CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-723

ENVIRONMENTAL ASSESSMENT/FONSI

REVIEW OF

ENVIRONMENTAL ASSESSMENT

FOR

PREGABALIN CAPSULES

Mgt of neuropathic pain associated with herpes zoster (post-herpetic neuralgia)

NDA 21-723

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products (HFD-120)

Date Completed: February 24, 2004

EXECUTIVE SUMMARY: **FONSI for NDA 21-723 is recommended.**

Pregabalin is a new molecular entity in a drug product indicated for 4 different conditions.

NDA 21-446 Management of neuropathic pain associated with peripheral neuropathy
NDA 21-723 Mgt of neuropathic pain associated with herpes zoster (post-herpetic neuralgia)
NDA 21-724 Treatment of epilepsy
NDA [redacted] Treatment of generalized anxiety disorder (GAD)

This EA Review is specific for NDA 21-723. However, the environmental topics in this review are copied from the EA Review done for NDA 21-446. If NDA 21-723 is approved, it will be merged into NDA 21-446. (E-mail from P Jani, Feb 9, 2004).

The EIC, — ppb, was calculated from the maximum annual production estimate in 2006, namely, — kg of pregabalin. Therefore, ecotoxicity data was provided for pregabalin because the total amount of pregabalin required for all indications listed above gives EIC greater than 1 ppb.

Pregabalin is not volatile and will not enter the air compartment. Pregabalin does not hydrolyze or photolyze. Pregabalin is not considered to be rapidly biodegradable under standard test conditions. However, the compound is an amino acid and has the potential to be metabolized or biodegraded as other aliphatic acids and / or amino substituted aliphatic acids. Pregabalin is not expected to bind significantly to sludge in [redacted] Its log octanol water partition coefficient is -1.35 at pH 7.4 and -1.90 at pH 1.0. Pregabalin is soluble in water (32 mg/L at pH 7.4) and is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration ($EIC_{aquatic}$) is — ppb assuming no metabolism, no hydrolysis and no photolysis. The Predicted Environmental Concentration (PEC) in the aquatic environment is — ppb. The PEC was calculated using 0.24 % sorption to sludge and a dilution factor of 10 for wastewater effluents discharged into the receiving waters.

Environmental effect data were generated for aquatic species. It is unlikely that pregabalin represents a significant risk to the aquatic environment based on the available data submitted.

Pregabalin Effects, Testing Data		
Microbial Inhibition	Aspergillus niger	MIC > 1000 mg/mL
	Trichoderma viride	MIC > 1000 mg/ml
	Clostridium perfringens	MIC > 997 mg/ml
	Bacillus subtilis	MIC > 1000 mg/ml
	Nostoc sp.	MIC > 1000 mg/ml
Daphnia, acute	48 hour EC_{50} > 1000 mg/L,	NOEC 1000 mg/L
Rainbow trout	96 hour EC_{50} > 1000 mg/L,	NOEC 1000 mg/L
Green alga (the most sensitive species)	72 hour EC_{50} > 300 mg/L, (based on cell density and growth rate)	NOEC 300 mg/L

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated April 11, 2003
   Chemist: Sharon L Kelly (HFD-170) (301) 827-6394
   Project Mgr: Jacqueline H Ware (HFD-120) (301) 594-2850

2. **Name of applicant/petitioner:** Pfizer Inc

   ADEQUATE

3. **Address:** 235 East 42nd Street, New York, NY 10017

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4. **Description of the proposed action:**

   a. Requested Approvals

   Pfizer Inc filed NDA 21-723 pursuant to section 505(b) of the Federal, Food, Drug & Cosmetic Act for Pregabalin Capsules indicated for neuropathic pain associated with herpes zoster (post-herpetic neuralgia). Pregabalin Capsules contain either 25, 50, 75, 100, 150, 200, 225 or 300 mg of pregabalin. Pregabalin Capsules are packaged in HDPE bottles and PVC/foil blisters.

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   b. Need for Action:

   Mgt of neuropathic pain associated with herpes zoster (post-herpetic neuralgia)

   ADEQUATE

   c. Expected Locations of Use (Drug Product):

   Pregabalin Capsules will be used in hospitals, clinics and patients' homes throughout the U.S.

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d. Disposal Sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages in accordance with their waste handling procedures. When used in the home, empty or partially empty packages containing Pregabalin Capsules will be disposed of by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed of in the sewer or septic systems.

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5. **Identification of the chemical that is the subject of the proposed action**:

a. Nomenclature
   i. Established Name (USAN): pregabalin
   ii. Trade Name: Lyrica is proposed but not yet approved
   iii. Chemical Name: (S)-3-(Aminomethyl)-5-methylhexanoic acid
b. CAS Registration Number: 148553-50-8
c. Molecular Formula: $C_8H_{17}NO_2$
d. Molecular Weight, salt: 159.23
e. Chemical Structure is in Section 5e of the EA, page 4

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6. Environmental Issues:

The original EA is in NDA 21-446. Three additional NDAs (21-723, 21-724 [ ] were created administratively from NDA 21-446. These 4 NDAs pertain to the same new molecular entity (pregabalin) in a drug product (Pregabalin Capsules) that is indicated for 4 different conditions.

NDA 21-446 Management of neuropathic pain associated with peripheral neuropathy
NDA 21-723 Mgt of neuropathic pain associated with herpes zoster (post-herpetic neuralgia)
NDA 21-724 Treatment of epilepsy
NDA [ ] Treatment of generalized anxiety disorder (GAD)

The maximum annual production estimate for all indications combined is [ ] kg of pregabalin in 2006. Ecotoxicity data was provided for pregabalin because $EIC_{aquatic}$ is more than —ppb, namely — ppb. GLPs and OECD or FDA EA-TAD testing procedures were used to obtain fate and effects data for pregabalin. The test reports established that scientifically sound methods were used to develop the data to support the Environmental Assessment.

Environmental Fate of Released Substances

i. Identification of Substances of Interest

Pregabalin is the active pharmaceutical ingredient. Following oral administration, pregabalin is mainly excreted in the urine (92% of the oral dose). Of the excreted amount, 89% is excreted as unchanged pregabalin with an additional 0.9% identified as the N-methylated derivative of pregabalin. As a result, pregabalin is considered to be a valid tracer for assessing environmental fate and effects in the aquatic environment.

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ii. Physical and Chemical Characterization

The aqueous solubility is reported to be 32 mg/mL at pH 7.4.

The pKa for the carboxyl group is 4.2. The pKa for the amine is 10.6. Therefore, pregabalin will exist as the zwitterion at environmental conditions.

The log of the n-octanol / water partition coefficient (log P_{ow}) at environmental conditions (pH 7.4) is -1.35. Because log P_{ow} is not more than — the probability for bioaccumulation, adsorption to particulate matter, humic acids and sediments is low.

The vapor pressure of pregabalin is virtually nil. Therefore, vaporization into the atmosphere is not expected.

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iii. Environmental Depletion Mechanisms

Sorption: The experimentally determined $K_{d\ sludge}$ is 13.3 in [redacted] The corresponding K_{OC} is [redacted] This is a low value typically observed for substances that are moderately to highly mobile in the aquatic environment. Therefore, pregabalin is not expected to sorb to sludge or wastewater solids including particulate matter, humic acids, suspended sediments or sediments.

Biodegradation: Pregabalin is not biodegradable according to results from the "Aerobic Biodegradation in Water" test (TAD 3.11). This observation does not necessarily mean that pregabalin is not biodegradable. Indeed, aerobic biodegradation is a consequence of the normal metabolic activity of bacteria and fungi in the environment. The test result may be consistent with slow biodegradation.

Hydrolysis: The molecular structure of pregabalin is not consistent with possible hydrolysis. Pregabalin is presumed to be stable to hydrolysis under environmental conditions (pH 7.4).

Chemical transformation: Pregabalin is an amino acid that may be converted to a lactam at pH 4 or pH 10. Although this degradation pathway is possible, it is likely to be a slow process at environmental temperature and pH.

Photolysis: Pregabalin does not exhibit ultra-violet absorption above 250 nm. Therefore, pregabalin is presumed to be photolytically stable in the environment.

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iv. Environmental Concentration, aquatic

The total amount of pregabalin required for all indications in the peak market year (2006) is [redacted] kg/year. (Ref: Confidential Appendix 1, page 18)

The Expected Introduction Concentration ($EIC_{aquatic}$) of pregabalin entering the external aquatic environment is [redacted] ppb ([redacted] mg/L). This assumes no metabolism. This is the concentration used in the risk assessment for effects on microorganisms and acute toxicity studies.

Adjusting $EIC_{aquatic}$ for removal by sorption (0.24 %) and 10 fold dilution when pregabalin is introduced into the aquatic compartment gives [redacted] ppb for the Predicted Environmental Concentration (PEC). EIC and PEC were not adjusted for removal by photolysis and hydrolysis because these depletion mechanisms do not apply to pregabalin.

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v. Summary

Pregabalin is expected to primarily enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Pregabalin is not volatile and therefore will not enter the air compartment. Pregabalin is not expected to be present in the terrestrial environment because it does not bind significantly to sludge and only a fraction of all sludge is applied as an amendment to farm lands.

Microbial metabolism and chemical degradation are likely to remove pregabalin from the aquatic environment.

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Environmental Effects of Pregabalin

Data about the environmental effects of pregabalin on aquatic species are on pages 8 to 10 of the EA dated April 11, 2003.

Pregabalin Effects, Testing Data		
Microbial Inhibition	Aspergillus niger	MIC > 1000 mg/mL
	Trichoderma viride	MIC > 1000 mg/ml
	Clostridium perfringens	MIC > 997 mg/ml
	Bacillus subtilis	MIC > 1000 mg/ml
	Nostoc sp.	MIC > 1000 mg/ml
Daphnia, acute	48 hour EC_{50} > 1000 mg/L,	NOEC 1000 mg/L
Rainbow trout, acute	96 hour EC_{50} > 1000 mg/L,	NOEC 1000 mg/L
Green alga, acute (the most sensitive species)	72 hour EC_{50} > 300 mg/L, (based on cell density and growth rate)	NOEC 300 mg/L

The introduction of the pregabalin into sewage treatment plants and into the aquatic environment through use and disposal of the product is not expected to pose an environmental risk.

Based on the Microbial Inhibition Test, pregabalin does not inhibit the growth of microbial strains or species at concentrations expected in wastewater treatment plants. Therefore it is not expected to disrupt the ecosystem.

The applicant performed acute toxicity testing with daphnia magna, rainbow trout and green alga. Green alga are the most sensitive species tested.

The 72 hour EC_{50} for green alga is > 300 mg/L; the NOEC is 300 mg/L. The Tier 1and Tier 2 Standards are satisfied because EC_{50} / EIC is greater than 1000 and the NOEC is more than 1000 times greater than the EIC [redacted] mg/L). These calculations indicate that no effects in the aquatic environment would be expected.

The predicted no effect concentration (PNEC) is calculated by dividing the NOEC for the most sensitive species tested by 100, the assessment factor (AF). Therefore the PNEC is 3.0 mg/L.

It is unlikely that pregabalin represents a significant risk to the aquatic environment based on the available data.

Summary Evaluation: Based on the above data, a FONSI is recommended for NDA 21-723.

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7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

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8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

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9. Preparers

Non Confidential EA: The names and professional experience of the EA preparers are provided.
Confidential Appendices: [ ] is the contract testing lab employed by Pfizer to determine ecotoxicity data.

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10. References

Four references are provided.

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11. Appendices

The EA contains a 2-page data summary table in the non-confidential Appendix 1. The confidential Appendixes 1, 2, 3 and 4 include calculations of EIC (MEEC), PEC and PNEC (predicted no effect concentration) based on the maximum annual production estimate in any of the next 5 years. Projected peak market usage will occur in 2006.

Confidential Appendix 5 (Determination of Sorption and Desorption Properties, TAD 3.08)
Results show that ^{14}C-pregabalin does not adsorb significantly to [ ] Sludge in [ ] solution. The test report (pages 23 to 67) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 6 (Determination of Aerobic Degradation in Water, TAD 3.11)
Results show that pregabalin does not degrade significantly in water in 28 days at pH 6.9 to 7.9 at 16°C to 23°C. The test report (pages 69 to 106) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 7 (Determination of Microbial Growth Inhibition, TAD 4.02)
Results show that pregabalin does not inhibit microbial growth at concentrations up to and including 1,000 mg/mL. The test report (pages 108 to 138) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 8 (Acute Toxicity to Daphnia Magna Under Static Conditions, TAD 4.02)
Results show that pregabalin does not immobilize daphnids; the 48-hour EC_{50} is estimated to be greater than 1,000 mg/mL; the NOEC is 1,000 mg/mL. The test report (pages 140 to 185) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 9 (Acute Toxicity to Rainbow Trout Under Static Conditions, OECD 203)
Mortality and adverse effects due to pregabalin were not observed; the 96-hour EC_{50} is estimated to be greater than 1,000 mg/mL; the 96-hour NOEC is 1,000 mg/mL. The test report (pages 187 to 230) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 10 (Toxicity to Freshwater Green Alga, OECD 201)
Biomass and growth rate were not changed significantly when exposed to 300 mg/mL pregabalin for 72 hours; the 72-hour EC_{50} for biomass (cell density) and growth rate is estimated to be greater than 300 mg/mL, the highest concentration tested; the 72-hour NOEC is 300 mg/mL. The test report (pages 232 to 295) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

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12. Certification

Certification that the information in the submitted EA is true, accurate and complete is provided by an executive of Pfizer.

ADEQUATE

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

/s/

Florian Zielinski
2/24/04 03:52:57 PM
ENV ASSESSMENT

Nancy Sager
2/25/04 08:06:25 AM
ENV ASSESSMENT

Moheb Nasr
2/25/04 10:14:45 AM
CHEMIST

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PREGABALIN CAPSULES

NDA 21-723

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products
(HFD-120)

February 24, 2004

FINDING OF NO SIGNIFICANT IMPACT, NDA 21-723

PREGABALIN

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.

In support of its new drug application for Pregabalin Capsules containing either 25, 50, 75, 100, 150, 200, 225 or 300 mg of pregabalin, Pfizer Inc prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 (b) which evaluates the potential environmental impact from the use and disposal of the product.

Pregabalin is a chemically synthesized drug that is indicated as an analgesic for the management of neuropathic pain associated with herpes zoster (post herpetic neuralgia).

Pregabalin, a new molecular entity, may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. Data indicate that the drug will not adsorb significantly to sludge and that it is not susceptible to hydrolysis and photolysis. It is not readily biodegradable although it is likely to slowly degrade chemically and microbiologically because it is an amino acid. The toxicity of pregabalin to environmental organisms was characterized. The results indicate that pregabalin is not expected to be toxic to organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. When used in the home, 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, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of 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
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Moheb M. Nasr
Acting Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

ENVIRONMENTAL ASSESSMENT

NONCONFIDENTIAL [FREEDOM OF INFORMATION ACT (FOIA)] SUBMISSION

(Referenced Confidential Information Has Been Provided Under Separate Cover)

PREGABALIN
NDA 21-446

Pregabalin for Use in the Management of Epilepsy, Neuropathic Pain, and Generalized Anxiety Disorder

April 2003

Pfizer Inc
235 East 42nd Street
New York, NY 10017

ENVIRONMENTAL ASSESSMENT

Pregabalin
25-, 50-, 75-, 100-, 150-, 200-, 225- and 300-mg Capsules

SUMMARY

Pfizer Inc. is providing an Environmental Assessment (EA) in support of Pregabalin Capsules (NDA 21-446). Pfizer Inc. anticipates no adverse effects to humans or environmental organisms as a result of excreted pregabalin entering publicly owned treatment works (POTW) and subsequent release environments.

1. **DATE:** April 11, 2003

2. **NAME OF APPLICANT/PETITIONER:** Pfizer Inc

3. **ADDRESS:** 235 East 42nd Street, New York, NY 10017

4. **DESCRIPTION OF PROPOSED ACTION:**

a. Requested Approval

Pfizer Inc. has submitted a NDA pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for pregabalin as an oral antiepileptic, as an analgesic agent for the management of chronic pain (neuropathic pain), and for the management of generalized anxiety disorder. The pregabalin NDA includes capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg pregabalin, which are packaged in HDPE bottles and PVC/foil blisters. An EA is being submitted pursuant to 21 CFR Part 25, following the Center for Drug Evaluation and Research, "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," dated July 1998.[1]

b. Need for Action

Pregabalin is an analogue of the mammalian neurotransmitter, γ-aminobutyric acid (GABA). Pregabalin has been shown to be effective as an oral antiepileptic, as an analgesic agent for the management of chronic pain (neuropathic pain), and for the management of generalized anxiety disorder. It is currently estimated that

there are more than 2 million patients in the United States requiring management of these disease states. Approval will offer qualifying patients in the United States an alternative and/or additional therapy to existing treatments.

c. Locations of Use

Pregabalin will be used as a prescription agent in home, clinic, and hospital environments throughout the world.

d. Disposal Sites

End-user disposal of empty or partially empty packages at US hospitals, pharmacies, or clinics will follow hospital, pharmacy, or clinic procedures. Empty or partially empty containers in residences will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and/or recycling. Minimal quantities of unused drug may be disposed of in sewer or septic systems.

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

a. Nomenclature

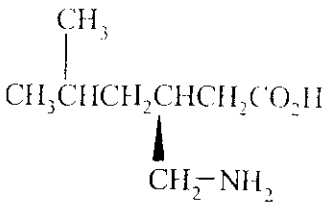
i. Established Name (USAN): Pregabalin
ii. Trade Name: LYRICA ™
iii. Chemical Name: (S)-3-(Aminomethyl)-5-methylhexanoic acid

b. Chemical Abstracts Service (CAS) Registration Number: 148553-50-8

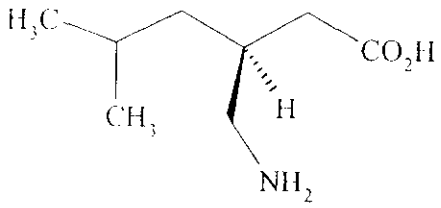
c. Molecular Formula: $C_8H_{17}NO_2$

d. Molecular Weight: 159.23

e. Structural Formula:



Structural Formula



Stereochemical Formula

6. ENVIRONMENTAL ISSUES:

Section One— Assessing Toxicity to Environmental Organisms

This EA focuses on the fate and effects of the active moiety pregabalin, for which the estimated concentration in the aquatic environment is projected to exceed 1 ppb at the point of entry. A tiered approach to testing was used. The physical-chemical, fate, and ecotoxicity protocols used in testing pregabalin followed the Technical Assistance Documents (TAD) as published in FDA's EA Technical Assistance Handbook and OECD (Organization for Economic Co-Operation and Development) Test Guidelines.

a. Environmental Fate of Released Substances

i. Identification of Substance of Interest:

Pregabalin is mainly excreted in the urine (92% of the oral dose). Of the excreted amount, 89% is excreted as unchanged pregabalin with an additional 0.9% identified as an N-methylated derivative of pregabalin.[2] Pregabalin is the primary entity released into the environment and is therefore a valid environmental tracer for assessing fate and effects. Pregabalin will reside mainly in the aquatic compartment, as described in Section 6.a.v.

ii. Physical and Chemical Characterization:

Refer to Data Summary Table (Appendix 1) for an overview of physical/chemical data for pregabalin.

- Water Solubility - The solubility of pregabalin ranges from 47 mg/mL at pH 10.1 to 107 mg/mL at pH 3.7. At pH's <3.7, pregabalin mainly exists

as a cation and is considered freely soluble. Refer to Section 3.2.S.1.3 General Properties.

- Dissociation Constant - Two pKa values were determined for pregabalin, 4.2 for the carboxyl group and 10.6 for the amine. Pregabalin will therefore exist as a zwitterion at environmental pH's. Refer to Section 3.2.S.1.3 General Properties.
- Octanol/Water Partition Coefficient - Log K_{ow} values range from -1.90 at pH 1 to -1.35 at pH 7.4. Pregabalin is not likely to partition into lipid based tissues or organic matter in the environment. Refer to Section 3.2.S.1.3 General Properties.
- Vapor Pressure (Vp estimate) - $<1 \times 10^{-7}$ mm Hg at 25°C. Vapor pressure estimates are based on the group and bond contribution methods of Hine and Mookerjee.[3] Pregabalin is not volatile and therefore would not enter the air compartment.

iii. Environmental Depletion Mechanisms

Based on the criteria defined in the Guidance for Industry document, pregabalin will not rapidly deplete in the aquatic environment by sorption, biodegradation, hydrolysis, or photolysis. Refer to Data Summary Table (Appendix 1) for an overview of depletion mechanism data for pregabalin.

- Sorption - Based on an experimentally determined $K_{d\ sludge}$ value of 13.3, pregabalin is unlikely to significantly sorb to wastewater solids and be removed through wastewater treatment. It is also not expected to highly sorb to particulate matter, humic acids, suspended sediments, and sediments due to its low $K_{d\ sludge}$ value, high solubility, and small molecular size. Refer to Confidential Appendix 5.
- Biodegradation - Based on the Guidance for Industry's aerobic biodegradation rapid depletion criteria of t½ ≤8 hours, pregabalin is not a readily biodegradable substance (no biodegradation observed in 28 days). Refer to Confidential Appendix 6.
- Hydrolysis - Formal hydrolysis experiments were not conducted as pregabalin has no constituents capable of being hydrolyzed. Based on the Guidance for Industry's hydrolysis rapid depletion criteria of t½ ≤24 hours, pregabalin will not deplete by this mechanism.

- Chemical Depletion (lactamization) - Pregabalin is essentially an amino acid. The main degradation pathway, although minimal, is lactamization. Based on the demonstrated degradation of pregabalin to lactam at approximately pH 4 and pH 10, there is a potential for pregabalin to slowly deplete at environmental pH's. Refer to Section 3.2.S.7.3.4 Stability Data Tables for additional stability data.

Exposure Conditions	% Pregabalin (w/w)	% Lactam (w/w)
0.1N HCL, 80°C, 24 hours	94.9	3.3
0.1N NaOH, 80°C, 6 hours	81.8	15.0

- Photolysis - The ultraviolet spectra of pregabalin dissolved in an aqueous media demonstrates no absorption occurring above 250 nm. With no chromophores present, normal mechanisms for photodegradation in the environment are not likely to apply. Refer to Section 3.2.S.1.3 General Properties.

iv. Environmental Concentrations

(1) Expected Introduction Concentration (EIC):

$$EIC_{aquatic}\ (ppm) = A \times B \times C \times D$$

Where: A = kg/yr produced for direct use (Confidential Appendix 1).
B = 1/L/day entering POTWs*.
C = years/365 days.
D = 1×10^6 mg/kg (conversion factor).

* 1.214×10^{11} L/day entering POTWs

The EIC entering the external aquatic environment ($EIC_{aquatic}$) from POTWs has been calculated (Confidential Appendix 2). The calculations are based on total projected usage of pregabalin. Using a conservative approach, no adjustments have been made to account for metabolism, other environmental depletion mechanisms, or for the dilution of wastewater effluents into the receiving waters.

(2) Expected Environmental Concentration (EEC):

The Expected Environmental Concentration (EEC), which is sometimes referred to as the Predicted Environmental Concentration (PEC), is calculated as follows:

$$PEC = EIC_{aquatic} \times [(100 - R)/(100 \times DF)]$$

Where: %Removal (R) = 0.24.
Dilution Factor (DF) = 10.

The PEC refines the original EIC estimate by accounting for removal on sludge during wastewater treatment and subsequent dilution into the receiving waters. The PEC was calculated using 0.24% for removal on sludge, based on an experimentally determined sludge sorption coefficient (K_d), and a dilution factor of 10 for dilution of waste water effluents into receiving waters (Confidential Appendix 3).

v. Summary

Pregabalin will enter the aquatic environment through effluents discharged by POTWs. Pregabalin is not volatile and therefore will not enter the air compartment. As noted in the Guidance for Industry document, generally, only a fraction of sludge from POTWs would be applied to soil. Based on the $K_{d\ sludge}$ for pregabalin, sludge applied to land would not result in a significant concentration of pregabalin in the soil compartment. Based on these environmental transport considerations, and an assessment of the physical-chemical properties, pregabalin will reside in the aquatic compartment. Consequently, environmental effects data were generated on aquatic species.

Pregabalin is not anticipated to be rapidly removed from the aquatic compartment through the depletion mechanisms of sorption, biodegradation, hydrolysis, and photolysis. Its removal from the environment is likely to result from microbial biotransformation and chemical degradation. Pregabalin, as an amino acid, has the potential to be co-metabolized or biodegraded as other aliphatic acids and/or amino substituted aliphatic acids.[4] Based on the stability data, there is also a

potential for pregabalin to slowly degrade in the environment through lactamization.

b. Environmental Effects of Released Substances

Refer to Data Summary Table (Appendix 1) for an overview of the environmental effects data for pregabalin.

i. Microbial Inhibition Testing - The microbial inhibition concentration (MIC) for all microorganisms tested is >995 mg/L. Based on this data, pregabalin has no significant potential to inhibit microorganisms and therefore would not disrupt wastewater treatment processes. Refer to Confidential Appendix 7.

ii. Tiered Ecotoxicity Testing - Tiered testing followed the approach described in the EA Guidance for Industry Document.[2] Effects testing was conducted in a tiered sequence, starting with acute testing. Testing progresses to more advanced tiers when the $L(E)C_{50}$/EIC ratios meet or exceed the decision criteria set for each tier. Advanced tiers require either acute testing on additional species or chronic testing in the most sensitive species previously tested.

Using a conservative approach, the acute toxicity of pregabalin was determined using 3 species from different taxonomic classes and with different functions within the aquatic ecosystem. Refer to Confidential Appendices 8 through 10.

Tier 1 and Tier 2 (Acute Ecotoxicity - Base Set Aquatic) - 3 Species

Decision criteria $L(E)C_{50}$/EIC ratio is ≥100.

Species	$L(E)C_{50}$
Daphnia magna	>1000 mg/L
Rainbow trout	>1000 mg/L
Green alga	>300 mg/L

The $L(E)C_{50}$/EIC ratio for green alga is >100 indicating no further testing is required.

iii. Predicted No Effect Concentration (PNEC)

The PNEC is calculated by applying an assessment factor (AF) to the effects data developed during the tiered testing.

$$PNEC = NOEC \text{ or } L(E)C_{50}/AF$$

The assessment factor represents the extent of uncertainty in extrapolating test data on a limited number of species to the natural environment. In general, the greater number of species tested and the longer the duration of the tests, the smaller the degree of uncertainty and the size of the assessment factor.

The PNEC for pregabalin is based on green alga, the most sensitive species and was calculated using the standard tier 2 assessment factor of 100. The PNEC for pregabalin is 3 mg/L.

iv. Summary

The ecotoxicity of pregabalin to 3 aquatic species was determined using either a FDA TAD Test Protocol or an OECD Test Guideline. Green alga was the most sensitive environmental species tested and therefore was used to determine the PNEC. For each species tested, the No Observable Effect Concentration (NOEC) is >300 mg/L and significantly greater than the EIC. It is therefore anticipated that pregabalin would not have an adverse affect on the environment.

c. Summary

Upon approval of the subject NDA, introduction of pregabalin into the environment through use and disposal by consumers is projected to result in an insignificant amount of pregabalin in the environment.

Based on the PEC/PNEC risk assessment, it is unlikely that pregabalin represents a risk to the aquatic environment. The PEC/PNEC risk assessment for total pregabalin usage was based on green alga, the most sensitive species tested. This risk assessment was conducted using a conservative estimate for the PEC. No adverse environmental effect was identified in this assessment, as demonstrated by a calculated PEC/PNEC ratio of approximately 4 orders of magnitude <1.0, the

threshold of concern. The PEC/PNEC risk assessment based on pregabalin usage is provided in Confidential Appendix 4.

Analysis of current data provides that "**No Further Action**" is required since the PEC/PNEC is substantially <1.0, and the green alga NOEC is substantially less than the PEC.

Section Two—Use of Fauna or Flora

The subject application does not include the use of fauna or flora.

7. MITIGATION MEASURES:

No adverse environmental effects have been identified. No mitigation measures are required.

8. ALTERNATIVES TO THE PROPOSED ACTION:

No potential effects have been identified for this proposed action. No alternatives to the proposed action are required.

9. LIST OF PREPARERS:

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The contract testing laboratory used for all studies is included in the relevant confidential appendices.

10. REFERENCES:

[1] "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," Center for Drug Evaluation and Research (CDER), Jul 1998.

[2] "A Study of the Mass Balance and Metabolism of [^{14}C] CI-1008 (Pregabalin) in Healthy Volunteers: Protocol 1008-5," Total Renal Pharmaceutical Research Institute, Inc, Feb 2000.

[3] "Hine J, Mookerjee PK. "The Intrinsic Hydrophilic Character of Organic Compounds. Correlations in Terms of Structural Contributions," *J. Org. Chem.* 1975;40:292-98 (Available upon request).

[4] Dias FF, Alexander M. "Effect of Chemical Structure on the Biodegradability of Aliphatic Acids and Alcohols," *Applied Microbiology*, 1971;22:1114-8

11. APPENDICES:

Nonconfidential:

1. Data Summary Table
2. Abbreviations

Confidential:

Projected Usage:

1. Projected Total Usage of Pregabalin

EIC/PEC/PNEC:

2. Basis for Expected Introduction Concentration (EIC) From Use Into the External Aquatic Environment
3. Basis for Predicted Environmental Concentration (PEC) From Use Into the External Aquatic Environment
4. Basis for PEC/PNEC Calculation

Environmental Fate Studies:

5. Determination of Sorption and Desorption Properties, TAD 3.08

6. Determination of Aerobic Biodegradation in Water, TAD 3.11

Environmental Effect Studies:

7. Determination of Microbial Growth Inhibition, TAD 4.02
8. Acute Toxicity to Daphnids (*Daphnia Magna*) Under Static Conditions, TAD 4.08
9. Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, OECD 203
10. Toxicity to Freshwater Green Alga (*Pseudokirchneriella subcapitata*), OECD 201

12. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Pfizer Inc's knowledge.

Name: Richard T. Williams, Ph.D.

Title:
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Richard T. Williams

Signature

15 April 2003

Date

APPENDIX 1

Data Summary Table
(Page 1 of 2)

Physical/Chemical Characterization	
Melting Point	190°C
Ultraviolet - Visible Spectrum	**Ext. Coefficient (L/mol-cm)**
194 nm	256
207 nm	40.1
216 nm	44.2
Water Solubility	**(mg/mL)**
pH 3.7	107
pH 7.4	32
pH 10.1	47
Dissociation Constant (pKa)	4.2
	10.6
Octanol/Water Partition Coefficient	**(log K_{ow})**
pH 1	-1.90
pH 4	-1.43
pH 7.4	-1.35
Vapor Pressure (estimate)	1×10^{-7} mm Hg
Sludge Sorption Coefficient (K_d)	13.3
Depletion Mechanisms	
Hydrolysis at Environmental Conditions	Stable
Aerobic Sludge Biodegradation (B.A.S.)	-2.19% after 28 days
Photolysis: half life (days)	Not applicable

Data Summary Table
(Page 2 of 2)

Environmental Effects	
Microbial Inhibition (MIC)	**(mg/L)**
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>997
Bacillus subtilis	>1000
Nostoc sp.	>1000
Acute Toxicity	
Daphnia Magna 48-hour EC_{50}	>1000
Rainbow trout 96-hour LC_{50}	>1000
Green alga 72-hour EC_{50}	>300
Daphnia Magna 48-hour NOEC	1000
Rainbow trout 96-hour NOEC	1000
Green alga 72-hour NOEC	>300

APPENDIX 2

Abbreviations

The following is a list of abbreviations and their definitions. They are grouped according to their use in the Environmental Assessment.

Regulatory

EA	Environmental Assessment
FDA	Food and Drug Administration
CDER	Center for Drug Evaluation and Research
NDA	New Drug Application
FOIA	Freedom of Information Act

Dosage Form, Packaging and Containers

HDPE	High Density Polyethylene
IM	Intramuscular
IV	Intravenous
PVC	Polyvinyl Chloride

Environmental Tests

C_{ss}	Concentration of substance on POTW suspended solids
C_{ww}	Concentration of substance in POTW aqueous phase
EC_{50}	Effective Concentration for 50% of test population
K_d	Sludge sorption coefficient
K_{oc}	Sorption coefficient corrected for organic content
LC50	Lethal Concentration to 50% of test population
$L(E)C_{50}$	Lethal or Effective Concentration for 50% of test population
Log K_{ow}	Log value of the octanol-water partition coefficient
MIC	Minimum Inhibitory Concentration
NOEC	No Observed Effect Concentration
OECD	Organization for Economic Co-operation and Development
pKa	Dissociation Constant
SW	Sludge wasted in grams
TAD	Technical Assistance Document
Vp	Vapor Pressure
POTW	Publicly Owned Treatment Works

Abbreviations (con't)

Environmental Models

A	Usage in Mature Market in Kilograms (Kg)
AF	Assessment Factor
D	Dilution
DF	Dilution Factor
EEC	Expected Environmental Concentration
EIC	Expected Introduction Concentration
P	Population in millions
PEC_{air}	Predicted Environmental Concentration in air
PEC_{soil}	Predicted Environmental Concentration in soil
PEC_{water}	Predicted Environmental Concentration in water
PEC/PNEC	Ratio of Predicted Environmental Concentration to Predicted No Effect Concentration
PNEC	Predicted No Effect Concentration
R	Percent removed via sorption, hydrolysis, biodegradation
$t_{½}$	Half life
V	Volume (L) /capita/day

Units

C	Celsius
kg/yr	Kilograms per year
mg	Milligrams
mg/kg	Milligrams per kilogram
mg/mL	Milligrams per milliliter
mg/L	Milligrams per liter
mg a.i./L	Milligrams of activity per liter
ng/L	Nanograms per liter
nm	Nanometers
ppb	Parts per billion (µg/L)
ppt	Parts per trillion (ng/L)
µg/kg	Micrograms per kilogram
µg/L	Micrograms per liter

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