5
5.1 Nomenclature .....	5
5.1.1 Established name (U.S. Adopted name - USAN) .....	5
5.1.2 Brand/Proprietary name/tradename .....	5
5.1.3 Chemical names .....	5
5.1.3.1 Chemical abstracts (CA) index name .....	5
5.1.3.2 Systematic chemical name .....	5
5.2 Chemical abstracts service (CAS) registration number .....	5
5.3 Molecular formula .....	5
5.4 Molecular weight .....	5
5.5 Structural (graphic) formula .....	6
6. ENVIRONMENTAL ISSUES .....	6
6.1 Environmental Fate of Released Substances .....	6
6.1.1 Identification of Substances of Interest .....	6
6.1.2 Physical and Chemical Characterization .....	8
6.1.3 Environmental Depletion Mechanisms .....	8
6.1.3.1 Aerobic biodegradation .....	8
6.1.3.2 Chemical stability (acidic degradation) .....	8
6.1.4 Environmental Concentrations .....	9
6.1.5 Summary of environmental fate .....	9
6.2 Environmental Effects of Released Substances .....	9
6.3 Summary of Environmental Fate and Effects .....	11
7. MITIGATION MEASURES .....	12
8. ALTERNATIVES TO THE PROPOSED ACTION .....	12

9.	LIST OF PREPARERS.....	12
10.	APPENDICES .....	13
10.1	Non-confidential appendices.....	13
10.1.1	Data Summary Table .....	13
10.2	Confidential Appendices.....	15

**1. DATE**

1 September 2006

**2. NAME OF APPLICANT/PETITIONER**

AstraZeneca LP

**3. ADDRESS**

AstraZeneca LP  
1800 Concord Pike  
PO Box 8355  
Wilmington, DE 19803-8355

**4. DESCRIPTION OF PROPOSED ACTION**

**4.1 Requested approval**

AstraZeneca LP is filing an NDA pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Nexium Delayed-Release Granules for Oral Suspension 10 mg packaged in an aluminum foil packet. An environmental assessment (EA) is being submitted pursuant to 21 CFR part 25. The EA is compiled in accordance with 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

**4.2 Need for action**

Nexium Granules for Oral Suspension are intended to be used in the 1-11 year old pediatric population.

**4.3 Locations of use**

Usage of Nexium Granules for Oral Suspension will occur in households, but also in hospitals throughout the United States.

**4.4 Disposal sites**

Empty or partially empty packages from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy, or clinic procedures.

## **5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION**

### **5.1 Nomenclature**

Refer to Nexium Capsules NDA 21-153, Section 2.0 Nomenclature and Section 3.0 Structure.

#### **5.1.1 Established name (U.S. Adopted name - USAN)**

Esomeprazole magnesium trihydrate

#### **5.1.2 Brand/Proprietary name/tradename**

Nexium (esomeprazole magnesium) Delayed-Release Granules for Oral Suspension

#### **5.1.3 Chemical names**

##### **5.1.3.1 Chemical abstracts (CA) index name**

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

##### **5.1.3.2 Systematic chemical name**

IUPAC name:

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

### **5.2 Chemical abstracts service (CAS) registration number**

217087-09-7

### **5.3 Molecular formula**

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

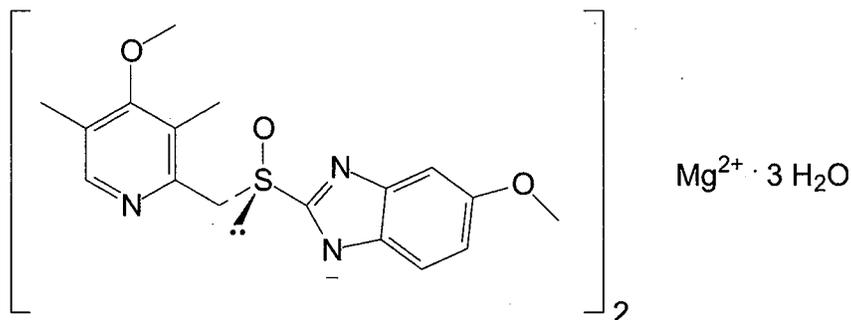
### **5.4 Molecular weight**

767.2 g/mol (trihydrate)

713.1 g/mol (anhydrous basis)

690.8 g/mol (esomeprazole)

## 5.5 Structural (graphic) formula



## 6. ENVIRONMENTAL ISSUES

Esomeprazole is the *S*-enantiomer of the racemate omeprazole. Due to the similarities between esomeprazole and omeprazole, omeprazole is included in evaluating the environmental characteristics of esomeprazole.

### 6.1 Environmental Fate of Released Substances

#### 6.1.1 Identification of Substances of Interest

Esomeprazole is the *S*-enantiomer of the racemic omeprazole. In humans, esomeprazole is eliminated almost completely by metabolism, as < 0.1% of the dose can be recovered in the urine as intact drug. The metabolites are mainly renally excreted (approx. 80%) whereas the remaining 20% are excreted via the faeces (Appendix I - **Confidential**). The metabolism of esomeprazole is extensive in that more than 10 metabolites are excreted, all representing less than 10% of the dose given.

The pharmacological effect of two renally excreted metabolites, hydroxy omeprazole (H 195/80) (Fig. 1) and the corresponding carboxylic acid (omeprazole acid, H 193/48) (Fig. 2) was tested in vitro (Appendix II - **Confidential**). The two metabolites represent 5 and 2.5% of the given dose, respectively. For these studies the racemic synthetic metabolites were used, and their effects were compared to that of omeprazole, the racemate. Both were about 100 times less potent than omeprazole and are unlikely to produce significant antisecretory effects in vivo. As omeprazole and esomeprazole are equipotent with respect to pharmacological effect in vitro (Appendix III - **Confidential**), their metabolites can also be expected to be equipotent, irrespective of whether they are formed from the racemate or the pure enantiomer. Thus, both metabolites can be expected to be 100 times less potent than each respective parent compound.

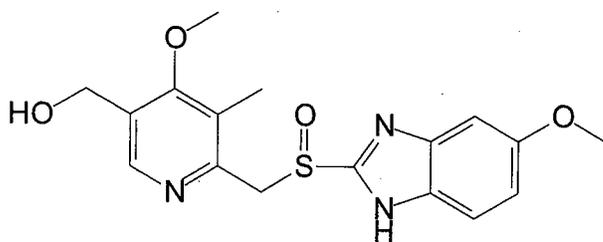


Figure 1. Structural formula of hydroxy omeprazole (H 195/80).

The chemical name for hydroxy omeprazole is: 5-methoxy-2-[[[(4-methoxy-3-methyl-5-hydroxymethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole.

CAS numbers: 92340-57-3 (racemate)  
196489-27-7 (*S*-enantiomer)  
196489-26-6 (*R*-enantiomer)

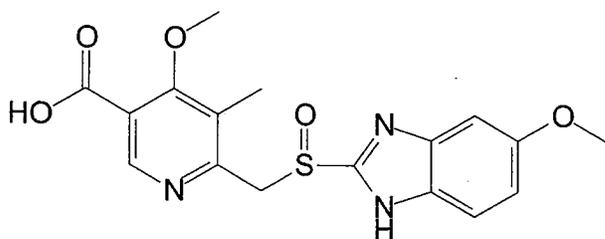


Figure 2. Structural formula of omeprazole acid (H 193/48).

The chemical name for omeprazole acid is: 5-methoxy-2-[[[(5-carboxy-4-methoxy-3-methyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole.

CAS numbers: 120003-72-7 (neutral form)  
120003-84-1 (di-sodium salt)

All other identified metabolites are equally or more hydrophilic (Appendix I - **Confidential**) than those tested *in vitro*, which means that they are not likely to pass through cell membranes and bind to intracellular receptors. Considering the hydrophilicity of the metabolites, and that they all are structurally related to those tested, their contribution to the antisecretory effect *in vivo* is expected to be insignificant.

In summary, esomeprazole is almost completely metabolised in the body and the resulting metabolites are excreted in urine (80%) and faeces (20%). Two major metabolites are ~100 times less potent than the parent compound and other metabolites are equally or more

hydrophilic. Most of the metabolites are predicted to enter the aquatic environment. Only a minor part of the used drug will be emitted as the parent compound.

### **6.1.2 Physical and Chemical Characterization**

Refer to Nexium Capsules NDA 21-153, Section 4.0 Physical and Chemical Characteristics.

#### **Water solubility**

300 mg/L (esomeprazole) (pH = 7)

#### **Dissociation constants (pKa)**

pKa<sub>1</sub> = about 4 (pyridinium ion)

pKa<sub>2</sub> = 8.8 (benzimidazole)

#### **Octanol/Water Partition Coefficient**

log K<sub>D</sub> (K<sub>ow</sub>) = 2.2

#### **Vapour pressure**

Not determined. Esomeprazole is a solid and hence its vapour pressure is assumed to be very low (<10<sup>-6</sup> Pa).

### **6.1.3 Environmental Depletion Mechanisms**

#### **6.1.3.1 Aerobic biodegradation**

The ready biodegradability of omeprazole has been investigated (OECD 301C) (Appendix IV - **Confidential**). In this test, aerobic microorganisms from a sewage treatment works are used to investigate their potential to easily degrade a substance. The results showed that omeprazole is:

Not readily biodegradable: BOD<sub>28</sub>/ThOD <0.6

Therefore, biodegradation can not be regarded as a rapid depletion mechanism for omeprazole. Since esomeprazole is an enantiomer of omeprazole, it can be assumed that esomeprazole is not readily biodegradable either. However, this does not necessarily indicate that omeprazole and esomeprazole are non-biodegradable, and further testing would be required to establish the potential of the compounds to degrade under more lenient conditions.

#### **6.1.3.2 Chemical stability (acidic degradation)**

The stability of esomeprazole in aqueous buffer solutions has been investigated. The sample solutions were protected from light. The half-life at 25°C (pH = 6.8) is about 20 hours, whereas the corresponding figure at 37°C is about 10 hours (Appendix V - **Confidential**). The half-life for the racemate omeprazole at 20°C (pH = 7) is about 30 hours (Appendix VI -

**Confidential**). The degradation rate is assumed to be the same for the enantiomer and the racemate.

The data indicate that esomeprazole and omeprazole are rapidly degraded at 25°C, whereas the depletion process is somewhat slower at lower temperatures.

#### **6.1.4 Environmental Concentrations**

The Expected Introduction Concentration (EIC) is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole. See Appendix VII – **Confidential**.

#### **6.1.5 Summary of environmental fate**

Esomeprazole magnesium is almost completely metabolised after consumption, and the resulting metabolites are subsequently excreted in urine (~80%) and faeces (~20%). Based on the physico-chemical properties of esomeprazole, ( $\log K_{ow} = 2.2$ , solubility = 300 mg/L, vapour pressure  $<10^{-6}$  Pa) it is predicted that any parent compound (esomeprazole) present will be partitioned into the aqueous phase during wastewater treatment.

By analogy, since the major metabolites are equally or more hydrophilic than the parent compound it is expected that most of the metabolites will also be partitioned to the water phase and eventually target the aquatic environment.

In the aquatic environment, esomeprazole is likely to be rapidly degraded abiotically. Data indicate that both esomeprazole and omeprazole are rapidly degraded at a neutral pH, 25°C, whereas the degradation rate is somewhat slower at lower temperatures. There is no evidence to suggest that biodegradation will be significant.

Only a small fraction is predicted to adsorb to sewage sludge and hence it is not expected that a significant amount will enter the terrestrial environment.

## **6.2 Environmental Effects of Released Substances**

Omeprazole sodium was used in all the ecotoxicological studies except for one green alga study where esomeprazole sodium was used. The ecotoxicity of the enantiomer esomeprazole is estimated to be equivalent to the effects noted in the studies with the racemic omeprazole. This assumption is supported by the nonclinical documentation on omeprazole and esomeprazole, from which it was concluded that the toxicological profile for both compounds is equivalent (Appendices VIII & IX- **Confidential**).

The following ecotoxicological studies were performed:

### **Activated sludge, respiration inhibition test**

The respiration inhibition of activated sludge was assessed according to guideline OECD 209 (Appendix IV - **Confidential**). No inhibition was observed at concentrations up to 100 mg/L.

According to the ecotoxicological tests, omeprazole shows short-term toxicity to green alga and zebrafish, but not to microorganisms in activated sludge or water-flea. Esomeprazole shows short-term toxicity to green alga.

No rapid, complete depletion mechanism has been identified for esomeprazole and omeprazole. However, the result from the microbial inhibition test above indicates that the drug substances do not inhibit respiration of activated sludge microorganisms. Therefore, they are not thought to disrupt wastewater treatment processes. Furthermore, as the  $\log K_{ow}$  is  $<3.5$  (see 6.1.2 Physical and Chemical Characterization), the compounds are not likely to bioaccumulate in aquatic organisms, and Tier 1\* is justified. However, since the ecotoxicity of all three aquatic base set test organisms (a fish, a crustacean and a microalga) have been tested, an assessment factor of 100 instead of 1000 has been used.

\*Tier 1. The most sensitive endpoint relevant to the environmental risk assessment is the toxicity (lethality) to zebrafish<sup>1</sup>:

96 h  $LC_{50}$  = 41.9 mg/L = 41900  $\mu$ g/L

$EC_{50}/EIC$  (Appendix VII - Confidential) = 41900/EIC  $\gg 100$  (assessment factor), i.e. no further testing is needed.

### 6.3 Summary of Environmental Fate and Effects

The intended use of esomeprazole (and omeprazole) will result mainly in metabolites entering the environment, since it is almost completely metabolised after consumption. Approximately 80% of the metabolites are excreted in the urine and 20% in the faeces. The metabolites are predicted to partition to the aqueous phase and eventually target the aquatic environment via sewage treatment.

In the aquatic environment, both esomeprazole and omeprazole are likely to be rapidly degraded abiotically at a neutral pH, 25°C, whereas the degradation rate is somewhat slower at lower temperatures. There is no evidence to suggest that biodegradation will be significant.

Only a small fraction is predicted to adsorb to sewage sludge and hence exposure to the terrestrial environment is not expected to be significant.

According to the ecotoxicological tests, omeprazole shows short-term toxicity to green alga and zebrafish, but not to microorganisms in activated sludge or water-flea. Esomeprazole shows short-term toxicity to green alga.

---

<sup>1</sup> In terms of toxicity to green alga, the endpoint growth rate (and not biomass) is scientifically preferred for use in environmental risk assessment, according to the OECD guideline 201. Therefore, the zebrafish endpoint is used in this assessment since it is lower than both the green alga growth rate and the *D. magna* immobilisation.

In the risk assessment, the excreted metabolites were assumed to exhibit the same ecotoxicity as the parent compound, since the pharmacological effects for most of the metabolites are not known. This is considered to represent a pragmatic worst case.

The most sensitive endpoint (lethality to zebrafish) in the ecotoxicological tests, and an EIC taking no metabolism into account (Appendix VII - **Confidential**), are used in the risk assessment.

The EIC is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole.

$EC_{50}/EIC = 41900 / EIC \gg 100$  (assessment factor)

In conclusion, since the ratio of the  $EC_{50}$  for the most sensitive of the base set test organisms to the expected introduction concentration is larger than the assessment factor, no adverse environmental effects are anticipated as a consequence of the use of esomeprazole and omeprazole.

## **7. MITIGATION MEASURES**

No adverse environmental effects are anticipated due to the use of esomeprazole and omeprazole. Therefore, no mitigation measures are needed.

## **8. ALTERNATIVES TO THE PROPOSED ACTION**

No potential adverse environmental effects have been identified for the proposed action. Therefore, no alternatives to the proposed action will be proposed.

## **9. LIST OF PREPARERS**

Gisela Holm, Ecotoxicologist, AstraZeneca since ten years, PhD Stockholm University, 19 years of experience in environmental research and consulting.

Persons consulted:

Anita Ehnåge, DMG, AstraZeneca Operations, DMG Mölndal, Sweden  
Bob Harrington, Group Reporting Services, AstraZeneca, Alderley Park, UK  
Richard Murray-Smith, BSc, AstraZeneca, Brixham, UK  
Lora Radzieta, Regulatory CMC, AstraZeneca, USA  
Lars Weidolf, PhD, AstraZeneca R&D Mölndal, Sweden

## 10. APPENDICES

### 10.1 Non-confidential appendices

#### 10.1.1 Data Summary Table

All test results from the environmental effects studies are expressed as ppm (mg/L) of esomeprazole sodium/omeprazole sodium.

DATA SUMMARY TABLE FOR ESOMEPRAZOLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	300 mg/L (esomeprazole) at pH 7
Dissociation Constants	pKa <sub>1</sub> = about 4 (pyridinium ion) pKa <sub>2</sub> = 8.8 (benzimidazole)
Log Octanol/Water Partition Coefficient (log K <sub>ow</sub> )	log K <sub>ow</sub> = 2.2 at pH 7
Vapour Pressure or Henry's Law Constant	No data
Sorption / Desorption (K <sub>oc</sub> )	No data
DEPLETION MECHANISMS	
Chemical stability (protected from light)	t <sub>1/2</sub> at 25°C (pH = 6.8) approx. 20 hours
Aerobic Biodegradation	Not readily biodegradable (BOD <sub>28</sub> /ThOD <0.6).
Soil Biodegradation	No data
Photolysis	No data
Metabolism	Almost completely metabolised, <0.1% of the dose can be recovered in the urine as intact drug

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Jon E. Clark  
2/13/2007 12:25:58 PM

Moheb.Nasr  
2/15/2007 11:49:05 AM