

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-992

ENVIRONMENTAL ASSESSMENT

REVIEW
OF
ENVIRONMENTAL ASSESSMENT
FOR

Desvenlafaxine Succinate Sustained-Release Tablets
100 and 200 mg

NDA 21-992

Antidepressive

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products

April 5, 2006

**Environmental Assessment Review #2, NDA 21-992
Desvenlafaxine Succinate Sustained-Release Tablets**

Executive Summary

A FONSI is recommended.

NDA 21-992 requests approval of Desvenlafaxine Succinate Sustained-Release (DVS SR) Tablets for the treatment of major depressive disorder.

The firm estimates that the total amount of Desvenlafaxine Succinate (DVS) manufactured for all indications for the US market is expected to be _____ kg in 2011. This peak production corresponds to an EIC of _____ ppb in the aquatic environment.

The firm provides environmental fate and effects data which demonstrate that DVS is not expected to be toxic to aquatic organisms at expected concentrations.

No inhibition of respiration of activated sludge was observed at concentrations up to 100 mg/L.

The 48-hour EC_{50} for *daphnia magna* immobilization is > 32.0 mg/L. This EC_{50} value divided by the MEEC is greater than _____. A FONSI is recommended for NDA 21-992 because EC_{50} is more than 1000 greater than EIC.

**Environmental Assessment Review #2, NDA 21-992
Desvenlafaxine Succinate Sustained-Release Tablets**

It was noted during the first review (February 12, 2006) of the May 4, 2005 EA that each page was marked confidential. The EA summary document and nonconfidential appendices are made available to the public (21 CFR 25.50(a) and (b)) and therefore should not contain confidential information, and should not be marked confidential. All confidential information should be located in a confidential appendix. The firm was contacted and this information was relayed (through the project manager for the application and Bai Nguyen (EA Staff)). In their March 13, 2006 response, Wyeth submitted a version of the EA summary document that was similar in content to the May 4, 2005 document, but with confidential information removed, and "confidential" in the footer changed to "non-confidential". Minor changes were also made to the drug substance nomenclature and pKa values. The confidential data and the confidential appendices were not resubmitted, and therefore the March 13, 2006 submission does not replace the May 4, 2005 submission.

I. DATE: May 4, 2005
March 13, 2006 (resubmission of a non-confidential version of the EA summary document; see note above)

II APPLICANT: Wyeth Pharmaceuticals, Inc.

III ADDRESS: P.O. Box 8299
Philadelphia, PA 19101-1245

IV PROPOSED ACTION:

NDA 21-992 requests approval of Desvenlafaxine Succinate Sustained-Release (DVS SR) Tablets for the treatment of major depressive disorder. DVS SR will be supplied as tablets in 100 mg and 200 mg strengths.

Information in Confidential Appendix I states that the total amount of Desvenlafaxine Succinate (DVS) manufactured for all indications for the USA market is expected to be kg in 2011. This peak production corresponds to an EIC of ppb in the aquatic environment.

DVS SR Tablets will be used primarily in the homes of patients, but also in hospitals, clinics and physician offices. Any returned, recalled, expired, or damaged product will be returned to Wyeth. These returned products will be handled and disposed of by incineration as special waste according to applicable laws and regulations. Patients using the product are expected to dispose of negligible, if any, quantities of the product.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

Established name (USAN): Desvenlafaxine Succinate

Brand/Proprietary Name/Tradename: not yet established

Chemical Name: 1-[(1*R,S*)-2-[Dimethylamino-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate

CAS Number: 386750-22-7

Molecular Formula: $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$

Molecular Weight: 263.38/ 381.47/ 399.49 (base/ succinate/ monohydrate)

Structural Formula: Provided on page 5

ADEQUATE

VI ENVIRONMENTAL ISSUES

Information in Confidential Appendix I states that the total amount of Desvenlafaxine Succinate (DVS) manufactured for all indications for the USA market is expected to be _____ in 2011. This peak production corresponds to an expected introduction concentration (EIC) = _____ ppb in the aquatic environment.

The EIC for the terrestrial compartment is estimated to be zero. DVS has a log P_{ow} of 0.33² and a moderate aqueous solubility of 32 g/L. In general, partitioning to solids/sediments is more likely to occur for a compound with a P_{ow} greater than 3.5. These values are also indicative of a compound that is lipophilic, and therefore DVS is not expected to bioaccumulate.

The EIC for the atmospheric compartment is estimated to be zero since DVS is a solid at room temperature and will have a negligible vapor pressure.

DVS has two pK_as, 8.34 (dimethylamino group) and 10.11 (phenolic group), so there will not be significant quantities of ionized species at environmental conditions.

The expected environmental concentration (EEC) of DVS is calculated to be 2.57×10^{-4} mg/L in the surface waters of the United States. This is a worst-case estimate since a conservative dilution factor of only one order of magnitude is used and no further depletion mechanisms are taken into account.

The maximum expected emitted concentration (MEEC) is equal to the EIC, which is _____ ppb.

No inhibition of respiration of activated sludge was observed at concentrations up to 100 mg/L

(OECD Guideline 209). Based on this result, DVS is not expected to negatively impact sludge microflora in wastewater treatment plants at expected concentrations.

An acute toxicity to Daphnia study was conducted (OECD Guideline 202). The 48-hour EC₅₀ for *daphnia magna* immobilization is > 32.0 mg/L DVS. This EC₅₀ value divided by the MEEC is greater than 12,000, which is greater than the Tier 1 assessment factor of 1000. Therefore, no further testing is required (Guidance for Industry; Environmental Assessment of Human Drug & Biologics Applications, July 1998, p 14). DVS is not expected to be toxic to aquatic organisms at expected concentrations.

A FONSI is recommended for NDA 21-992.

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARER

Preparer, job title and qualifications are provided.

ADEQUATE

X REFERENCES

Listed. The referenced data was not provided.

ADEQUATE

XI APPENDIX

DVS production estimates are provided in Confidential Appendix I. The peak production estimate is _____ kg in 2011.

The EIC calculation is provided in Confidential Appendix II. The EIC was determined to be _____ ppb, or _____ mg/l.

ADEQUATE

Review by: Ruth Ganunis on April 5, 2006
Chemist, Center for Drug Evaluation and Research

14 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Bai Nguyen
4/13/2006 03:22:15 PM
CHEMIST

Bai Nguyen
4/13/2006 03:23:01 PM
CHEMIST

Jon E. Clark
4/21/2006 05:32:59 PM
CHEMIST

Moheb Nasr
4/23/2006 01:33:10 PM
CHEMIST

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: April 12, 2006

From: Bai Nguyen, Chemist, OPS, CDER, FDA, HFD-354

To: Administrative Files: NDA 21-992

Subject: Finding of No Significant Impact (FONSI) for Desvenlafaxine Succinate Sustained-Release Tablets 100 and 200 mg

The following FONSI was completed after reviewing the corresponding environmental assessment, by a contract reviewer, Dr. Ruth Ganunis (reference number: 1007548). As a chemist reviewer from Office of Pharmaceutical Science/IO and a supervisor for this project, I am responsible for technical content as well as entering of this FONSI into Division File System. If you have questions regarding this review, please feel free to contact me directly.

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT

FOR

**Desvenlafaxine Succinate Sustained-Release Tablets
100 and 200 mg**

NDA 21-992

Treatment of major depressive disorder

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

Division of Neuropharmacological Drug Products

April 5, 2006

FINDING OF NO SIGNIFICANT IMPACT
NDA 21-992

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 Desvenlafaxine Succinate Sustained-Release (DVS SR) Tablets, Wyeth Pharmaceuticals, Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product.

In this application, Wyeth Pharmaceuticals, Inc. requests approval of Desvenlafaxine Succinate Sustained-Release (DVS SR) Tablets for the treatment of major depressive disorder.

Desvenlafaxine succinate may enter the aquatic environment from patient use and disposal. The toxicity of desvenlafaxine succinate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, 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

Ruth Ganunis

Chemist, Center for Drug Evaluation and Research

CONCURRED BY

Bai Nguyen

Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY

Jon Clark

Associate Director for Policy, Office of Pharmaceutical Science, Center for Drug Evaluation and Research

CONCURRED BY

Moheb Nasr.

Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

TABLE OF CONTENTS

TABLE OF CONTENTS.....1
SUMMARY.....2
ENVIRONMENTAL ASSESSMENT3
1.0 IDENTIFICATION OF SUBSTANCES4
 1.1 Nomenclature.....4
2.0 ENVIRONMENTAL ISSUES.....6
 2.1 Expected Introduction Concentration (EIC) From Use.....6
 2.2 Expected Introduction Concentration From Disposal6
 2.3 Expected Environmental Concentration (EEC).....7
 2.4 Maximum Expected Emitted Concentration (MEEC).....7
 2.5 Fate Of Emitted Substances In The Environment7
 2.6 Potential Toxicity Effects8
3.0 MITIGATION MEASURES.....9
4.0 ALTERNATIVES TO THE PROPOSED ACTION9
5.0 LIST OF PREPARERS10
REFERENCES11
APPENDICES12

SUMMARY

Wyeth Pharmaceuticals, Inc. is seeking approval for Desvenlafaxine Succinate Sustained-Release Tablets (100 and 200 mg) for the treatment of major depressive disorder. This environmental assessment, arranged as specified in the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July, 1998), is part of the New Drug Application. The proposed action is not expected to result in any adverse impact to the environment.

**Appears This Way
On Original**

ENVIRONMENTAL ASSESSMENT

Desvenlafaxine Succinate

DATE

March 13, 2006

NAME OF APPLICANT

Wyeth Pharmaceuticals, Inc.

ADDRESS

P.O. Box 8299
Philadelphia, PA 19101-1245

REQUEST FOR APPROVAL

Pursuant to Title 21CFR25, this environmental assessment is prepared for this NDA. Wyeth Pharmaceuticals (Wyeth) is seeking approval for Desvenlafaxine Succinate Sustained-Release (DVS SR) Tablets for the treatment of major depressive disorder. DVS SR will be supplied as tablets in 100 and 200 mg strengths. This environmental assessment has been prepared in accordance with FDA guidance¹.

NEED FOR ACTION

The proposed action is to seek approval for DVS SR Tablets for the treatment of major depressive disorder.

LOCATIONS OF USE

The product will be used primarily in the homes of patients, but also in hospitals, clinics, and physician offices. The product will be widely used in the United States.

DISPOSAL SITES

Any returned, recalled, expired, or damaged product will be returned to Wyeth. These returned products will be handled and disposed of by incineration as special waste according to applicable laws and regulations. Patients using the product are expected to dispose of negligible, if any, quantities of the product.

1.0 IDENTIFICATION OF SUBSTANCES

Desvenlafaxine succinate (DVS) is the active ingredient of the medicinal product and is the only substance of concern in this environmental assessment. The remaining ingredients [hydroxypropylmethylcellulose, microcrystalline cellulose, talc, magnesium stearate, carboxymethylcellulose sodium, maltodextrin, dextrose monohydrate, titanium dioxide, purified stearic acid and iron oxide (red, black and yellow)] are commonly used in medicinal products and are deemed to be of no concern.

1.1 Nomenclature

Established Name (USAN): Desvenlafaxine Succinate

Brand/Proprietary Name/Tradename: not yet established

Chemical Name(s): 4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol succinate monohydrate

V IDENTIFICATION OF CHEMICALS

Established name (USAN): Desvenlafaxine Succinate

Brand/Proprietary Name/Tradename: not yet established

Chemical Name: 1-[(1*R,S*)-2-[Dimethylamino-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate

CAS Number: 386750-22-7

Molecular Formula: $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$

Molecular Weight: 263.38/ 381.47/ 399.49 (base/ succinate/ monohydrate)

Structural Formula: Provided on page 5

ADEQUATE

VI ENVIRONMENTAL ISSUES

Information in Confidential Appendix I states that the total amount of Desvenlafaxine Succinate (DVS) manufactured for all indications for the USA market is expected to be _____ kg in 2011. This peak production corresponds to an expected introduction concentration (EIC) = _____ ppb in the aquatic environment.

The EIC for the terrestrial compartment is estimated to be zero. DVS has a log P_{ow} of 0.33² and a moderate aqueous solubility of 32 g/L. In general, partitioning to solids/sediments is more likely to occur for a compound with a P_{ow} greater than 3.5. These values are also indicative of a compound that is lipophilic, and therefore DVS is not expected to bioaccumulate.

The EIC for the atmospheric compartment is estimated to be zero since DVS is a solid at room temperature and will have a negligible vapor pressure.

DVS has two pKas, 8.34 (dimethylamino group) and 10.11 (phenolic group), so there will not be significant quantities of ionized species at environmental conditions.

The expected environmental concentration (EEC) of DVS is calculated to be _____ mg/L in the surface waters of the United States. This is a worst-case estimate since a conservative dilution factor of only one order of magnitude is used and no further depletion mechanisms are taken into account.

The maximum expected emitted concentration (MEEC) is equal to the EIC, which is _____ ppb.

No inhibition of respiration of activated sludge was observed at concentrations up to 100 mg/L

DVS SR - MDD

1.12 Other Correspondence
1.12.14 Environment Analysis

1-[(1*R,S*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol
succinate monohydrate

(±)-1-[α-[Dimethylamino)methyl]-p-hydroxybenzyl]cyclohexanol
succinate monohydrate

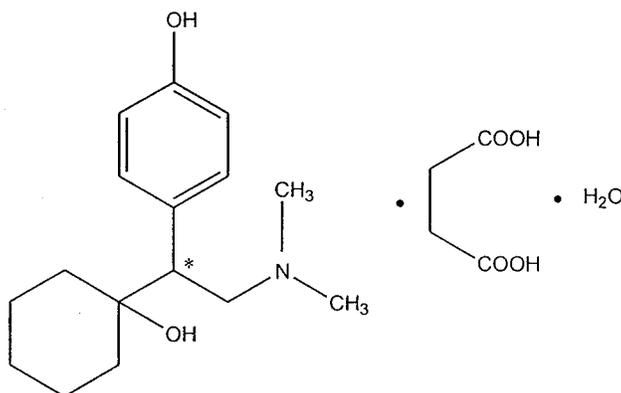
CAS Name: 1-[(1*R,S*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol
hydrogen butanedioate monohydrate

CAS Number: 386750-22-7

Empirical (Molecular) Formula: $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$

Molecular Weight: 399.48 (as the succinate, monohydrate)/ 263.38 (as the free base)

Structural Formula:



* Denotes chiral center, the compound is racemic.

2.0 ENVIRONMENTAL ISSUES

2.1 Expected Introduction Concentration (EIC) From Use

Confidential Appendix I contains a five-year forecast of the bulk requirements for DVS through 2011.

The EIC for the aquatic compartment, assuming all DVS will be used and evenly distributed throughout the United States, is listed below.

$$\text{EIC} = \text{ppb}$$

Calculation of the EIC is found in Confidential Appendix II.

The EIC for the terrestrial compartment is estimated to be zero. DVS has a log P_{ow} of 0.33² and a moderate aqueous solubility of 32 g/l. In general, partitioning to solids/sediments is more likely to occur for a compound with a log P_{ow} greater than 3.5. Therefore, DVS is not expected to partition to sewage sludge or sediments.

The EIC for the atmospheric compartment is estimated to be zero since DVS is a solid at room temperature and will have a negligible vapor pressure.

2.2 Expected Introduction Concentration From Disposal

The EIC from disposal is zero since all expired, returned or damaged product, rejected batches, and pharmaceutical waste containing DVS are disposed of via incineration. The amount of DVS expected to be disposed of in the sewer system, due to manufacturing equipment washdown and cleaning, will not be significant. Patients are expected to dispose of negligible quantities of the product.

2.3 Expected Environmental Concentration (EEC)

The expected environmental concentration (EEC) of DVS is calculated to be mg/l. This concentration is calculated by taking the EIC (mg/l), a worst-case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The result, mg/l, is a conservative estimate of the concentration of DVS in the surface waters of the United States. This is a worst-case estimate since no further depletion mechanisms have been taken into account in this calculation.

2.4 Maximum Expected Emitted Concentration (MEEC)

The maximum expected emitted concentration (MEEC) is equal to the expected environmental concentration (EEC), or the expected introduction concentration (EIC), whichever is greater. In the case of DVS, the MEEC is mg/l or ppb.

2.5 Fate Of Emitted Substances In The Environment

As discussed in Section 2.1, DVS is expected to remain primarily in the aquatic compartment. DVS is not expected to partition to sewage sludge or sediments because of its low log P_{ow} and moderate aqueous solubility. These values are also indicative of a compound that is not lipophilic, and therefore DVS is not expected to bioaccumulate.

DVS has two pK_as, 8.34 (dimethylamino group) and 10.11 (phenolic group), so there will not be significant quantities of ionized species at environmental conditions.

Based on the data from venlafaxine³, DVS is not expected to significantly biodegrade. DVS is the major active metabolite of the structurally novel antidepressant venlafaxine and is very similar in structure.

2.6 Potential Toxicity Effects

Two studies were conducted to assess the environmental toxicity of DVS. These studies are summarized here.

Activated Sludge Respiration Inhibition: A respiration inhibition study with DVS and activated sludge from a conventional aerobic wastewater treatment plant was conducted following OECD Test Method 209⁴. Five DVS test concentrations were evaluated: 1.0, 3.1, 9.2, 31.5, and 101.7 mg/l respectively. No inhibitory effects of DVS were observed at the concentrations tested, except at 9.2 mg/l, which had a result of 24.8 % inhibition. The overall test results were valid since the respiration rates of the two controls were within 15 percent of each other, and the EC50 of the reference item 3,5-dichlorophenol was in the acceptable range of the OECD method. The inhibition noted at 9.2 mg/l DVS was concluded to be an outlier, not unusual for this type of study. The EC50 value of DVS was determined to be ≥ 100 mg/l.

Based on this result, DVS is not expected to negatively impact sludge microflora in wastewater treatment plants at expected concentrations.

Acute Toxicity to *Daphnia*: An acute toxicity study with DVS was conducted following OECD Test Method 202⁵. *Daphnia magna* were exposed to six concentrations of DVS (10-90 mg/l, nominal) and to a negative control under static conditions for 48 hours. The 48 hour EC50 was determined to be 32.0 mg/l DVS, with a 95% confidence interval of 27.6 – 37.1 mg/l.

A substance is considered potentially toxic to aquatic organisms if the EC50 or LC50 of the substance divided by the MEEC is less than an assessment factor of 1000, 100, or 10. In the case of DVS, an assessment factor of 1000 is used because only daphnid toxicity study results are available. In the case of DVS, the daphnid EC50 of 32.0 mg/l divided by the MEEC of mg/l is greater than . Therefore, DVS is not expected to be toxic to aquatic organisms at expected concentrations.

3.0 MITIGATION MEASURES

Mitigation measures to control the environmental release of DVS are not necessary. Releases from the manufacturing process and disposal are well controlled and regulated, and therefore are deemed to be negligible. Use of fauna and flora are not required for the production of DVS (active moiety or product).

Releases from the use of the product have been evaluated by conservatively estimating an environmental concentration (ie, the MEEC), and assessing its environmental fate and toxicity. After applying a conservative assessment factor of 1000, it can be concluded that the proposed action will not have any adverse impact on organisms in the environment.

4.0 ALTERNATIVES TO THE PROPOSED ACTION

No alternatives to the proposed action have been evaluated or are needed.

**Appears This Way
On Original**

5.0 LIST OF PREPARERS

Harry Yekel
Principal Project Engineer
Wyeth Pharmaceuticals, Inc.

Mr. Yekel has over 20 years' experience in environmental-, health- and safety-related fields. At Wyeth, Mr. Yekel is responsible for preparing and reviewing all environmental assessment documents for FDA New Drug Applications and European Dossiers, and coordinating environmental fate testing for new drug substances. Mr. Yekel has BS and MS degrees in Environmental Engineering from Pennsylvania State University and Drexel University, respectively.

**Appears This Way
On Original**

REFERENCES

-
- ¹ Center for Drug Evaluation and Research, Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications, July, 1998.
 - ² Determination of n-Octanol / Water Partition Coefficient of DVS-233, OECD Method 117, Battelle Memorial Institute, Study No. N102096, January 15, 2005.
 - ³ Determination of the Inherent Biodegradability of Venlafaxine Hydrochloride by the Modified SCAS Test, OECD Method 302A, Springborn Smithers Laboratories, Study No. 1029.001.799, April 5, 2005.
 - ⁴ DVS-233 Succinate Monohydrate: Activated Sludge, Respiration Inhibition Test (OECD 209), Battelle Geneva Research Centres, Study No. E-53-04-01, March 21, 2005.
 - ⁵ DVS-233: A Study on the Acute Toxicity to *Daphnia*, OECD Method 202, Battelle Marine Sciences Laboratory, Study No. MSL 04-0001, April 27, 2005.

DVS SR MDD

**1.12 Other Correspondence
1.12.4 Environment Analysis**

APPENDICES

Appendix I Five-Year US Forecast of DVS Requirements (Confidential)

Appendix II Environmental Introduction Concentration Calculation (Confidential)

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

/s/

Bai Nguyen
4/13/2006 03:39:51 PM

Jon E. Clark
4/21/2006 05:33:19 PM

Moheb Nasr
4/23/2006 01:33:46 PM