CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

ENVIRONMENTAL ASSESSMENT and/or FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

for

CADUET

Norvasc (amlodipine besylate) and Lipitor (atorvastatin calcium)

NDA 21-540

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
(HFD-110)

December 4, 2003

FINDING OF NO SIGNIFICANT IMPACT, NDA 21-540

CADUET
Norvasc (amlodipine besylate) and Lipitor (atorvastatin calcium)

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, Pfizer Inc prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 (b) that evaluates the potential environmental impacts of the use and disposal from use of the product. NDA 21-540 requests approval of Caduet, a combination tablet for long-term treatment of both hypertension / angina and hyperlipidemia.

Caduet contains amlodipine besylate (Norvasc) and atorvastatin calcium (Lipitor). The FDA determined that, in the absence of extraordinary circumstances, ecotoxicity data are not required unless the EIC is greater than 1 ppb. No ecotoxicity data was provided for amlodipine besylate because its EIC is not more than 1 ppb. This Environmental Assessment focused on the potential environmental effects of atorvastatin calcium.

Atorvastatin calcium may enter the environment from patient use and disposal. It is expected to enter predominately into the aquatic environment. Atorvastatin calcium is susceptible to photolysis. However, because Atorvastatin calcium is expected to persist in the environment for some time, its toxicity to environmental organisms was characterized. The results indicate that it is not expected to be toxic to aquatic 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

NON-CONFIDENTIAL [FREEDOM OF INFORMATION ACT (FOIA)] SUBMISSION

(Referenced Confidential Information Has Been Provided
Under Separate Cover)

Caduet®

Amlodipine Besylate/Atorvastatin Calcium for Use in the
Treatment of Hypertension/Angina and Hyperlipidemia

NDA # 21-540

December 2002

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

ENVIRONMENTAL ASSESSMENT

Norvasc®/Lipitor®

NDA # 21-540

SUMMARY:

An environmental assessment to support NDA # 21-540 for Caduet, a fixed dose Norvasc/Lipitor combination tablet offering dual therapy for the treatment of both hypertension/angina and hyperlipidemia, was conducted. Based on current usage and projected usage pending approval of the subject NDA, the environmental assessment of Norvasc and Lipitor are addressed as follows:

Norvasc - Pfizer Inc. claims a categorical exclusion in accordance with the criteria defined in 21 CFR Part 25.31(b).

Lipitor - Pfizer Inc. conducted an environmental assessment pursuant to 21 CFR Part 25, following the Center for Drug Evaluation and Research "Guidance for Industry for the Submission of an Environmental Assessment," dated July 1998.

The categorical exclusion for Norvasc and the environmental assessment of Lipitor are provided in this Environmental Assessment Section of NDA # 21-540.

ENVIRONMENTAL ASSESSMENT

Norvasc®

NDA # 21-540

Fixed-Dose Combination Tablet
Amlodipine besylate / Atorvastatin calcium

5/10mg, 5/20mg, 5/40mg, 5/80mg, 10/10mg, 10/20mg,
10/40mg and 10/80mg

Claim for Categorical Exclusion According to 21 CFR Part 25.15 (a),(d)

Pfizer Inc claims a categorical exclusion to the environmental assessment requirements in accordance with categorical exclusion criteria 21 CFR Part 25.31 (b): Action on a NDA; the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion. Pfizer Inc claims that to the best of our knowledge no extraordinary circumstances exist.

Preparers:

Lisa A. Constantine, Senior Chemical Safety and Control Coordinator, Environmental Sciences within the Chemical Research and Development Department of Pfizer Global Research and Development. BS in Chemistry, MBA, Certified Industrial Hygienist with 18 years experience in EH&S, including 4 years with Chemical Research and Development.

Richard T. Williams, Ph.D., Assistant Director, Environmental Sciences, Chemical Research and Development Department of Pfizer Global Research and Development. Ph.D. in Microbiology / Ecology with 21 years of experience in EH&S, including 11 years experience within Chemical Research and Development.

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

Name:	Title:
Richard T. Williams, Ph.D.	Assistant Director Environmental Sciences Chemical Research and Development Pfizer Global Research and Development Groton, CT 06340

Signature

11/07/2002
Date

ENVIRONMENTAL ASSESSMENT

Lipitor®

NDA # 21-540

Fixed-Dose Combination Tablet
Amlodipine besylate / Atorvastatin calcium

5/10mg, 5/20mg, 5/40mg, 5/80mg, 10/10mg, 10/20mg,
10/40mg and 10/80mg

SUMMARY:

The Applicant certifies that the Environmental Assessment (EA) provided in support of Lipitor® Tablets (NDA # 20-702; Finding of No Significant Impact) is valid for this Norvasc/Lipitor dual therapy NDA. Pfizer anticipates no adverse effects to humans or environmental organisms as a result of excreted atorvastatin calcium entering into publicly owned treatment works (POTW) and subsequent release environments.

1. **DATE:** December 27, 2002

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 filed NDA# 21-540, pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for the use of amlodipine besylate/atorvastatin calcium as a dual therapy for the treatment of comorbid hypertension/angina and hyperlipidemia. Atorvastatin calcium (Lipitor®) is currently approved for use as an adjunct to diet to reduce elevated total LDL-C levels in patients with primary hypercholesterolemia (Type IIa) including heterozygous and homozygous familial hypercholesterolemia and combined hyperlipidemia (Type IIb) when the response to a diet restricted in saturated fat and cholesterol is inadequate (NDA# 20-702). Amlodipine besylate (Norvasc®) is currently approved for use in the treatment of hypertension, chronic stable angina and confirmed or suspected vasospastic angina, collectively termed hypertension/angina (NDA# 19-787). Norvasc/Lipitor dual therapy is being submitted for approval as a fixed-dose combination tablet containing both amlodipine besylate and atorvastatin calcium formulated for oral administration in 8 dose combinations: 5/10mg, 5/20mg, 5/40mg, 5/80mg, 10/10mg, 10/20mg, 10/40mg and 10/80mg. The tablets will be packaged in HDPE bottles and foil/foil blisters. The subject EA has been submitted to support the comorbid hypertension/angina and hyperlipidemia NDA # 21-540, pursuant to 21 CFR Part 25, following the Center for Drug

Evaluation and Research "Guidance for Industry for the Submission of an Environmental Assessment," dated July 1998.

b. Need for the Action: Amlodipine besylate is a member of the 1,4-dihydropyridine structural class of calcium channel blockers. It is has been approved for the treatment of hypertension, chronic stable angina and confirm or suspected vasospastic angina. Atorvastatin calcium, a synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, is approved for use in the treatment of hypercholesterolemia and hyperlipidemia. As a dual therapy, amlodipine besylate/atorvastatin calcium combination tablets are equivalent to Norvasc and Lipitor tablets co-administered in matching doses. The combination tablets, like Norvasc and Lipitor tablets administered in monotherapy, can be taken at any time of day, with or without food, with no significant variation expected in benefit or risk. The dual therapy will offer treatment for both hypertension/angina and hyperlipidemia in the convenience of a single tablet for patients with both conditions.

c. Locations of Use: Amlodipine besylate/atorvastatin calcium will be used as a prescription agent in home and hospital environments throughout the U.S.

d. Disposal Sites:
End-user disposal at US hospitals, pharmacies or clinics of empty or partially empty packages 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 to sewer or septic systems.

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

a. Nomenclature

i. Established Name (USAN): Atorvastatin calcium

ii Trade Name: Lipitor®

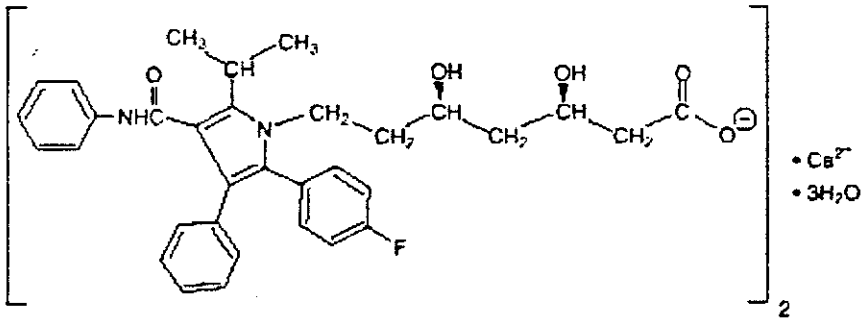
ii. Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

b. Chemical Abstracts Service (CAS) Registration Number: 134523-03-8

c. Molecular Formula: $(C_{33}H_{34}FN_2O_5)_2\,Ca \cdot 3H_20$

d. Molecular Weight: 1209.42

e. Structural Formula:



6. **ENVIRONMENTAL ISSUES:**

Assessing Toxicity to Environmental Organisms

The physical-chemical, fate and ecotoxicity protocols used in testing atorvastatin generally followed the Technical Assistance Documents (TAD) as published in FDA's EA Technical Assistance Handbook.

a. ENVIRONMENTAL FATE OF RELEASED SUBSTANCES

i. Identification of Substance of Interest

Administration of a single daily oral dose of unlabeled atorvastatin to healthy male volunteers for two weeks followed by a single oral dose of radiolabeled atorvastatin, resulted in mean cumulative urinary and fecal recoveries of 1.23% and 89.4% of the administered dose, respectively. Fecal excretion is the primary route of elimination. Further evaluation of fecal samples demonstrated that for the highest radioactivity/gram of feces tested, 11.7% of the radioactivity is attributed to the para-hydroxy metabolite, 18.2% to the ortho-hydroxy metabolite and 8.3% to unchanged atorvastatin. Due to the structural similarity of atorvastatin to its identified human metabolites, atorvastatin is considered a valid environmental tracer for assessing fate and effects from the use of Caduet®. Atorvastatin will reside mainly in the aquatic environment.

ii. Physical and Chemical Characterization

The solubility of atorvastatin is relatively low, 0.7 mg/L at pH 7.4. Atorvastatin will exist as an anion at most environmental pH's, with a pKa of about 4.6. As an anion, it is not anticipated to adsorb to particulate matter in humic acids, though it is anticipated to moderately adsorb to sediments and soils. Refer to the Data Summary Table (Appendix 1) for the physical/chemical data for atorvastatin.

iii. Environmental Depletion Mechanisms

Sludge sorption during wastewater treatment is expected to be minimal. Atorvastatin is anticipated to be hydrolytically stable at environmental pH's, though at pH's < 7, it will be acid catalyzed to an equilibrium mixture of the lactone and the free acid. In dilute acid, the equilibrium mixture contains approximately 60% lactone and 40% free atorvastatin.[2] Biodegradation and photolysis have been identified as potential depletion mechanisms for atorvastatin. A 28-day aerobic water biodegradation study demonstrated biodegradation, though minimal at <10%. An exploratory photolysis study demonstrated a potential depletion mechanism for atorvastatin in the environment. After 6 hours under UV light or after 1 week under fluorescent light, essentially no atorvastatin remained in 100 µg/ml solutions prepared in acetonitrile:water (1:1).[3] While no one depletion mechanism would be considered substantial, both mechanisms combined provide an overall approach for potential elimination of atorvastatin residues in the environment. Refer to the Data Summary Table (Appendix 1) for review of depletion mechanism data for atorvastatin.

iv. Environmental Concentrations

(1) Expected Introduction Concentration (EIC):

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

Where: A = kg/yr produced for direct use (Confidential Appendix 1)
B = 1/ liters per day entering POTW*
C = years/ 365 days
D = 1 X 10^6 mg/kg (conversion factor)

* 1.214 X 10^{11} liters per day entering POTW

The EIC entering into the external aquatic environment ($EIC_{aquatic}$) has been calculated (Confidential Appendix 2). The calculations are based on total annual atorvastatin usage in the U.S., including the incremental amount from the subject NDA filing. No adjustments have been made to account for metabolism, other environmental depletion mechanisms, or for the dilution of wastewater effluents into 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:

$PEC = EIC_{aquatic} X [(100-R) / (100 X D.F.)]$

Where: % Removal (R) = 1
Dilution Factor (D.F.) = 10

The PEC refines the original EIC estimate by accounting for atorvastatin's removal on sludge during wastewater treatment and subsequent dilution into the receiving waters. Taking a conservative approach, the PEC was not adjusted for atorvastatin's removal by photolysis or biodegradation mechanisms. The PEC was calculated using 1% for removal on sludge, based on an estimated sludge sorption coefficient (K_d), and a dilution factor of 10 for dilution of wastewater effluents into the receiving waters (Confidential Appendix 3).

v. Summary

Introduction of atorvastatin into the environment through use and disposal as a result of approval of the subject NDA is projected to result in approximately a 25% increase in atorvastatin and its associated metabolites to the current baseline.

Atorvastatin will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Atorvastatin is not volatile and therefore will not enter the air compartment. Generally, only a fraction of sludge from POTW's throughout the U.S. would be applied to soil. Based on the $K_{d\ sludge}$ for atorvastatin, sludge applied to land would not result in a significant concentration of atorvastatin in the soil compartment. As atorvastatin will reside mainly in the aquatic environment, environmental effects data were generated on aquatic species.

It is anticipated that atorvastatin will be slowly removed from the aquatic environment as a result of the combined depletion mechanisms of biodegradation and photolysis.

b. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

i. Microbial Inhibition Testing - Atorvastatin presented no inhibition to microorganisms at relevant concentrations and therefore is not expected to disrupt wastewater treatment processes. Refer to the Data Summary Table (Appendix 1).

ii. Tiered Ecotoxicity Testing

Tiered testing followed the approach described in the EA Guidance for Industry Document.[1] Effects testing is conducted in a tiered sequence, starting with an acute study in one species. Testing progresses to more advanced tiers when the $L(E)C_{50}$ / EIC ratios do not meet the decision criteria set for each tier. Advanced tiers require either acute testing on additional species or chronic testing on the most sensitive species previously tested. Refer to the Data Summary Table (Appendix 1) for the effects data for atorvastatin.

Tier 1 'Acute Ecotoxicity - 1 Species'

Decision criteria $L(E)C_{50}$ / EIC ratio is ≥ 1000

Testing on *Daphnia magna* was completed as described in the initial NDA # 20-702. At the time of the original NDA, the $L(E)C_{50}$ / EIC ratio was greater than 1000, indicating no further testing was required. Based on an increase in marketing usage since the original filing, a recalculation of the $L(E)C_{50}$ / EIC ratio is required. This updated ratio remains greater than 1000, indicating no additional testing is required.

Tier 2 'Acute Ecotoxicity - Base Set Aquatic'

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

Not applicable.

Tier 3 'Chronic Toxicity'

Decision criteria: EC_{50} / EIC ratio is ≥ 10 and NOEC > EIC

Not applicable.

iii. Predicted No Effect Concentration (PNEC)

The PNEC is calculated by applying an assessment factor (AF) to the effects data developed in the tiered testing; where

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

The assessment factor represents the degree of uncertainty associated with extrapolating test data from a limited number of species to the real environment. In general, the greater the number of species tested and the longer the duration of tests, the lower the degree of uncertainty and the magnitude of the assessment factor.

The PNEC for atorvastatin was calculated using the standard tier 1 assessment factor of 1000. The PNEC is based on *Daphnia magna*. The PNEC for atorvastatin is 2.0×10^{-01} mg/L, as calculated in Confidential Appendix 4.

iv. Summary

The toxicity of atorvastatin to *Daphnia magna* was investigated using a FDA TAD test protocol. The No Observable Effect Concentration (NOEC) is greater than the EIC by several orders of magnitude.

c. SUMMARY

Introduction of atorvastatin into the environment through use and disposal by consumers, upon approval of the subject NDA, is projected to result in approximately a 25% increase in atorvastatin and its associated metabolites to the current baseline.

Based on the PEC/PNEC risk assessment, it is unlikely that atorvastatin represents a risk to the aquatic environment. The PEC/PNEC assessment for total atorvastatin usage is based on *Daphnia magna.* The PEC is conservative since it does not take into account depletion via biodegradation or photolysis. No adverse environmental effect was identified in this assessment, as demonstrated by the calculated PEC/PNEC ratio of < 1.0. The PEC/PNEC risk assessment based on total atorvastatin usage in the U.S. is provided in Confidential Appendix 4.

Review of current data provides that **"No Further Action"** is required since the EC_{50} / EIC ratio is > 1000 and there was no observable effect at the EIC (*Daphnia magna* NOEC > EIC).

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:

Lisa A. Constantine, Senior Chemical Safety and Control Coordinator, Environmental Sciences, Chemical Research and Development, Pfizer Global Research and Development. BS in Chemistry, MBA, Certified Industrial Hygienist with 18 years experience in EH&S, including 4 years experience with Chemical Research and Development.

Jon F. Ericson, Project Leader, Environmental Sciences, Chemical Research and Development, Pfizer Global Research and Development. Analytical chemist with M.S. and 17 years experience in drug metabolism and environmental sciences.

Richard T. Williams, Assistant Director, Environmental Sciences, Chemical Research and Development, Pfizer Global Research and Development. Ph.D. in Microbiology / Ecology with 21 years of experience in EH&S, including 11 years experience with Chemical Research and Development.

10. REFERENCES:

1. "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements," Center for Drug Evaluation and Research (CDER), July 1998.
2. Kearney, Albert S., Lee F. Crawford, Surendra C. Mehta, and Galen W. Radebaugh, "Interconversion Kinetics, Equilibrium, and Solubilities of the Lactone and Hydroxyacid Forms of the HMG-CoA Reductase Inhibitor, CI-981," *Pharmaceutical Research*, Vol. 10, No.10, 1993.
3. NDA # 20-702, Environmental Assessment Lipitor®
4. Kenaga, E.E. and. C.A.I Goring,. 1980. Relationship Between Water Solubility, Soil Sorption, Octanol Water Partitioning and Bioconcentration of Chemicals in Biota, pp. 78 - 115. In J. C. Eaton, P. R. Parrish, and A.C. Hendricks, Eds. Aquatic Toxicology. ASTM STP 707. American Society for Testing and Materials, Philadelphia, PA. (Available upon request)

11. APPENDICES:

1. Data Summary Table

11A. CONFIDENTIAL APPENDICES:

1. Projected Total Usage of Atorvastatin
2. Basis for Expected Introduction Concentration (EIC) into the External Aquatic Environment
3. Basis for Predicted Environmental Concentration (PEC) into the External Aquatic Environment
4. Basis for PEC/PNEC (Predicted No Effect Concentration) Calculation

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:
Assistant Director,
Environmental Sciences

Department:
Chemical Research and Development
Pfizer Global Research and Development,
Groton, CT 06340

Signature

11/27/2002
Date

APPENDIX 1

Data Summary Table

Physical/Chemical Characterization	
Melting Point	156 ° C
Ultraviolet - Visible Spectrum	Ext. Coefficient (L/mol-cm)
240 nm	0.037(mg)
Water Solubility	(mg/L)
Water	0.11
0.1N HCl	0.01
pH 7.4	0.7
Dissociation Constant (pKa)	4.6
Octanol/Water Partition Coefficient	(log K_{ow})
0.1M HCl	3.66
pH 4.0	3.18
pH 7.4	1.42
Sludge Sorption Coefficient (K_d) (estimated)	56
Soil Sorption Coefficient (K_{oc})	280 - 810
Depletion Mechanisms	
Hydrolysis at Environmental Conditions	Stable
28-day Aerobic Biodegradation in Water	< 10% biodegraded
Photolysis:	Percent remaining
UV	0% after 6 hours
fluorescent	0.4% after 7 days
Environmental Effects	
Microbial Inhibition (MIC)	(mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	100
Bacillus subtilis	200
Nostoc sp.	600
Acute Toxicity	
Daphnia magna 48 hour EC_{50}	200
Daphnia magna 48 hour NOEC	81

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

/s/

Nancy Sager
12/5/03 12:17:43 PM

Moheb Nasr
12/7/03 12:19:57 PM

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF

ENVIRONMENTAL ASSESSMENT

For

CADUET®

(Norvasc & Lipitor)

NDA 21-540

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
(HFD-110)

Date Completed: December 4, 2003

EXECUTIVE SUMMARY:

FONSI recommended.

NDA 21-540 pertains to a combination drug product (Caduet) containing Norvasc (amlodipine besylate) and Lipitor (atorvastatin calcium).

The FDA determined that, in the absence of extraordinary circumstances, ecotoxicity data are not required unless the EIC is greater than 1 ppb. Therefore, no ecotoxicity data was provided for amlodipine besylate because its EIC is not more than 1 ppb.

A FONSI was approved for Lipitor (NDA 20-702 / S-025) on Oct 26, 2000 based on an EIC for atorvastatin calcium greater than 1 ppb. NDA 21-540 refers to that FONSI and contains an updated maximum annual production estimate ([redacted]) for atorvastatin calcium in 2007.

Atorvastatin calcium is not volatile and will not enter the air compartment. Atorvastatin calcium degradation is less than 10% in water. Atorvastatin calcium is expected to bind moderately-to-tightly to soils in 0.01 M $CaCl_2$ and reagent water. Its log octanol water partition coefficient is 1.42 at pH 7.4 and 3.66 at pH 1.0. Atorvastatin calcium has relatively low solubility in water (0.7 mg/L at pH 7.4) but, it is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration ($EIC_{aquatic}$) is [redacted] assuming no metabolism, no hydrolysis and no photolysis. The Predicted Environmental Concentration (PEC) in the aquatic environment is [redacted] The PEC was calculated using 1% sorption to sludge and a dilution factor of 10 for wastewater effluents discharged into the receiving waters.

UV photolysis is complete after exposure for 6 hours; fluorescent light photolysis is virtually complete (0.4% remaining) after exposure for 7 days.

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

Atorvastatin calcium Effects, Testing Data		
Microbial Inhibition	Aspergillus niger	MIC > 1000 mg/mL
	Trichoderma viride	MIC > 1000 mg/ml
	Clostridium perfringens	MIC > 100 mg/ml
	Bacillus subtilis	MIC > 200 mg/ml
	Nostoc sp.	MIC > 600 mg/ml
Daphnia, acute	48 hour EC_{50} = 200 mg/L , NOEC 81 mg/L	

Summary: No significant environmental impact is anticipated based on the data submitted.

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated December 27, 2002
   Chemist: Ram Mittal (301) 594-5353
   Project Mgr: Denise Hinton (301) 594-5300

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

   ADEQUATE

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

   ADEQUATE

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

   a. **Requested Approval (NDA 21-540):**

   Pfizer Inc filed NDA 21-540 pursuant to section 505(b) of the Federal, Food, Drug & Cosmetic Act for Caduet (Lipitor and Norvasc). Caduet is a fixed dose combination tablet containing both Lipitor (atorvastatin calcium) and Norvasc (amlodipine besylate) formulated for oral administration in 8 dose combinations expressed as mg Norvasc / mg Lipitor: 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80.

   This submission (NDA 21-540) requests approval of Caduet for use in dual-therapy for co morbid hypertension / angina and hyperlipidemia.

   ADEQUATE

   b. **Need for Action:**

   This submission requests approval of Caduet for use in dual-therapy for co morbid hypertension / angina and hyperlipidemia.

   ADEQUATE

   c. **Expected Locations of Use (Drug Product):**

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

   ADEQUATE

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 Caduet 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 system.
ADEQUATE

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

Caduet is the trade name for the combination tablet containing atorvastatin calcium (Lipitor) and amlodipine besylate (Norvasc). Information provided below pertains to atorvastatin calcium (Lipitor) only because amlodipine besylate (Norvasc) qualifies for categorical exclusion

a. Nomenclature
   i. Established Name (USAN): Atorvastatin calcium
   ii. Trade Name: Lipitor
b. CAS Registration Number: 134523-03-8
c. Molecular Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$
d. Molecular Weight, salt: 1209.42
e. Chemical Structure is in Section 5e of the EA, page 6

ADEQUATE

6. Environmental Issues:

NDA 21-540 pertains to a combination drug product (Caduet) containing Norvasc (amlodipine besylate) and Lipitor (atorvastatin calcium).

The FDA determined that, in the absence of extraordinary circumstances, ecotoxicity data are not required unless the EIC is greater than 1 ppb. Therefore, no ecotoxicity data was provided for amlodipine besylate because its EIC is not more than 1 ppb.

A FONSI was approved for Lipitor (NDA 20-702 / S-025) on Oct 26, 2000 based on an EIC for atorvastatin calcium greater than 1 ppb. NDA 21-540 refers to that FONSI and contains an updated maximum annual production estimate [redacted] for atorvastatin calcium in 2007.

The EA in NDA 21-540 refers to physiochemical, fate and effects data for atorvastatin calcium in the EA in NDA 20-702 / S-025. Testing procedures were performed according to GLPs and FDA EA-TAD to support approval of NDA 20-702 / S-025.

Environmental Fate of Released Substances

i. Identification of Substances of Interest

Atorvastatin calcium is the active ingredient in Lipitor (NDA 20-702) and Caduet (NDA 21-540). Summing all production estimates for all indications, the maximum annual production estimate is [redacted] in 2007. This is equivalent to EIC = [redacted] in the aquatic environment.

The major identified human metabolites (18.2 % ortho- and 11.7 % para-hydroxy metabolites) are structurally similar to the atorvastatin anion. Therefore, atorvastatin calcium is considered to be a valid environmental tracer for assessing fate and effects of atorvastatin and its metabolites in the aquatic environment.

ADEQUATE

ii. Physical and Chemical Characterization

Atorvastatin calcium exists as a anion in the environmental pH range. Solubility is reported to be relatively low (0.7 mg/mL at pH 7.4 with pKa about 4.6). The anion is expected to bind moderately to sediments and soils.

The log of the n-octanol / water partition coefficient (log P_{ow}) at environmental conditions (pH 7.4) is 1.42. Because log P_{ow} is not more than 3, the probability for bioaccumulation, adsorption to particulate matter, humic acids and sediments is low.

Vapor pressure of atorvastatin calcium is virtually nil. Therefore, vaporization into the atmosphere is not expected.

ADEQUATE

iii. Environmental Depletion Mechanisms

Atorvastatin calcium is stable to hydrolysis under environmental conditions (pH 7.4). Aerobic biodegradation is less than 10% in 28 days.

Photolysis (6 hr UV or 1 week fluorescent light) of atorvastatin calcium (100 µg/L in 1:1 acetonitrile:water) is virtually complete suggesting that photolysis is an effective means for eliminating atorvastatin calcium from the environment.

ADEQUATE

iv. Environmental Concentration, aquatic

The total amount of atorvastatin calcium required for all indications in the peak market year (2007) is [redacted] (Ref: Confidential EA, Appendix 1, page 14)

The Expected Introduction Concentration ($EIC_{aquatic}$) of atorvastatin calcium entering the external aquatic environment is [redacted]). 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 (1%) and 10 fold dilution when atorvastatin calcium is introduced into the aquatic compartment gives [redacted] for the Predicted Environmental Concentration (PEC). To be conservative, EIC and PEC are not adjusted for removal by photolysis and hydrolysis.

ADEQUATE

v. Summary

Atorvastatin calcium will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Atorvastatin calcium is not volatile and therefore will not enter the air compartment. Atorvastatin calcium is not expected to be persistent in the environment due to its potential for photolysis.

ADEQUATE

Environmental Effects of atorvastatin calcium

Environmental effect data for aquatic species are the EA dated Aug 3, 2000 for NDA 20-702, S-025. It is unlikely that atorvastatin calcium represents a risk to the aquatic environment based on the available data.

Atorvastatin calcium Effects Testing Data		
Microbial Inhibition	Aspergillus niger	MIC > 1000 mg/mL
	Trichoderma viride	MIC > 1000 mg/ml
	Clostridium perfringens	MIC > 100 mg/ml
	Bacillus subtilis	MIC > 200 mg/ml
	Nostoc sp.	MIC > 600 mg/ml
Daphnia, acute	48 hour EC_{50} = 200 mg/L , NOEC 81 mg/L	

No significant environmental impact is anticipated based on the data submitted.

Summary of Atorvastatin Calcium Effects Data

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

Based on the Microbial Inhibition Test, atorvastatin calcium 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. The 48 hour EC_{50} = 200 mg/L, the NOEC measured is 81 mg/L. The EC_{50} to EIC ratio is greater than 1000. The NOEC is more than 1000 times greater than the EIC, namely [redacted], indicating that no effects would be expected.

ADEQUATE

Summary Evaluation: Based on the above data, a FONSI is recommended

7. Mitigation Measures

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

ADEQUATE

8. Alternatives to the proposed action

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

ADEQUATE

9. Preparers

The names and professional experience of the EA preparers are provided

ADEQUATE

10. References

Four references are provided.

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11. Appendices

The EA contains a 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 2007.

ADEQUATE

12. Certification

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

ADEQUATE

Reviewed by Florian Zielinski, December 4, 2003

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/s/

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