

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-314

ENVIRONMENTAL ASSESSMENT



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

Memorandum

Date: February 27, 2009

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Lyudmila Soldatova
OPS/DPMI/ONDQA

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: **NDA 22-314 Exforge HCT[®] Tablets**
(Amlodipine/Valsartan/Hydrochlorothiazide) 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg,
10/160/25 mg, and 10/320/25 mg fixed dose combination film-coated tablets (New NDA)

Novartis Pharmaceutical Corporation
One Health Plaza
East Hanover, NJ

I. Background

Novartis Pharmaceutical Corporation is requesting approval of **NDA 22-314 Exforge HCT[®]** (Amlodipine/Valsartan/Hydrochlorothiazide) film-coated tablets for treatment of hypertension. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

II. Discussion

The following review was conducted by Ruth Ganunis, Ph. D., under contract to CDER/OPS on January 26, 2009, and approved by Raanan A. Bloom, Ph.D., OPS/IO/PARS, Senior Environmental Officer.

Executive Summary

NDA 22-314 requests approval of Exforge HCT[®] (Amlodipine/Valsartan/Hydrochlorothiazide) film-coated tablets for treatment of hypertension. All environmental fate and effects study reports for the drug substances were previously submitted and

reviewed by the agency: NDAs _____, 20-665, 20-818, and 21-283 for valsartan, NDA 19-787 for amlodipine besylate, and NDA 20-818 for hydrochlorothiazide. For convenience, the firm provided summaries of the results in this submission. b(4)

Novartis provided updated peak production requirements covering all Novartis products on the US market for the year 2011-2012 in Confidential Appendix 11.2.1. Exforge HCT[®] Tablets will qualify for a categorical exclusion with regard to the active moieties amlodipine and hydrochlorothiazide. The peak production year requirements for valsartan for all Novartis products containing valsartan for all indications are expected to be NMT _____ kg. This peak production estimate corresponds to EIC = _____ in the aquatic environment (Confidential Appendix 11.2.2). b(4)

In the case of valsartan, by using the 72-hour EC₅₀ from the green algae study and the calculated EIC, an assessment factor of 16,423 is obtained (confidential appendix 11.2.3). Since the assessment factor calculated for valsartan is greater than _____, the results suggest valsartan would be nontoxic in the aquatic environment. b(4)

Valsartan may enter the aquatic environment from patient use and disposal. The toxicity of valsartan to environmental organisms was previously characterized and reviewed. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

A FONSI is recommended.

Review of May 22, 2008 Environmental Assessment

I. DATE: 22-MAY-2008

Reference is also made to related Exforge and Diovan NDAs:

Exforge Tablets, NDA 21-990	
Original Submission	22-FEB-2006
Diovan [®] Capsules, NDA 20-665	
Original submission:	20-NOV-1995
Amendment	30-MAY-1996
Amendment	22-OCT-1996
Diovan HCT [®] Tablets, NDA 20-818	
Original approval	06-MAR-1998
Supplement (S-012)	12-SEP-2001
Diovan [®] Tablets, NDA 21-283	
Original submission	03-AUG-2000
Supplement (S-001)	05-JUL-2001

Supplement (S-011)

31-OCT-2003

All environmental fate and effects study reports for valsartan drug substance were previously submitted to the above NDAs and were previously reviewed by the Agency. New environmental fate and effects data are not included in this Assessment.

II. APPLICANT: Novartis Pharmaceutical Corporation

III. ADDRESS: One Health Plaza
East Hanover, New Jersey 07936-1080

IV. PROPOSED ACTION:

- a. Requested Approval: Novartis is requesting approval for 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg (Amlodipine/Valsartan/Hydrochlorothiazide) fixed dose combination film-coated tablets. This EA has been submitted pursuant to 21 CFR part 25.
- b. Need for Action: Amlodipine, valsartan and hydrochlorothiazide (HCT) are currently approved separately, as well as in combinations in various dosage forms and strengths for the treatment of hypertension. This supplement provides for fixed combinations of amlodipine, valsartan and HCT in the form of 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg film coated tablets. Approval of this submission is expected to benefit patients unlikely to achieve control of blood pressure with a single agent.
- c. Locations of Use: Hospital, clinics and patients homes throughout the United States.
- d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system.

ADEQUATE

V. IDENTIFICATION OF CHEMICALS

Chemical identification for amlodipine, valsartan, and hydrochlorothiazide are provided on pages 3-6 of the EA.

ADEQUATE

VI. ENVIRONMENTAL ISSUES

Expected Introduction Concentration

Updated information in Confidential Appendix 11.2.1 indicates that the peak production year (2011/2012) requirements for amlodipine for all Novartis products containing amlodipine for all indications are expected to be NMT 1.0×10^{-6} mg/L. This peak production estimate corresponds to EIC 1.0×10^{-6} mg/L in the aquatic environment (Confidential Appendix 11.2.2). Exforge HCT[®] Tablets

b(4)

will qualify for a categorical exclusion with regard to the active moiety amlodipine, since the concentration of amlodipine is significantly less than 1 ppb.

b(4)

Updated information in Confidential Appendix 11.2.1 indicates that the peak production year (2011/2012) requirements for hydrochlorothiazide for all Novartis products containing hydrochlorothiazide for all indications are expected to be NMT 1×10^{-6} mg/L. This peak production estimate corresponds to EIC = 1×10^{-6} in the aquatic environment (Confidential Appendix 11.2.4). Exforge HCT[®] Tablets will qualify for a categorical exclusion with regard to the active moiety hydrochlorothiazide, since the concentration of hydrochlorothiazide is significantly less than 1 ppb.

b(4)

Updated information in Confidential Appendix 11.2.1 indicates that the peak production year (2011/2012) requirements for valsartan for all Novartis products containing valsartan for all indications are expected to be NMT 1×10^{-6} mg/L. This peak production estimate corresponds to EIC = 1×10^{-6} in the aquatic environment (Confidential Appendix 11.2.2).

b(4)

Environmental fate and effects data for valsartan are provided by cross-reference to the EAs for NDA 21-990, NDA 20-665, NDA 20-818, and NDA 21-283. No new data are provided in this EA. For convenience, the data is summarized in this submission.

Physical and Chemical Characterization

Valsartan is pharmacologically active and is rapidly absorbed following oral administration. Valsartan is not metabolized significantly. Valsartan is predominately excreted as unchanged drug through feces. Valsartan is relatively soluble in water over the environmental pH range. Based on its low log P (log K_{ow}) value, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb to organic particles. Since the log K_{ow} was less than 3 at all pH levels tested, no further sorption/desorption properties (log K_{oc}) were considered.

Depletion mechanisms

Valsartan is hydrolytically stable, and does not biodegrade aerobically or anaerobically. It does not photolyze, as it does not absorb above 290 nm. Based upon the Henry's Law Constant, valsartan would not be expected to release into the air.

Environmental Effects

Test	Result
Microbial Growth Inhibition (MIC)	<i>Clostridium perfringens</i> > 1000 ppm <i>Nostoc sp.</i> 200 ppm <i>Bacillus subtilis</i> 1000 ppm <i>Trichoderma viride</i> > 1000 ppm <i>Aspergillus niger</i> > 1000 ppm
Algae toxicity (green algae)	EC ₅₀ (72 h) = 90 mg/L NOEC = 58 mg/L
Acute toxicity in <i>Daphnia Magna</i>	EC ₅₀ (48 h) = 580 mg/L NOEC = 280 mg/L
Acute toxicity in <i>Salmo gairdneri</i>	LC ₅₀ (96h) >100 mg/L

b(4)

(= <i>Onocorhynchus mykiss</i> , rainbow trout)	NOEC = 100 —
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b(4)

Assessment factor

Green algae are the most sensitive species, with an EC₅₀ of 90 mg/L. The assessment factor EC₅₀ (green algae)/EIC aquatic = 90 mg/L / 0.00548 ppm = 16,423. No further testing is required, since the tier 1 assessment factor is > 1000. (It is noted that based on the data provided, the firm could use the tier 2 factor of >100.)

No significant environmental impact is expected from use or disposal of Exforge HCT[®] tablets. A FONSI is recommended.

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

The job title and qualifications of Birgit Hoeger, Ph.D. were provided.

ADEQUATE

X. REFERENCES

Provided.

ADEQUATE

XI. APPENDIX

Non-confidential appendices

11.1.1 Curriculum vitae of contributor

Confidential appendices

11.2.1 Production estimates of amlodipine, valsartan and HCT drug substance requirements

11.2.2 Expected Introduction Concentration (EIC) of amlodipine, valsartan and HCT based upon production estimates

11.2.3 Calculation of assessment factor for valsartan

ADEQUATE

III. Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs and in FDA guidance, and on the scientific validity of the “no effects” conclusions of the EA, no significant adverse environmental impacts are expected from the introduction of amlodipine, valsartan and Hydrochlorothiazide residues into the environment due to the use of Exforge HCT[®] film-coated tablets for treatment of hypertension

A Finding of No Significant Impact (FONSI) is recommended. The FONSI is applicable to the combination product.

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

/s/

Raanan Bloom
2/27/2009 02:52:28 PM
ENV ASSESSMENT

Jon E. Clark
3/4/2009 04:16:06 PM
CHEMIST

FINDING OF NO SIGNIFICANT IMPACT

for

Exforge HCT[®] Tablets

(Amlodipine/Valsartan/Hydrochlorothiazide)

**5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg
fixed dose combination film-coated tablets**

NDA 022-314

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.

NDA 022-314 requests approval of Exforge HCT[®] (Amlodipine/Valsartan/Hydrochlorothiazide) film-coated tablets for treatment of hypertension. Approval of this submission is expected to benefit patients unlikely to achieve control of blood pressure with a single agent. In support of its application for Exforge HCT[®], Novartis Pharmaceuticals Corporation prepared an environmental assessment (EA; attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product with regard to valsartan. Amlodipine and hydrochlorothiazide in Exforge HCT[®] Tablets will qualify for a categorical exclusion since the expected environmental concentrations is expected to be significantly less than 1 ppb. Therefore, the EA focuses on the environmental impact of Valsartan.

Valsartan is a chemically synthesized drug currently approved for use in the treatment of hypertension (alone and in combination with other hypertensive agents). Valsartan may enter the aquatic environment from patient use and disposal. The toxicity of valsartan to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

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

incineration and recycling. Minimal quantities of the unused drug are expected to be disposed of in the sewer system.

No adverse effects are anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places. The Center for Drug Evaluation and Research has concluded that no adverse environmental effects are expected from the use and disposal of this product. The information provided supports the conclusion that a Finding of No Significant Impact (FONSI) is appropriate.

PREPARED BY:

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CONCURRED BY:

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

CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: May 22, 2008, Environmental Assessment (confidential appendices removed)

Global Pharma Environment

Exforge HCT®

(Amlodipine/Valsartan/Hydrochlorothiazide)

5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg,
10/320/25 mg fixed dose combination film-coated tablets

VEA489_ABBR_EA

Environmental assessment

Authors: Hoeger Birgit
Date: 22-May-2008
Status: Final
Number of pages: 16

Property of Novartis

1 Date

23-May-2008

Reference is made to Environmental Assessments submitted to related Exforge and Diovan NDAs:

Exforge Tablets, NDA 21-990

Original NDA submission: Document dated 22-Feb-2006

Diovan Capsules, NDA 20-665

Original NDA submission: Document dated 20-Nov-1995

Amendment original NDA: Submitted 30-May-1996

Amendment original NDA: Submitted 22-Oct-1996

Diovan HCT Tablets, NDA 20-818

Original NDA approval : 06-Mar-1998

Supplement (S-012): Document dated 14-Sep-2001

Diovan Tablets, NDA 21-283

Original NDA submission: Document dated 03-Aug-2000

Supplement (S-001): Document dated 05-Jul-2001

Supplement (S-011) Document dated 31-Oct-2003

All environmental fate and effects study reports for amlodipine, valsartan and hydrochlorothiazide drug substance previously submitted within NDA 20-818, NDA 20-665 and NDA 21-990 and reviewed by the Agency have not been included in this Assessment.

2 Name of applicant/petitioner

Novartis Pharmaceuticals Corporation

3 Address

One Health Plaza
East Hanover, NJ 07936-1080

4 Description of proposed action

4.1 Requested approval

Novartis has filed NDA 22-314 pursuant to section 505b of the FD&C Act for VEA489 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg 10/160/25 mg and 10/320/25 mg amlodipine/valsartan/hydrochlorothiazide film-coated tablets. An Environmental Assessment (EA) is submitted pursuant to 21 CFR part 25.

4.2 Need for action

Amlodipine, valsartan and hydrochlorothiazide (HCT) are currently approved separately, as well as in combinations in various dosage forms and strengths for the treatment of hypertension. This supplement provides for fixed combinations of amlodipine, valsartan and HCT in the form of 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg 10/160/25 mg and 10/320/25 mg film-coated tablets, for the treatment of hypertension. Approval of this submission is expected to benefit patients unlikely to achieve control of blood pressure with a single agent.

4.3 Locations of use

Patients with hypertension will use Exforge HCT® film-coated tablets in their homes, in clinics and in hospitals.

4.4 Disposal sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

5 Identification of substances that are the subject of the proposed action

a) Amlodipine besylate

5.1 Nomenclature

5.1.1 Established name (U.S. Adopted Name – USAN)

Amlodipine besylate

5.1.2 Chemical name

5.1.2.1 Chemical Abstracts Index name

5.1.2.2 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate

5.1.2.3 Systemic chemical name (IUPAC)

Benzenesulfonate 2-[4-(2-chloro-phenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro-pyridin-2-ylmethoxy]-ethyl-ammonium

5.1.3 Other names

UK 48340-26

5.2 Chemical Abstract Service (CAS) registration number

111470-99-6

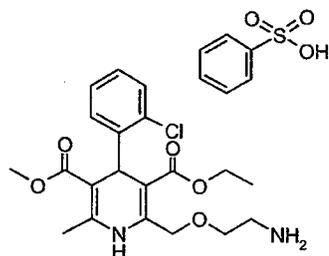
5.3 Molecular formula

$C_{20} H_{25} Cl N_2 O_5 \cdot C_6 H_6 O_3 S$

5.4 Molecular weight

567.06

5.5 Structural formula



b) Valsartan

5.6 Nomenclature

5.6.1 Established name (U.S. Adopted Name – USAN)

Valsartan

5.6.2 Trade name

Diovan®

5.6.3 Chemical names

5.6.3.1 Chemical Abstracts Index name

L-Valine, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

5.6.3.2 Systematic chemical name (IUPAC)

(*S*)-2- {*N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid

5.6.4 Other names

CGP 48933 (research code)

5.7 Chemical Abstracts Service (CAS) registration number

137862-53-4

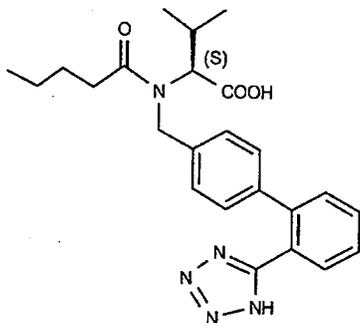
5.8 Molecular formula

C₂₄H₂₉N₅O₃

5.9 Molecular weight

435.5

5.10 Structural formula



c) Hydrochlorothiazide

5.11 Nomenclature

5.11.1 Established name (U.S. Adopted Name – USAN)

Hydrochlorothiazide

5.11.2 Trade name

Esidrix®

5.11.3 Chemical name

5.11.3.1 Chemical Abstracts Index name

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide

5.11.3.2 Systemic chemical name (IUPAC)

6-Chloro-1,1-dioxo-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide

5.11.4 Other names

HCT

HCTZ

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

5.12 Chemical Abstract Service (CAS) registration number

58-93-5

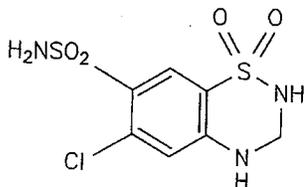
5.13 Molecular formula

$C_7H_8ClN_3O_4S_2$

5.14 Molecular weight

297.7

5.15 Structural formula



6 Environmental issues

6.1 Physical and chemical characterization

Valsartan

All environmental fate and effects study reports for valsartan drug substance have been previously submitted to and reviewed by the Agency and have not been included in this assessment: NDA 21-990 (EA document: 22-Feb-2006), NDA 20-665 (submitted 28-Dec-1995; approved by FDA on 23-Dec-1996), NDA 20-818 (submitted 18-Mar-1997, approved 6-Mar-98) and NDA 21-283 (submitted 03-Aug-2000, approved 14-Aug-2002). The Data is summarized in a Summary Table (Table 1) located at the end of this report.

Based on its low log P [$\log K_{ow}$] value, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb to organic particles. Since the $\log K_{ow}$ was less than 3 at all pH levels tested, no further sorption/desorption properties ($\log K_{oc}$) were considered. Based upon the Henry's Law Constant, valsartan would not be expected to be released into the air or have a significant vapor pressure.

Amlodipine besylate

Environmental fate and effects study reports for amlodipine drug substance have been initially reported to the agency in Pfizer's Norvasc (amlodipine besylate) Tablets Original NDA 19-787 (approved 5-12-1995) and numerous submitted and approved supplement NDAs (not listed individually). This information has been previously submitted to and reviewed by the Agency, and is not included in the present assessment. The information is summarized in Data Summary Table (Table 2) located at the end of this report.

Based on its low log P [$\log K_{ow}$] value, amlodipine is not expected to significantly bioconcentrate in living organisms or to sorb to organic particles. Since the $\log K_{ow}$ was less than 3, no further sorption/desorption properties ($\log K_{oc}$) were considered. Amlodipine has been stated to display negligible vapour pressure and would thus not be expected to be released into the air.

Hydrochlorothiazide

Physical and chemical properties and constants were determined for hydrochlorothiazide drug substance and initially reported in the Diovan HCT Tablet Original NDA 20-818 (submitted 18-Mar-1997; approved 06-Mar-1998). This information has been previously submitted to and reviewed by the Agency, and is not included in the present Assessment. This information is summarized in Data Summary Table (Table 3) located at the end of this report.

Based on its low log P value of 0.9, HCT is not expected to significantly bioconcentrate in aquatic organisms or to sorb to organic particle.

6.2 Environmental depletion mechanisms

Valsartan

Valsartan is hydrolytically stable at pH 5, 7 and 9 and was found not to be biodegradable aerobically or anaerobically to any significant extent. Since the molecule does not absorb light above 290 nm, photoinstability is not regarded a relevant environmental depletion mechanism. Results are reported in the Data Summary Table (Table 1).

Amlodipine besylate

Amlodipine is not readily biodegradable. It is not expected to bioaccumulate, based on its physico-chemical properties and its high susceptibility to oxidative metabolism in higher organisms [CTD 2.5 Clinical Overview]. According to the original manufacturer, it has a tendency to sorb to sludge and sediments [Pfizer MSDS 2003].

Based on the UV/VIS absorption spectra [Drug substance elucidation of structure and other characteristics, Module 3], significant absorption is seen above 290 nm for amlodipine and photolability has actually been found for this compound. Hydrolytically, amlodipine has been found to be stable at environmental pH [Abdoh et al. 2004].

Hydrochlorothiazide

HCT is not readily biodegradable. Based on the UV/VIS absorption spectra, significant absorption is seen above 290 nm. Photoinstability of HCT has been observed under laboratory conditions with solar simulator and direct sunlight [Brigante et al. 2005].

6.3 Environmental concentration

6.3.1 Expected Introduction Concentration (EIC)

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications³, the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

$$\text{EIC-Aquatic (ppb)} = A \times B \times C \times D$$

where:

A = kg / yr produced for direct use (as active moiety)

B = 1 / 1.214 x 10¹¹ liters per day entering POTWs [1996 Needs Survey, Report to Congress]

C = 1 year / 365 days per year

D = 10⁹ µg/kg (conversion factor)

The EIC of amlodipine, valsartan and HCT has been calculated for the peak production year estimates of the drug substance requirements for all Novartis products containing amlodipine, valsartan and HCT, including the new Exforge HCT® formulations, and for all approved indications. An estimate of drug substance production requirements for the peak years (2011/2012) is presented in [Confidential Appendix 11.2.1]. The calculated EICs for amlodipine, valsartan and HCT are provided in [Confidential Appendix 11.2.2].

Novartis is confident that the actual EICs will not exceed these estimates by an order of magnitude.

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis certifies that this submission for VEA489 film-coated tablets, for the treatment of hypertension qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety amlodipine and hydrochlorothiazide will be significantly less than 1 ppb.

Further, Novartis states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment for amlodipine or HCT.

6.4 Summary

6.4.1 Valsartan - aquatic environment

Valsartan is pharmacologically active and is rapidly absorbed following oral administration. Since valsartan exists as a di-anion with a double negative charge at physiological pH, the compound is very hydrophilic, and may therefore be a poor substrate for metabolizing enzymes.

A study using radiolabeled valsartan solution showed that valsartan is metabolized to a small extent only. The only notable metabolite detectable in the plasma is the valeryl-4-hydroxy valsartan (M1), an oxidized form of valsartan. Since this metabolite has not demonstrated any pharmacological activity *in vitro*, the biotransformation of valsartan to M1 can be described as an additional minor elimination process.

Valsartan is predominantly excreted as unchanged drug through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged

valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.

Studies were conducted to determine the water solubility and partition coefficient of valsartan at pH 5.0, 7.0 and 9.0 at 25 ± 2 °C (Data Summary Table 1). The results of the water solubility study indicate that valsartan would be relatively soluble in water over the environmental pH range. The n-octanol/water partition coefficient, which indicates the tendency of a non-ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that valsartan would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.) The calculated results presented in Table 3 for the bioconcentration factor (BCF) and in Table 4 for the soil adsorption coefficient (K_{oc}) further support the conclusion that valsartan would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

Results of the ultraviolet/visible spectra scan indicated absorbance below 290 nm in aqueous buffer solutions over the environmental pH range. Direct photodegradation would not be considered a potential mechanism of depletion.

Investigations of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment.

Five-year production estimates for Diovan drug products indicate that during the peak year, the EIC of valsartan at the point of entry into the aquatic environment will be significantly greater than 1 ppb.

Based upon these factors, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

6.5 Valsartan - environmental effects of released substances

The environmental effects of valsartan were evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA Guidance for Industry³). With no rapid, complete environmental depletion mechanism identified, microbial inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02⁴. Additionally, acute toxicity testing was conducted in algae, daphnia and fish, utilizing standard methods according to either TAD 4.08⁴, EU standard methodology⁵ or OECD guidelines respectively. All studies were conducted under FDA Good Laboratory Practices (GLPs). Results indicate valsartan is non-inhibitory to microorganisms, which may be found in activated sludge and does not show deleterious effects on algae, daphnia and fish up to high concentrations. Algae proved to be the most sensitive species, with an EC_{50} of 90 mg/L. Results are reported in the Data Summary Table (Table 1).

6.5.1 Valsartan - assessment factor

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications³, an Assessment Factor is a toxicity ratio which provides a consistent regulatory basis for determining if and when additional ecotoxicity testing should be performed, using a tiered approach. The Assessment Factor may be calculated by dividing an appropriate acute toxicity test endpoint by the MEEC (Maximum Expected Environmental Concentration). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of valsartan, by applying the 72-hour EC₅₀ from the green algae study and the EIC from [Confidential Appendix 11.2.2], an Assessment Factor of 16'423 is obtained. (Calculation of the Assessment Factor is provided in [Confidential Appendix 11.2.3]). Thus, no additional ecotoxicity testing would be required for valsartan. Since the Assessment Factor calculated for valsartan is 16 times greater than that reported in the Guidance Document, the results suggest valsartan is unlikely to be toxic in the aquatic environment.

7 Mitigation measures

Based upon the information and data presented in this environmental assessment, Novartis has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of Exforge HCT[®] film-coated tablets within the United States. No mitigation measures are considered necessary.

8 Alternatives to the proposed action

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the packaging, distribution, use or disposal of EXFORGE film-coated tablets. The use of Exforge HCT[®] film-coated tablets will directly benefit patients with hypertension.

It is our conclusion that approval of this application is therefore preferable to non-approval.

9 List of preparers

Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in [Non-confidential Appendix 11.1.1].

10 References

1. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.
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 5. Annex V to EU Directive 67/548/EEC, Part C. Available online at: <http://ecb.jrc.it/testing-methods/> (accessed January 2006).
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 8. Kumar, K.A., Ganguly, K., Mazumdar, K., Dutta, N.K., Dastidar, S.G., Chakrabarty, A.N. 2003. Amlodipine: a cardiovascular drug with powerful antimicrobial property. *Acta Microbiol Pol* 52: 285-92 (2003).
 9. Pfizer MSDS 2003. Official Material Safety Data Sheet for Amlodipine besylate. Last Revision Date: Jan 31 2003.
 10. Kenaga, E.E., Goring, C.A.I., 1980. Relationship between water solubility, soil sorption, octanol-water partitioning, and concentration of chemicals in biota. *American Society for Testing and Materials Spec. Tech. Publ. 707, Aquat. Toxicol.*, pp. 78-115.

11 Appendices

11.1 Non-confidential appendices

- [11.1.1] Curriculum vitae of contributor

11.2 Confidential appendices

- [11.2.1] Production estimates of amlodipine, valsartan and HCT drug substance requirements
- [11.2.2] Expected Introduction Concentration (EIC) of amlodipine, valsartan and HCT based upon production estimates
- [11.2.3] Calculation of assessment factor for valsartan

Table 1 Data summary table – valsartan

DATA SUMMARY TABLE		
ENDPOINT	RESULTS	METHODOLOGY
Water solubility – mean (mg/L)	2990 @ pH 5 8210 @ pH 7 1470 @ pH 9	TAD Section 3.01
Dissociation constants (mean pKa's)	3.76 (carboxylic group) and 5.60 (tetrazole group)	TAD Section 3.04
Log n-octanol/water partition coefficient (Log K _{ow})	1.51 @ pH 5 in 9.85 x 10 ⁻⁴ moles/L buffer 1.50 @ pH 5 in 1.07 x 10 ⁻⁴ moles/L buffer -1.17 @ pH 7 in 1.04 x 10 ⁻³ moles/L buffer -1.01 @ pH 7 in 1.09 x 10 ⁻⁴ moles/L buffer -1.84 @ pH 9 in 1.04 x 10 ⁻³ moles/L buffer -1.74 @ pH 9 in 1.10 x 10 ⁻⁴ moles/L buffer	TAD Section 3.02
Henry's Law Constant (H)	< 1.30 x 10 ⁻⁸	TAD Section 3.03
Ultraviolet-visible absorption spectrum	No absorption peaks @ pH 5. One main peak at 209 nm @ pH 7. One main peak at 207 nm @ pH 9.	TAD Section 3.05
DEPLETION MECHANISMS		
Hydrolysis	t _½ ≥ 1 year at 25 °C	TAD Section 3.09
Aerobic biodegradation	0.02 % ¹⁴ C evolved over 28-day aerobic study	TAD Section 3.11, modified
Metabolism	Valsartan is predominantly excreted unchanged through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days: Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and	Clinical studies

	urine.	
ENVIRONMENTAL EFFECTS		
Microbial inhibition	<p>Species</p> <p><i>Aspergillus niger</i> > 1000 <i>Trichoderma viride</i> > 1000 <i>Clostridium perfringens</i> > 1000 <i>Bacillus subtilis</i> 1000 <i>Nostoc</i> sp. 200</p> <p>MIC (mg/L)</p>	TAD section 4.02
Algae toxicity (green algae)	<p>EC₅₀ (72h) = 90 mg/L NOEC = 58 mg/L</p>	EU standard method 92/69/EC (L383) C.3 * Algal inhibition test.
Acute toxicity in <i>Daphnia magna</i>	<p>EC₅₀ (48h) = 580 mg/L NOEC = 280 mg/L</p>	TAD 4.08
Acute toxicity in <i>Salmo gairdneri</i> (= <i>Oncorhynchus mykiss</i> , rainbow trout)	<p>LC₅₀ (96h) >100 mg/L NOEC = 100 mg/L</p>	OECD 203, Fish, acute toxicity test (1992)

Table 2 Data summary table - amlodipine

DATA SUMMARY TABLE		
ENDPOINT	RESULTS	METHODOLOGY
Water solubility – mean (mg/L)	Slightly soluble (0.2%, w/v, 24°C)	source: Pfizer
Dissociation constants (mean pKa's)	8.6 (primary amine)	source: Pfizer
Log n-octanol/water partition coefficient (Log K _{ow})	2.759 (at 20° C, pH 7)	source: Pfizer
Henry's Law Constant (H)	Negligible vapour pressure (MP = 199.4°C)	source: Pfizer
Ultraviolet-visible absorption spectrum	Maxima at 240nm, 360 nm	source: Pfizer
DEPLETION MECHANISMS		
Hydrolysis	<10% (8d, RT, pH 7, 0.2M phosphate buffer)	Abdoh et al., Pharmacol Dev Technol 9 :15-24 (2004)
Aerobic biodegradation	Not readily biodegradable	source: Pfizer
Metabolism	<p>Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with</p> <p>10% of the parent compound and 60% of the metabolites excreted in the urine.</p>	Clinical studies

ENVIRONMENTAL EFFECTS										
Microbial inhibition	<table border="1"> <thead> <tr> <th>Species</th> <th>MIC (mg/L)</th> </tr> </thead> <tbody> <tr> <td><i>E. coli</i></td> <td>10mg/l</td> </tr> <tr> <td><i>Pseudomonas putida</i></td> <td>10mg/l</td> </tr> <tr> <td><i>Bacillus spp.</i></td> <td>10 mg/l</td> </tr> </tbody> </table>	Species	MIC (mg/L)	<i>E. coli</i>	10mg/l	<i>Pseudomonas putida</i>	10mg/l	<i>Bacillus spp.</i>	10 mg/l	Agar plate dilution method. Kumar et al., Acta Microbiol Pol 52:285-92 (2003)
Species	MIC (mg/L)									
<i>E. coli</i>	10mg/l									
<i>Pseudomonas putida</i>	10mg/l									
<i>Bacillus spp.</i>	10 mg/l									
Algae toxicity (green algae)	EC ₅₀ (72h) = 5.6 mg/L	NPDES, Source: Pfizer								
Acute toxicity in <i>Daphnia magna</i>	EC ₅₀ (48h) = 9.9 mg/L	TAD 4.08 / OECD, Source: Pfizer								
Acute toxicity in <i>Pimephales promelas</i> (fathead minnow)	LC ₅₀ (48h) 2.7 mg/L	NPDES, Source: Pfizer								

Table 3 Data summary table - hydrochlorothiazide

DATA SUMMARY TABLE	
PHYSICAL / CHEMICAL CHARACTERIZATION	
Water solubility – mean (mg/L)	0.6g/l (25°C) source: KSO
Dissociation constants (mean pKa's)	10.17
Log n-octanol/water partition coefficient (Log K _{ow})	~ 0.9 (25°C) - 0.4
DEPLETION MECHANISMS	
Aerobic biodegradation (OECD 301 E, mod. OECD screening test)	26.3%
Metabolism	Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney in humans. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours.
ENVIRONMENTAL EFFECTS	
Microbial inhibition [activated sludge (3h)]	EC20: >100mg/l EC50: >100mg/l EC80: >100mg/l
Acute toxicity in <i>Daphnia magna</i>	EC50: >100mg/l NOEC: 58mg/l
Acute toxicity in Zebra fish (<i>Brachydanio rerio</i>)	LC50 (96h): >100mg/l

12 Calculated environmental fate results for valsartan

Table 4 Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined water solubility

	pH 5	pH 7	pH 9
Water solubility (mg/L)	2990	8210	1470
BCF ^a	6.77	3.83	10.12
K_{oc} ^b	53.5	30.7	79.1

^a $\text{Log (BCF)} = 2.791 - 0.564 \text{ Log (S)}$, where S = water solubility in mg/L.

^b $\text{Log (}K_{oc}\text{)} = 3.64 - 0.55 \text{ Log (S)}$, where S = water solubility in mg/L.

Table 5 Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined partition coefficient ($\text{log } K_{ow}$)

	Range	
	Low	High
BCF ^a	0.014	6.21
K_{oc} ^b	2.38	158

The lowest (-1.84) and highest (1.51) $\text{log } K_{ow}$ values were used to calculate the BCF and K_{oc} .

^a $\text{Log (BCF)} = (0.79 \times \text{log } K_{ow}) - 0.40$ (Kenaga and Goring, 1980)

^b $\text{Log (}K_{oc}\text{)} = (0.544 \times \text{log } K_{ow}) + 1.377$ (Kenaga and Goring, 1980)

Appendix 11.1.1

Birgit Hoeger, Ph.D.

Global Pharma Environment

Relevant Professional Experience

- 2006 - Environmental Risk Assessment Officer at Novartis Pharma AG.
- 2005-2006 Contractual Agent at the European Commission - Joint Research Centre, Ispra, Italy, European Centre for the Validation of Alternative Methods (ECVAM), Task Officer for Environmental Toxicology.
- 2004-2005 Postdoctoral student, Environmental Toxicology, University of Konstanz (Prof. Dr. D.R. Dietrich). Toxicological investigations on bioconcentration of human pharmaceuticals and their effects on the immune system in brown trout (*Salmo trutta f. fario*).

Education

- 2004 Ph.D. Biology (Environmental Toxicology) at the University of Konstanz, Germany (Prof. Dr. D.R. Dietrich). Effects of sewage treatment plant effluent on the immune system of rainbow trout (*Oncorhynchus mykiss*).
- 2000 Diplom in Biology, University of Konstanz, Germany.

Publications

> 6 peer reviewed publications

Co-author of several project reports and a book chapter on effects of pollution of the aquatic environment on the immuno-competence of fishes.

Professional Memberships

SETAC (Society of Environmental Toxicology and Chemistry (2006 -)
Reach Implementation Project 3.3-2, Endpoint Working Group 10 (Aquatic Bioaccumulation and Avian Toxicity) (2006 - 2007)

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