CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-056

ENVIRONMENTAL ASSESSMENT

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

Prilosec® (omeprazole magnesium) Delayed-Release Oral Suspension (2.5 mg or 10 mg)

NDA 22-056

Food and Drug Administration
Center for Drug Evaluation and Research

Office of New Drug Quality Assessment

February 20, 2007

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

Prilosec® (omeprazole magnesium)
Delayed-Release Oral Suspension (2.5 mg or 10 mg)

NDA 22-056

EXECUTIVE SUMMARY

This environmental assessment (EA), dated November 17, 2006, supports the new drug application for Prilosec® (omeprazole magnesium) Delayed-Release Oral Suspension (2.5 mg or 10 mg) for the treatment of symptomatic gastroesophageal reflux disease, [redacted] healing of erosive esophagitis, [redacted] b(4)

[redacted]. In support of the new drug application, AstraZeneca LP prepared an environmental assessment in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

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. The expected introduction concentration (EIC) is based on all AstraZeneca LP drug products containing esomeprazole and omeprazole. This includes Nexium® (omeprazole magnesium) products for which EAs were submitted under NDAs 22-101 and 21-153 S-023.

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 include ecotoxicological studies of fish, daphnia, and algae, and show that the most sensitive species tested is Zebrafish. The EC_{50}/EIC ratio for 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 ——— . This value is nearly identical to that provided in the Nexium® EAs for NDAs 22-101 and 21-153 S-023 ——— and the EIC values are the same. The environmental fate and effects data provided in the present EA are identical to that provided under NDAs 22-101 and NDA 21-153 S-023. For a review of the EA, refer to the review conducted under NDA 21-153 S-023. Based on the provided information, FONSIs were prepared for NDAs 22-101 and NDA 21-153 S-023. b(4)

A FONSI is recommended for NDA 22-056.

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/s/

Raanan Bloom
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ENV ASSESSMENT

Jon E. Clark
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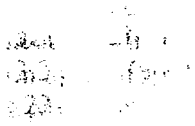
CHEMIST



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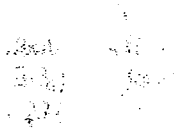

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Prilosec® (omeprazole magnesium) Delayed-Release Oral Suspension (2.5 mg or 10 mg)

NDA 22-056

Food and Drug Administration
Center for Drug Evaluation and Research

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February 20, 2007

FINDING OF NO SIGNIFICANT IMPACT

for

NDA 22-056

Prilosec® (omeprazole magnesium)
Delayed-Release Oral Suspension (2.5 mg or 10 mg)

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

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

This new drug application requests approval of Prilosec® (omeprazole magnesium) Delayed-Release Oral Suspension (2.5 mg or 10 mg) for the treatment of symptomatic gastroesophageal reflux disease, [redacted] healing of erosive esophagitis, [redacted] b(4)

[redacted] . In support of its new drug application, AstraZeneca LP prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Esomeprazole magnesium is a chemically synthesized drug currently approved for treatment of gastric esophageal reflux disease and maintenance and healing of erosive esophagitis. 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 magnesium and its metabolites may enter the aquatic environment from patient use and disposal. In the aquatic environment, both esomeprazole and omeprazole are likely to be rapidly degraded abiotically. The toxicity of esomeprazole magnesium to environmental organisms was characterized. The results indicate that the compound and its metabolites are not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may

include landfills, incineration and recycling, while minimal quantities of unused drug are expected to be disposed of through the sanitary sewer system.

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:

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Attachment:

Environmental Assessment
Appended Electronic Signature Page

AstraZeneca

Environmental Assessment	
Drug Substance	Omeprazole magnesium
Document No.	GI.000-109-616
Date	17 November 2006

Environmental Assessment of Omeprazole Magnesium

Author: Gisela Holm, PhD
Ecotoxicologist
Global SHE Operations

TABLE OF CONTENTS PAGE

1. DATE

17 November 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 Prilosec (omeprazole magnesium) For Delayed-Release Oral Suspension (2.5 mg or 10 mg) in unit dose packages of 30. 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

Prilosec is currently marketed for the treatment of symptomatic gastroesophageal reflux disease, maintenance and healing of erosive esophagitis, short-term treatment of active duodenal ulcer, eradication of *Helicobacter pylori*, and for the treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

4.3 Locations of use

Usage of Prilosec (omeprazole magnesium) For Delayed-Release Oral Suspension will occur in households and/or 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. In households, empty or partially

empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling.

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

5.1 Nomenclature

All information regarding the drug substance omeprazole magnesium was originally approved in the Prilosec OTC NDA 21-229. The information on the drug substance is not repeated in this NDA, and is instead cross-referenced to the Prilosec OTC NDA.

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

Omeprazole magnesium

5.1.2 Brand/Proprietary name/tradename

Prilosec (omeprazole magnesium) For Delayed-Release Oral Suspension

5.1.3 Chemical names

5.1.3.1 Chemical abstracts (CA) index name

Magnesium, bis[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-.kappa.O]-1H-benzimidazolato-.kappa.N1]-, (T-4)-

5.1.3.2 Systematic chemical name

IUPAC name:

Magnesium bis(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benzimidazolide)

5.2 Chemical abstracts service (CAS) registration number

95382-33-5

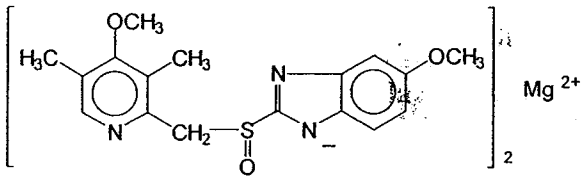
5.3 Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

5.4 Molecular weight

713.1 g/mol (anhydrous)
785.2 g/mol (tetrahydrate)

5.5 Structural (graphic) formula



6. ENVIRONMENTAL ISSUES

Due to the similarities between the two compounds, data for both omeprazole and esomeprazole have been included in this assessment, where appropriate.

6.1 Environmental Fate of Released Substances

6.1.1 Identification of Substances of Interest

Omeprazole is eliminated almost completely by metabolism in humans, 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 feces (Appendix I - **Confidential**). There are two main excreted human metabolites of omeprazole, of which both are excreted via the urine: hydroxy omeprazole (H 195/80) (Fig. 1) representing 15%, and the corresponding carboxylic acid (omeprazole acid, H 193/48) (Fig. 2) representing 10% of the given dose (Appendix I - **Confidential**). Corresponding figures for these metabolites after intake of esomeprazole are 5 and 2.5% of the given dose, respectively (Appendix II – **Confidential**). The remaining metabolites are each found in amounts representing less than 10% of given dose.

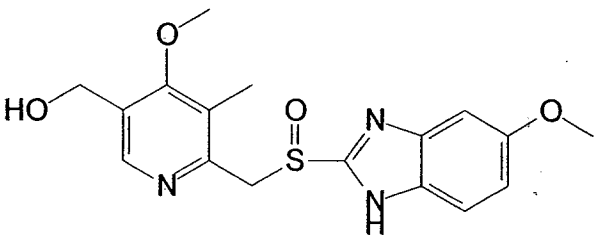


Figure 1. Structural formula of hydroxy omeprazole (H 195/80).

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)

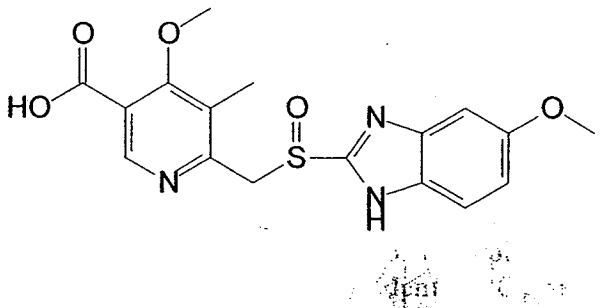


Figure 2. Structural formula of omeprazole acid (H 193/48).

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)

The pharmacological effect of the two main renally excreted metabolites (H 195/80 and H 193/48) was tested in vitro (Appendix II - **Confidential**). Both were about 100 times less potent than omeprazole and are unlikely to produce significant antisecretory effects in vivo. All other major 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.

Omeprazole and esomeprazole are equipotent with respect to pharmacological effect in vitro (Appendix III – **Confidential**), and their metabolites can also be expected to be equipotent, irrespective of whether they are formed from the racemate or the pure enantiomer. Thus the two main metabolites from both compounds can be expected to be 100 times less potent than each respective parent compound.

6.1.2 Physical and Chemical Characterization

All information regarding the drug substance omeprazole magnesium was originally approved in the Prilosec OTC NDA 21-229. The information on the drug substance is not repeated in this NDA, and is instead cross-referenced to the Prilosec OTC NDA.

Water solubility

130 mg/L at pH 7, 22°C (omeprazole)

Dissociation constants (pKa)

pKa_1 = about 4 (pyridinium ion)
pKa_2 = 8.8 (benzimidazole)

Octanol/Water Partition Coefficient (20°C)

log K_D (K_{ow}) = 2.24

Vapour pressure

Not determined. Omeprazole 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 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: $BOD_{28}/ThOD$ <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 also not readily biodegradable. 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 environmental conditions.

6.1.3.2 Chemical stability (acidic degradation)

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

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

Omeprazole 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 omeprazole, (log K_{ow} = 2.24, solubility = 130 mg/L, vapour pressure $<10^{-6}$ Pa) it is predicted that any residual parent compound (omeprazole) 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, omeprazole is likely to be rapidly degraded abiotically. Data indicate that both omeprazole and esomeprazole 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.

Green alga, *Selenastrum capricornutum*

The toxicity of esomeprazole sodium to green alga, (*Selenastrum capricornutum*) was assessed according to the OECD guideline 201 (Appendix X - **Confidential**).

Based on the area under the growth curve (0 to 72 hours):

No observed effect (P=0.05) concentration (NOEC) = 3.9 mg/L
Median effective concentration, biomass (E_bC_{50}) = 19 mg/L

Based on the growth rate (0 to 72 hours):

NOEC (P=0.05)	= 8.4 mg/L
Median effective concentration, growth rate (E_rC_{50})	= 85 mg/L

The toxicity of omeprazole sodium to green alga, (*S. capricornutum*) was assessed according to the OECD guideline 201 (Appendix XI - **Confidential**).

Based on the area under the growth curve (0 to 72 hours):

No observed effect (P=0.05) concentration (NOEC)	< 1.81 mg/L
Median effective concentration, biomass (E_bC_{50})	= 30.1 mg/L

Based on the growth rate (0 to 72 hours):

NOEC (P=0.05)	= 1.81 mg/L
Median effective concentration, growth rate (E_rC_{50})	> 75.9 mg/L

Water-flea, *Daphnia magna*

The acute toxicity of omeprazole sodium to *Daphnia magna* was assessed according to guideline OECD 202, Part I (Appendix XII - **Confidential**).

48 h EC_{50} >100 mg/L
48 h NOEC = 50 mg/L
48 h LOEC = 100 mg/L

Zebrafish (*Danio rerio*, former *Brachydanio rerio*)

The toxicity of omeprazole sodium to zebrafish was assessed according to OECD 203 (Appendix XIII - **Confidential**).

96 h LC_{50} = 41.9 mg/L
96 h NOEC = 23.2 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 omeprazole and esomeprazole. 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 green 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[1]:

96 h LC_{50} = 41.9 mg/L = 41900 µg/L

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

6.3 Summary of Environmental Fate and Effects

The intended use of omeprazole (and esomeprazole) 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 omeprazole and esomeprazole 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.

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 omeprazole and esomeprazole.

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[1] 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 LC_{50} is used in this assessment since it is lower than the EC_{50} for both the green alga growth rate and the *D. magna* immobilisation.

EC_{50}/EIC = 41900 / EIC >>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 omeprazole and esomeprazole.

7. MITIGATION MEASURES

No adverse environmental effects are anticipated due to the use of omeprazole and esomeprazole. 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:

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Richard Murray-Smith, BSc, AstraZeneca, Brixham, UK
Per Niklasson, Regulatory CMC, AstraZeneca, Sweden
Linda Marino, Regulatory Affairs, AstraZeneca, USA
Lars Weidolf, PhD, AstraZeneca R&D Mölndal, Sweden

10. APPENDICES

10.1 Nonconfidential Appendices

10.1.1 Data Summary Table

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

DATA SUMMARY TABLE FOR OMEPRAZOLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	130 mg/L (omeprazole)
Dissociation Constants	pKa_1 = about 4 (pyridinium ion) pKa_2 = 8.8 (benzimidazole)
Log Octanol/Water Partition Coefficient (log K_{ow})	log K_{ow} = 2.24 at pH 7
Vapour Pressure or Henry's Law Constant	No data
Sorption / Desorption (K_{oc})	No data
DEPLETION MECHANISMS	
Chemical stability (protected from light)	t½ at 20°C (pH = 7) approx. 30 hours
Aerobic Biodegradation	Not readily biodegradable (BOD_{28}/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

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	No inhibition up to 100 mg/L (ppm) (omeprazole Na)
Acute Toxicity	**Green alga** (*S. capricornutum*) (esomeprazole Na): Biomass 72 h NOEC = 3.9 ppm Biomass 72 h EC50 = 19 ppm Growth rate 72 h NOEC = 8.4 ppm Growth rate 72 h EC50 = 85 ppm **Green alga** (*S. capricornutum*) (omeprazole Na): Biomass 72 h NOEC <1.81 ppm Biomass 72 h EC50 = 30.1 ppm Growth rate 72 h NOEC = 1.81 ppm Growth rate 72 h EC50 >75.9 ppm **Water flea** (*D. magna*) (omeprazole Na): 48 h EC50 >100 ppm 48 h NOEC = 50 ppm **Zebrafish** (*D. rerio*) (omeprazole Na) 96 h LC50 = 41.9 ppm 96 h NOEC = 23.2 ppm
Chronic Toxicity	No data

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/s/

Jon E. Clark
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Moheb Nasr
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