

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204655Orig1s000**

**ENVIRONMENTAL ASSESSMENT**

## **Finding of No Significant Impact**

**NDA 204-655**

**Esomeprazole Magnesium Delayed-Release-Capsules  
Over-the-Counter (OTC) 20 mg (NEXIUM<sup>®</sup> 24HR)**

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

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

AstraZeneca LP requests approval of NDA 204-655, NEXIUM<sup>®</sup> 24HR (esomeprazole magnesium) delayed-release capsules, 20 mg, for the over-the-counter (OTC) treatment of frequent heartburn (i.e., occurrences of two or more days per week). This product is not intended for immediate relief of heartburn. In support of its application, AstraZeneca prepared an environmental assessment (EA; attached), in accordance with 21 CFR Part 25, which evaluates the potential environmental impact from the use and disposal of this product.

The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and other information and has carefully considered the potential environmental impact due to approval of this application. Based on the CDER review and information available to date, FDA has determined that approval of the present application for NEXIUM<sup>®</sup> 24HR (esomeprazole magnesium) is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachment: May 17, 2013, Environmental Assessment

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**Environmental Assessment**

Drug Substance	Esomeprazole
Document No.	GI.000-230-694
Date	17 May 2013

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**Environmental Assessment of Esomeprazole**

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**1. DATE**

17 May 2013

**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 a New Drug Application (NDA) pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for esomeprazole Delayed-Release-Capsules Over-the-Counter (OTC) 20 mg. 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**

This new drug application provides for the use of esomeprazole Delayed-Release-Capsules Over-the-Counter (OTC) 20 mg, for the approved over-the-counter use in patients to treat frequent heartburn (occurs 2 or more days a week).

**4.3 Locations of use**

The product will be sold in mass retail outlets and/or pharmacies for home use.

**4.4 Disposal sites**

In US households, empty or partially empty containers will typically be disposed of through a community's solid waste management system; this may include landfills, incineration, and recycling. Some minimal quantities of the unused drug could be disposed of in the sewer system.

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

See 3.2.S.1.1 Nomenclature and 3.2.S.1.2 Structure in Module 3.

### 5.1 Nomenclature

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

Esomeprazole magnesium

#### 5.1.2 Brand/Proprietary name/tradename

NEXIUM 24HR<sup>®</sup>

#### 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)

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<sub>34</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>Mg · 3H<sub>2</sub>O

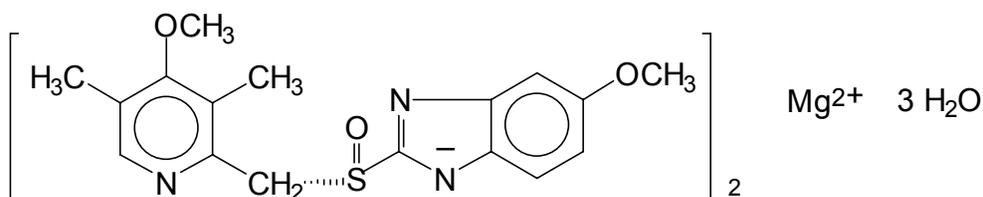
### 5.4 Molecular weight

767.2 g/mol (trihydrate)

713.1 g/mol (anhydrous basis)

690.8 g/mol (2 · 345.4 g/mol) (active moiety, parent compound)

### 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. Esomeprazole is eliminated almost completely by metabolism, as < 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 1 - 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 2 - 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 3 - 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.

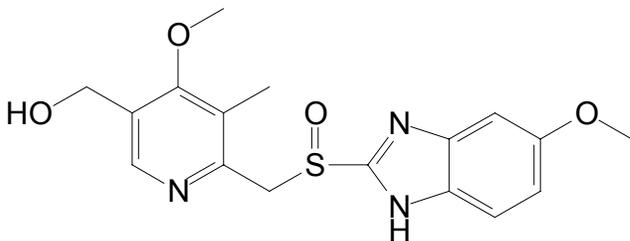


Figure 1. Structural formula of hydroxy omeprazole (H 195/80)

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)

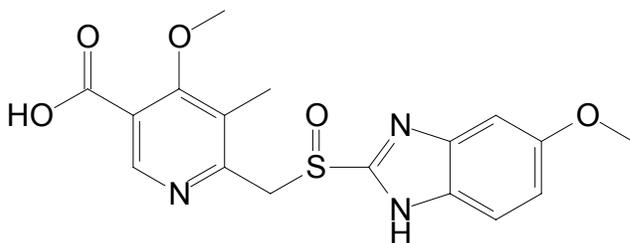


Figure 2. Structural formula of omeprazole acid (H 193/48).

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 1 - 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

See 3.2.S.1.3 'General Properties' in Module 3.

#### Water solubility

0.3 mg/mL (esomeprazole) at pH 7

#### Dissociation constants (pKa)

pKa = 8.8 (benzimidazole)

pKa = approximately 4 (pyridinium ion)

In a neutral aquatic environment, the drug substance exists as esomeprazole.

#### Octanol/Water Partition Coefficient

log  $D_{ow}$  = 1.7 (esomeprazole) at pH 5

log  $D_{ow}$  = 1.6 (esomeprazole) at pH 7

log  $D_{ow}$  = 1.5 (esomeprazole) at pH 9

(Appendix 7 – Confidential)

## Vapour pressure

Not determined. Esomeprazole is a solid and hence its vapour pressure is assumed to be very low ( $<10^{-6}$  Pa).

### 6.1.3 Environmental Depletion Mechanisms

#### 6.1.3.1 Ready Biodegradation

The ready biodegradability of omeprazole has been investigated (OECD 301C) (Appendix 4 - 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:  $BOD_{28}/ThOD < 0.6$

Therefore, biodegradation cannot 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 5 - Confidential). The half-life for the racemate omeprazole at 20°C (pH = 7) is about 30 hours (Appendix 6 - 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.

### 6.1.3.3 Adsorption to sludge

The adsorption and desorption to sludge was assessed according to the OPPTS guideline 835.1110 ([Appendix 8 - Confidential](#)). The  $K_{d(ads)}$  was 48, indicating that esomeprazole is likely to partition into the aqueous phase during wastewater treatment. The  $K_{d(des)}$  was 242, however the variability was large (-1147 to 3444) due to the limited adsorption and desorption.

### 6.1.3.4 Aerobic transformation in aquatic sediment systems

The aerobic transformation in aquatic sediment systems was assessed according to the OECD guideline 308 ([Appendix 9 - Confidential](#)). Two different sediments were used, one with high organic matter (HOM) and one with low organic matter (LOM) content. Radio-labelled test substance was dosed into the overlying water and the subsequent dissipation from the water phase, and partitioning and/or degradation in the sediment, was observed over a 100 day test period

In both the high and low organic matter test vessels rapid dissipation of [<sup>14</sup>C]esomeprazole from the overlying water was observed, with very low concentrations measured onwards from Day 7 and 14, respectively. A maximum concentration of [<sup>14</sup>C]esomeprazole was observed in the high sediment extracts on Day 3 (21% of the applied radioactivity), which died away to <10% of the applied radioactivity by the end of the study. In the low sediment extracts the maximum concentration of [<sup>14</sup>C]esomeprazole was observed on Day 14 (25% of the applied radioactivity). In both high and low organic matter test vessels this died away to <10% of the applied radioactivity by the end of the study.

The results can be summarised as follows:

	Compartment	Simple first order (SFO) dissipation half-life (d)
High organic matter sediment	Overlying water	2.2
	Sediment extract	20.6
	Total system	3.1
Low organic matter sediment	Overlying water	3.0
	Sediment extract	25.2
	Total system	6.3

Overall, the evidence from this study suggests that esomeprazole will not be persistent in the aquatic environment.

### 6.1.4 Environmental Concentrations

The Expected Introduction Concentration (EIC) is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole. See [Appendix 10 – Confidential](#).

### 6.1.5 Summary

Esomeprazole is almost completely metabolised after administration and the resulting metabolites are subsequently excreted in urine (~80%) and faeces (~20%). Based on the physico-chemical properties of esomeprazole, (LogDow = 1.6 (pH 7), solubility = 340 mg/L, vapour pressure  $<10^{-6}$  Pa), as well as the low measured adsorption to sludge, it is predicted that most of the parent compound (esomeprazole) will be partitioned into the aqueous phase during wastewater treatment. In a neutral aquatic environment, the drug substance exists as esomeprazole.

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 25°C in darkness, whereas the degradation rate is somewhat slower at lower temperatures. Biodegradation is not predicted to be a rapid depletion mechanism for esomeprazole and omeprazole, however, the evidence suggests that these compounds are unlikely to be persistent in the environment.

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

All available environmental studies have been undertaken with esomeprazole sodium and omeprazole sodium. These are summarized in Section 10.1.1.

### 6.2.1 Tiered assessment

The result from the microbial inhibition test above indicates that neither esomeprazole or omeprazole inhibit respiration of activated sludge microorganisms. Therefore, they are not thought to disrupt wastewater treatment processes. Furthermore, as the bioconcentration factor is low (see 6.1.2 Physical and Chemical Characterization), they are not likely to bioaccumulate in aquatic organisms, therefore, Tier 1 is justified.

Since chronic data are available for fish, *D. magna* and microalga, a Tier 3 assessment has been undertaken, which means an assessment factor of 10 is justified. The most sensitive endpoint was established in the fathead minnow, *Pimephales promelas* chronic toxicity study. However, since no EC<sub>50</sub> was generated in this study, the LOEC has been used as a worst case.

32-day LOEC = 3200 µg/L

LOEC/EIC ([Appendix 10 - Confidential](#)) = 3200/EIC >10 (assessment factor), and no effects were observed at the Maximum Expected Environmental Concentration (MEEC), i.e. no further testing is needed.

### 6.2.2 Summary

The intended use of esomeprazole (and omeprazole) will result mainly in metabolites entering the environment, since it is almost completely metabolised after administration. 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. Only a small fraction is predicted to adsorb to sewage sludge and hence exposure to the terrestrial environment is not expected to be significant.

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

The most sensitive endpoint (the LOEC for all endpoints in the fathead minnow study) in the chronic ecotoxicological tests, and an EIC taking no metabolism into account ([Appendix 10 - Confidential](#)), are used in the risk assessment.

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

LOEC/EIC = 3200/EIC >10 (assessment factor)

In conclusion, since the ratio of the LOEC for the most sensitive of the chronic 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 presented.

## **9. LIST OF PREPARERS**

Ruth Swarbrick, SHE Specialist, AstraZeneca, BSc University of Liverpool, 20 years of experience in environmental research and consulting.

Persons consulted:

Gisela Holm, Ecotoxicologist, Senior SHE Specialist, AstraZeneca  
Richard Murray-Smith, BSc, AstraZeneca, Brixham, UK  
Lori White, Regulatory Affairs, AstraZeneca Pharmaceuticals, USA  
Judy Firor, US Regulatory Affairs Director, AstraZeneca Pharmaceuticals, USA  
Birgitta Hedin, GRL, AstraZeneca Pharmaceuticals, USA  
Tommy Andersson, Drug Metabolism and Pharmacokinetics  
Dick Johansson, PharmDev  
Phil Matton, Global Brand Director  
Martin Billger, Global Safety Assessment

Testing laboratory:

(b) (4)

## 10. APPENDICES

### 10.1 Non-confidential Appendices

#### 10.1.1 Data Summary Table

DATA SUMMARY TABLE FOR ESOMEPRAZOLE AND OMEPRAZOLE (NB: All data are for esomeprazole sodium unless otherwise stated)	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	0.3 mg/mL (esomeprazole) at pH 7
Dissociation Constants	pKa = 8.8 (benzimidazole) pKa = approximately 4 (pyridinium ion)
Log Octanol/Water Partition Coefficient (log D <sub>ow</sub> )	log D <sub>ow</sub> = 1.7 at pH 5 log D <sub>ow</sub> = 1.6 at pH 7 log D <sub>ow</sub> = 1.5 at pH 9 (Appendix 7 – Confidential)
Log Octanol/Water Partition Coefficient (log D <sub>ow</sub> )	log D <sub>ow</sub> = 2.2 at pH 7 (omeprazole)
Vapour Pressure or Henry's Law Constant	No data. Presumed to be very low
Adsorption to sludge	K <sub>d(adsorption)</sub> = 48 (Appendix 8 – Confidential)
DEPLETION MECHANISMS	
Hydrolysis (preliminary study)	t <sub>1/2</sub> at 25°C approx. 20 hours (pH 6.8)
Aerobic Biodegradation	Not readily biodegradable (BOD <sub>28</sub> /ThOD<0.6) (Appendix 4 – Confidential)
Transformation in aquatic sediment systems	Dissipation half-life as: DT50 in HOM, total system = 3.1 days DT50 in LOM, total system = 6.3 days Evidence suggest that the substance will not be persistent in the aquatic environment. (Appendix 9 – Confidential)
Metabolism	Almost completely metabolised, <1% of the dose can be recovered in the urine as intact drug

<b>ENVIRONMENTAL EFFECTS</b>	
Microbial Inhibition	3h EC <sub>50</sub> >100 mg/L 3h NOEC = 100 mg/L (Appendix 11 – Confidential)
Acute toxicity	<b>Water flea (<i>D. magna</i>)</b> (omeprazole Na): 48 h EC <sub>50</sub> >100 mg/L 48 h NOEC = 50 mg/L (Appendix 12 – Confidential)  <b>Zebrafish (<i>D. rerio</i>)</b> (omeprazole Na) 96 h LC <sub>50</sub> = 41.9 mg/L 96 h NOEC = 23.2 mg/L (Appendix 13 – Confidential)
Chronic Toxicity	<b>Esomeprazole Na studies</b> <b>Green alga (<i>P. subcapitata</i>)</b> Biomass 72 h NOEC = 3.9 mg/L Biomass 72 h EC <sub>50</sub> = 19 mg/L Growth rate 72 h NOEC = 8.4 mg/L Growth rate 72 h EC <sub>50</sub> = 85 mg/L (Appendix 14 – Confidential)  <b>Water flea (<i>D. magna</i>)</b> Reproduction and length, 21 d NOEC = 10 mg/L (Appendix 15 – Confidential)  <b>Fathead minnow (<i>P. promelas</i>)</b> Hatch, survival, length and dry weight, 32 d NOEC = 1.0 mg/L 32 d LOEC = 3.2 mg/L (Appendix 16 – Confidential)  <b>Freshwater midge (<i>C. riparius</i>)</b> Emergence 28 d NOEC = 400 mg/kg (dry weight) 28 d LOEC = 1000 mg/kg (dry weight) (Appendix 17 – Confidential)  <b>Omeprazole Na study</b> <b>Green alga (<i>P. subcapitata</i>)</b> Biomass 72 h NOEC <1.81 mg/L Biomass 72 h EC <sub>50</sub> = 30.1 mg/L Growth rate 72 h NOEC = 1.81 mg/L Growth rate 72 h EC <sub>50</sub> >75.9 mg/L (Appendix 18 – Confidential)

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/s/  
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JAMES P LAURENSEN  
02/27/2014



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmaceutical Science/Immediate Office**

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**Memorandum**

**Date:** February 27, 2014

**From:** James P. Laurenson  
OPS/ONDQA

**To:** Rebecca McKnight  
OPS/ONDQA

**Subject:** Review of Environmental Assessment (EA) for NDA 204-655, Esomeprazole Magnesium Delayed-Release-Capsules Over-the-Counter (OTC) 20 mg (NEXIUM<sup>®</sup> 24HR)

**Sponsor:** AstraZeneca LP

**A. Summary**

AstraZeneca has filed a new drug application (NDA) pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for NEXIUM<sup>®</sup> 24HR (esomeprazole magnesium) delayed-release capsules, 20 mg, for the over-the-counter (OTC) treatment of frequent heartburn (i.e., occurrences of two or more days per week) and is not intended for immediate relief of heartburn. AstraZeneca provided an environmental assessment (EA) for esomeprazole pursuant to 21 CFR part 25 and in accordance with Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications (USFDA 1998). This memorandum provides a review of this EA. The two key goals of this review are to (1) determine whether this EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) determine whether the proposed action will significantly affect the environment.

The intended use of esomeprazole (and omeprazole) will result mainly in metabolites entering the environment, since it is almost completely metabolised after administration. The metabolites are predicted to partition to the aqueous phase and eventually target the aquatic environment via sewage treatment. Excreted metabolites were assumed to exhibit the same ecotoxicity as the parent compound. The most sensitive endpoint—the lowest-observed-effects concentration (LOEC) for all endpoints in the fathead minnow study) in the chronic ecotoxicity tests, and an expected introduction concentration (EIC) taking no metabolism or treatment effects into account are used in the risk assessment. Furthermore, the EIC is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole. The sponsor calculated that the LOEC/EIC = 3,200/EIC >10 (assessment factor), and that since the ratio of the LOEC for the most sensitive of the chronic 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. FDA used alternative, more protective assumptions to obtain a similar result. Due to the low risk quotient (RQ), an optional cumulative assessment was not conducted for other drugs with a similar mode of action.

In summary, the EA provided by the sponsor is adequate for approval because it contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment. Furthermore, the results of the risk characterizations in the EA and this review suggest that the specific use of NEXIUM<sup>®</sup> 24HR capsules will not significantly impact the environment. Based on the information available to date, therefore, a finding of no significant impact (FONSI) is recommended for this application.

## B. Background

AstraZeneca has filed an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for NEXIUM<sup>®</sup> 24HR (esomeprazole magnesium) delayed-release capsules, 20 mg, for the over-the-counter (OTC) treatment of frequent heartburn (i.e., occurrences of two or more days per week) and is not intended for immediate relief of heartburn in adults. AstraZeneca included an EA for esomeprazole because the product does not meet the requirements for a categorical exclusion pursuant to 21 CFR part 25 and in accordance with Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications (USFDA 1998). In particular, approval of this product would likely increase the use of esomeprazole, and the calculated expected introduction concentration for the aquatic environment (EIC) would be more than 1 part per billion (ppb). Several similar EAs were submitted previously, including for NDAs 21-153, 21-957, 22-056, and 22-101.

The esomeprazole delayed-release capsules prescription (Rx) 20 mg was previously approved and is used as (b) (4)

The two key goals of this review are to (1) determine whether this EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) determine whether the proposed action will significantly affect the environment.

## C. Environmental Assessment Review

A summary of the EA provided by the sponsor is provided below. Comments based on the FDA review of the EA are provided in italics.

**1. EA Date:** May 17, 2013; submitted May 30, 2013

2. **Author:** Ruth Swarbrick, AstraZeneca LP
3. **Address:** 1800 Concord Pike, PO Box 8355, Wilmington, DE 19803-8355
4. **Proposed Action:** AstraZeneca has submitted an NDA for an esomeprazole magnesium product, 20 mg, utilizing delayed-release capsules. This NDA is for a partial switch to OTC pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Treatment is for frequent heartburn (i.e., occurrences of two or more days per week) and not for immediate relief of heartburn in adults.

## 5. Identification of Chemicals

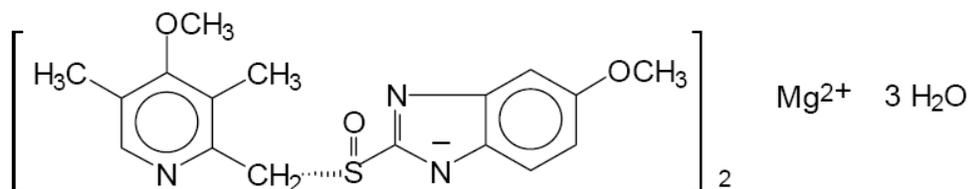
Esomeprazole is eliminated almost completely by metabolism, with < 1% of the dose recovered in the urine as intact drug. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, and 20% as metabolites in the feces. More than 10 metabolites are excreted, with each representing less than 10% of the dose given.

- (i) Established Name: Esomeprazole magnesium
- (ii) Brand/Proprietary Name/Tradename: NEXIUM<sup>®</sup> 24HR
- (iii) Chemical Abstracts Names: Esomeprazole magnesium (USAN)

Systematic Chemical Name: Bis(5-methoxy-2-{(S)[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol-1-yl)magnesium

- (iv) Chemical Abstract Services Number (CASN): 217087-09-7
- (v) Molecular Formula: C<sub>34</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>Mg · 3H<sub>2</sub>O
- (vi) Molecular Weight: 767.2 g/mol (trihydrate)  
713.1 g/mol (anhydrous basis)  
690.8 g/mol (2 · 345.4 g/mol; active moiety, parent compound)

- (vii) Chemical Structure:



*Review Comments:* The above data address the active moiety only (esomeprazole) and not any metabolites, degradants, other structurally related substances (SRSs), excipients, or impurities. Two metabolites, however, are addressed below. Also, the nonclinical

*review (USFDA 2014b) noted that the proposed product does not contain novel excipients and that none of the specified impurities exceed the qualification threshold.*

## 6. Environmental Characterization

A summary of the physical/chemical values, environmental depletion mechanisms, environmental fate and effects, and risk characterization for this product is provided in the following subsections.

### Physical/Chemical Values

The sponsor provided the following physical/chemical values for esomeprazole:

- Water solubility: 0.3 mg/mL at pH 7
- Dissociation constants (pKa):
  - pKa = 8.8 (benzimidazole)
  - pKa = approximately 4 (pyridinium ion)
  - In a neutral aquatic environment, the drug substance exists as esomeprazole.
- Octanol/Water Partition Coefficient:
  - log  $K_{ow}$  = 1.7 (esomeprazole) at pH 5
  - log  $K_{ow}$  = 1.6 (esomeprazole) at pH 7
  - log  $K_{ow}$  = 1.5 (esomeprazole) at pH 9
- Vapor pressure: Not determined. Esomeprazole is a solid and hence its vapor pressure is assumed to be very low ( $<10^{-6}$  Pa).

*Review Comments: The above data for log  $K_{ow}$  differ slightly from previous EAs (log  $K_{ow}$  of 2.2), but this is due to the more recent assessment (per Appendix 7 of the EA).*

### Environmental Depletion Mechanisms

The ready biodegradability of omeprazole—the racemate of esomeprazole and thus assumed to be similar in terms of biodegradability—was investigated. Omeprazole was found to not be readily biodegradable and thus it can be assumed that esomeprazole is not readily biodegradable either.

The stability of esomeprazole also was assessed. 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.

Adsorption and desorption to sludge was assessed according to the OPPTS guideline 835.1110, with a finding indicating that esomeprazole is likely to partition into the aqueous phase during wastewater treatment.

The aerobic transformation in aquatic sediment systems was assessed according to OECD guideline 308. Overall, the evidence from this study suggests that esomeprazole will not be persistent in the aquatic environment.

Notwithstanding these data, the sponsor ultimately used a screening-level scenario in which no such depletion mechanisms exist.

*Review Comments: These are reasonable assumptions for the screening-level EA used by the sponsor. Nevertheless, metabolism, treatment, dilution, and environmental degradation are depletion mechanisms that would be expected to reduce the environmental loading and concentration of this product. Also, metabolites, degradants, and other SRSs are expected to enter or exist in the environment. As noted in the EA Guidance (USFDA 1998), the majority of pharmaceuticals are metabolized to some extent in humans to SRSs that are more polar, less toxic, and less pharmacologically active than the parent compound. Exceptions exist, however, and therefore this review includes a confirmatory assessment of the relevant nonclinical and clinical data provided to FDA, as reviewed by FDA (USFDA 2014b, a).*

*The clinical and nonclinical reviews provide a more extensive description of the absorption and metabolism of esomeprazole than provided in the EA. These reviews note that esomeprazole is acid labile and is administered orally as enteric-coated granules. The absorption of esomeprazole is rapid, with peak plasma levels (C<sub>max</sub>) occurring approximately 1 to 2 hours after dose. The absolute bioavailability is reported as 50% after a single dose of 20 mg and increases to 68% after repeated once-daily administration. For 40 mg esomeprazole the corresponding values are 64% and 89%, respectively.*

*This drug is noted as completely metabolized by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. About 70 metabolites were identified in urine using mass spectrometric detection. Nine were considered as major, each constituting  $\geq 5\%$ , and together representing  $\geq 59\%$ . Two key metabolites are addressed in the EA—hydroxy omeprazole and the corresponding carboxylic acid (omeprazole acid)—representing 5 and 2.5% of the given dose, respectively.*

### **Environmental Fate and Effects**

The sponsor uses a screening-level scenario in which 100% of the product will remain in the aquatic environment following wastewater treatment and discharge of effluents. The sponsor thus developed an EIC of (b) (4) for esomeprazole into the aquatic environment, using the mass balance method described in the EA Guidance for the EIC (USFDA 1998). This EIC is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole.

Regarding effects, in mammals esomeprazole inhibits specifically the gastric H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. Esomeprazole is acid labile and is therefore formulated as gastro-resistant capsules containing a multitude of entericcoated pellets of esomeprazole magnesium trihydrate. The result from the microbial inhibition test indicates that neither esomeprazole or omeprazole inhibit respiration of activated sludge microorganisms. Therefore, these products are not thought to disrupt wastewater treatment processes. Furthermore, as the bioconcentration factor is low, they are not likely to bioaccumulate in aquatic organisms, and thus the Tier 1 assessment noted in the EA guidance would be justified. Since chronic data are available for fish, *D. magna*, and microalgae, however, as summarized in the table on the next page, a Tier 3 assessment was undertaken. Because a Tier 3 assessment would be used, an assessment factor (AF) of 10 is justified.

The most sensitive endpoint for esomeprazole was established in the fathead minnow, *Pimephales promelas*, chronic toxicity study. The sponsor notes, however, that since no EC50 was generated in this study, the 32-day LOEC of 3,200 µg/L would be used as a worst case instead.

*Review Comments:* The EIC used by the sponsor was based on a five-year projection of production that was conducted in 2008, and thus the value represents a projection for 2012. The current EA was conducted in 2013, however, and thus the projection should have been for 2018 production. Furthermore, the projection should have addressed the potential increase in production from the switch to OTC. Therefore, FDA estimated the production of esomeprazole for the post-switch to OTC by examining omeprazole, the likely primary competition with esomeprazole for market share (Mahecha 2006). With omeprazole already switched to OTC, a maximum estimate assumption would be the 100% shift of the omeprazole market to esomeprazole. In 2012, the total production amount for all formulations of omeprazole was approximately (b) (4) (IMS 2013). In 2012, the total production amount for all formulations of esomeprazole was approximately (b) (4). Assuming the incidence of frequent heartburn does not change, and a five-year population growth at the current rate of approximately 0.75% per year, then the maximum production of esomeprazole resulting from this action would be approximately (b) (4). This amount would result in an EIC (b) (4).

The clinical and nonclinical reviews note that esomeprazole has not shown any relevant reproductive toxic or genotoxic effects. Furthermore, the major metabolites of esomeprazole are noted as having no effect on gastric acid secretion, and thus presumably an equivalently lower effect in terms of aquatic toxicity. Thus, the LOEC noted above appears to be a reasonable toxicity value to use. The no-observed-effects concentration (NOEC) of (b) (4) would provide further protection.

<b>ENVIRONMENTAL EFFECTS</b>	
Microbial Inhibition	3h EC <sub>50</sub> >100 mg/L 3h NOEC = 100 mg/L (Appendix 11 – Confidential)
Acute toxicity	<b>Water flea (<i>D. magna</i>) (omeprazole Na):</b> 48 h EC <sub>50</sub> >100 mg/L 48 h NOEC = 50 mg/L (Appendix 12 – Confidential)  <b>Zebrafish (<i>D. rerio</i>) (omeprazole Na)</b> 96 h LC <sub>50</sub> = 41.9 mg/L 96 h NOEC = 23.2 mg/L (Appendix 13 – Confidential)
Chronic Toxicity	<b>Esomeprazole Na studies</b> <b>Green alga (<i>P. subcapitata</i>)</b> Biomass 72 h NOEC = 3.9 mg/L Biomass 72 h EC <sub>50</sub> = 19 mg/L Growth rate 72 h NOEC = 8.4 mg/L Growth rate 72 h EC <sub>50</sub> = 85 mg/L (Appendix 14 – Confidential)  <b>Water flea (<i>D. magna</i>)</b> Reproduction and length, 21 d NOEC = 10 mg/L (Appendix 15 – Confidential)  <b>Fathead minnow (<i>P. promelas</i>)</b> Hatch, survival, length and dry weight, 32 d NOEC = 1.0 mg/L 32 d LOEC = 3.2 mg/L (Appendix 16 – Confidential)  <b>Freshwater midge (<i>C. riparius</i>)</b> Emergence 28 d NOEC = 400 mg/kg (dry weight) 28 d LOEC = 1000 mg/kg (dry weight) (Appendix 17 – Confidential)  <b>Omeprazole Na study</b> <b>Green alga (<i>P. subcapitata</i>)</b> Biomass 72 h NOEC <1.81 mg/L Biomass 72 h EC <sub>50</sub> = 30.1 mg/L Growth rate 72 h NOEC = 1.81 mg/L Growth rate 72 h EC <sub>50</sub> >75.9 mg/L (Appendix 18 – Confidential)

### **Risk Characterization**

The LOEC/EIC = 3,200/2.8 >10. Because no effects were observed at the maximum expected environmental concentration (MEEC), no further testing would be needed.

*Reviewer Comments: Whether the LOEC or NOEC are used, the ratio to the EIC would still be >10. Using the NOEC with the risk quotient (RQ) approach, the EIC/NOEC would result in an RQ of (b) (4). This RQ is substantially lower than 1, which is the RQ at which additional assessment would be conducted when an RQ is obtained using a screening-level assessment such as the one conducted as part of this EA. Due to this low RQ, an optional cumulative assessment was not conducted for other drugs with a similar mode of action.*

### **7. Mitigation Measures and Alternatives**

No significant adverse environmental impact is expected from this NDA based on the information available to date, and therefore no mitigation measures or alternatives are addressed other than the monitoring of scientific literature for potential environmental impacts.

(b) (4)

(b) (4)



(b) (4)



(b) (4)  
**E. Conclusions**

The EA is adequate for approval of the NDA. It contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and supporting reports, in FDA guidance, and of the scientific validity of the “no significant effects” conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA for NEXIUM<sup>®</sup> 24HR capsules.

Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

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JAMES P LAURENSEN  
02/27/2014

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>			<b>EAS REVIEW REQUEST</b>	
<b>TO:</b>  <b>ENVIRONMENTAL ASSESSMENT STAFF</b>  <b>E-mail to: CDER OPS IO EA</b> <b>Paper mail to: WO Bldg 51, Room 4193</b>			<b>FROM (Name, Title, Office/Division):</b> <b>Rebecca McKnight, ONDQA, 301-796-1765</b>	
<b>REQUEST DATE</b> 08/26/2013	<b>IND #</b>	<b>NDA / ANDA (Supplement) #</b> 204655	<b>TYPE OF DOCUMENT</b>	<b>DATE OF DOCUMENT</b> 05/30/2013
<b>NAME OF DRUG</b> Nexium Delayed-Release- Capsules OTC		<b>PRIORITY CONSIDERATION</b> Standard	<b>PDUFA DATE</b> 03/30/2014	<b>DESIRED COMPLETION DATE</b>
<b>NAME OF APPLICANT OR SPONSOR: AstraZeneca</b>				
<b>GENERAL PROVISIONS IN APPLICATION</b>				
<input checked="" type="checkbox"/> ENVIRONMENTAL ASSESSMENT				
<input type="checkbox"/> CLAIM OF CATEGORICAL EXCLUSION				
<input type="checkbox"/> ENVIRONMENTAL IMPACT STATEMENT				
<input type="checkbox"/> OTHER				
<b>EDR Link:</b>				
<b>eCTD Sequence Number: 3</b>				
<b>COMMENTS / SPECIAL INSTRUCTIONS: Please perform an environmental assessment for NDA 204655. Please contact the CMC reviewer, Sheldon Markovsky, if you have any questions. Thank you.</b>				
<b>SIGNATURE OF REQUESTER:</b> Rebecca McKnight		<b>DOCUMENTS FOR REVIEW DELIVERED BY (Check all that apply):</b>  <input checked="" type="checkbox"/> EDR <input type="checkbox"/> E-MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND		

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REBECCA A MCKNIGHT  
08/26/2013

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>			<b>EAS REVIEW REQUEST</b>	
<b>TO:</b>  <b>ENVIRONMENTAL ASSESSMENT STAFF</b>  <b>E-mail to: CDER OPS IO EA</b> <b>Paper mail to: WO Bldg 51, Room 4193</b>			<b>FROM (Name, Title, Office/Division):</b> Luz E Rivera, ONDQA PM 301 796 4013	
<b>REQUEST DATE</b> 6/20/2013	<b>IND #</b>	<b>NDA / ANDA (Supplement) #</b> NDA 204655	<b>TYPE OF DOCUMENT</b>	<b>DATE OF DOCUMENT</b> 5/30/2013
<b>NAME OF DRUG</b> Nexium® Delayed-Release Capsules OTC		<b>PRIORITY CONSIDERATION</b>	<b>PDUFA DATE</b> (74 Day Filing Issues date: 8/12/2013) Original NDA goal: 3/30/2014	<b>DESIRED COMPLETION DATE:</b> 11/01/2013
<b>NAME OF APPLICANT OR SPONSOR:</b> AstraZeneca LP				
<b>GENERAL PROVISIONS IN APPLICATION</b>				
<input checked="" type="checkbox"/> <b>ENVIRONMENTAL ASSESSMENT</b>				
<input type="checkbox"/> <b>CLAIM OF CATEGORICAL EXCLUSION</b>				
<input type="checkbox"/> <b>ENVIRONMENTAL IMPACT STATEMENT</b>				
<input type="checkbox"/> <b>OTHER</b>				
<b>EDR Link:</b> <a href="\\cdsesub1\evsprod\nda204655\0002\m1\us\environmental-assessment-esomeprazole.pdf">\\cdsesub1\evsprod\nda204655\0002\m1\us\environmental-assessment-esomeprazole.pdf</a>				
<b>EA Appendix:</b> <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <span style="float: right;">(b) (4)</span>				
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b>  Please evaluate the environmental assessment submitted by the applicant				
<b>SIGNATURE OF REQUESTER:</b> Luz E Rivera, ONDQA PM			<b>DOCUMENTS FOR REVIEW DELIVERED BY (Check one):</b> <input type="checkbox"/> <b>EDR</b> <input checked="" type="checkbox"/> <b>E-MAIL</b> <input type="checkbox"/> <b>MAIL</b> <input type="checkbox"/> <b>HAND</b>	

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LUZ E RIVERA  
06/20/2013