CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022545Orig1s000

ENVIRONMENTAL ASSESSMENT

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

Memorandum

Date: June 23, 2010

From: Emily A. McVey, Ph.D.
OPS/IO

To: Michael Monteleone
ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO

Subject: **NDA 22-545: Aliskiren / Amlodipine 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg**
Sponsor: Novartis Pharmaceuticals Corporation

Review of Environmental Assessment

A. Background

Novartis, Inc. requests approval of Aliskiren/Amlodipine fixed dose combination tablets (150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg) for the treatment of hypertension. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

B. Discussion

Executive Summary

This Environmental Assessment, dated September 24th, 2009, supports the NDA for Aliskiren/Amlodipine fixed dose combination tablets (150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg) for the treatment of hypertension. The EA was prepared in accordance with 21 CFR Part 25 by Novartis Pharmaceuticals Corporation.

The sponsor estimates an EIC of (b) (4) for Aliskiren and (b) (4) for Amlodipine , based on an estimate of (b) (4) for 2014 for Aliskiren and (b) (4) for 2011 for Amlodipine used in the United States. Since the EIC for Aliskiren is higher than 1 ppb, an Environmental Assessment was submitted. The submitted information was as recommended

in the CDER/CBER Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998).

The sponsor used acute ecotoxicology data to estimate a an assessment factor (using the most sensitive EC_{50} from a daphnia manga 48 h acute toxicity test over the calculated EIC) and determined an assessment factor of 24,669. Since this factor is greater than 1000, they concluded that this level of Aliskiren did not pose an environmental concern based on the amount expected to enter the environment in the next five years.

C. Environmental Assessment Review

1. **Date:** June 23, 2010
2. **Applicant:** Novartis Pharmaceuticals Corporation
3. **Address:** One Health Plaza, East Hanover, NJ 07936-1080
4. **Proposed Action:** Novartis Pharmaceuticals Corporation is filing an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Aliskiren/Amlodipine fixed dose combination tablets (150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg) for the treatment of hypertension.

Reference is also made to Environmental Assessments submitted to related aliskiren NDAs:

Tekturna Tablets, NDA 21-985
Original NDA submission: Document dated 24-Jan-2006

Norvasc (amlodipine besylate) Tablets, NDA 19-787
Original NDA submission: approved 5-12-1995

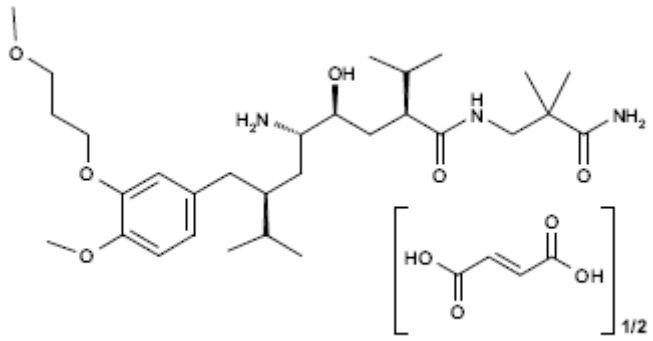
Another Environmental Assessment was also reviewed, related to the NDA:

Aliskiren / Valsartan, NDA 22-217
Document dated 12-Sept-2008

5. **Identification of Chemicals**

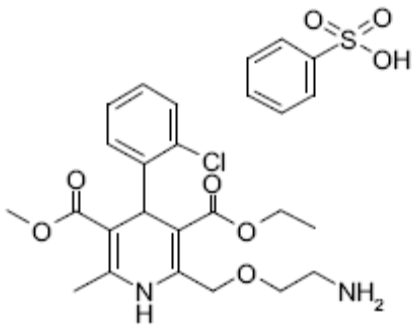
(i) Established Name: Aliskiren hemifumarate **and** Amlodipine besylate
(ii) Brand/Proprietary Name/Tradename: Rasilez®/Tekturna®
(iii) Chemical Name: Benzeneoctanamide, δ-amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)-,(αS,γS,δS,ζS)- (E)-2-butenedioate (2:1) (salt) **and** 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate
(iv) Chemical Abstract Registration Number: 173334-58-2 (hemifumarate), 173334-57-1 (free base) **and** 111470-99-6

(v) Molecular Formula: C30H53N3O6 . 1/2 C4 H4 O4 **and** C20 H25 Cl N2 O5 . C6 H6 O3 S
(vi) Molecular Weight: 609.8 g/Mol **and** 567.06
(vii) Chemical Structure:



Aliskiren hemifumarate

AND



Amlodipine besylate

6. Environmental Characterization

Aliskiren Data Table

Physical / chemical characterization		
ENDPOINT	RESULTS	METHODOLOGY
Water solubility	>800 g/L in buffered water pH7, 22°C >350 g/L @ pH 1, 25°C >350 g/L @ pH 4.7, 25°C >350 g/L @ pH 7.4, 25°C	67/548/EEC, Annex V, A.6[4]
Dissociation constant (pKa)	9.18 (22°C) The undissociated form will only occur at pH >10.5, which is not environmentally relevant.	
Log octanol/water partition coefficient (Log K_{ow})	1.01 (22°C, phosphate buffer pH 7.4) 3.1 (30°C, 0.1 M phosphate buffer pH 7) 3.9-4.5 (estimated) in unbuffered solution	67/548/EEC, Annex V, A.8[4]
Henry's Law Constant (H)	Not determined, as not expected to significantly partition into air, based on molecular weight and melting point > 95°C	
Ultraviolet-visible absorption spectrum	No significant absorption peaks at environmental pH above 290 nm	Drug substance elucidation of structure and other characteristics, Module 3
Depletion mechanisms		
Hydrolysis	Very slow hydrolysis (17%, 3d @100 °C)	
Aerobic biodegradation	5% in 28 days (22 °C)	67/548/EEC, Annex V, C.4-A[4]
Photolysis	No photolysis expected, based on absorption spectrum.	
Metabolism	Very low rate of metabolism. Above 97% of dose remains unabsorbed after oral absorption and is excreted unchanged, mainly through feces. Only about 1% is excreted through urine. Metabolites account for less than 1% of dose.	Module 2.5 Clinical Overview
Environmental effects		
Microbial Inhibition (Activated sludge)	3h-IC_{50} = 4470 mg/L	67/548/EEC, Annex V, C.11[4]
Acute Toxicity to algae (*Scenedesmus spp.*)	72h-EC_{50} > 100 mg/L 72h-NOEC = 100 mg/L	67/548/EEC, Annex V, C.3[4]

Acute Toxicity in *Daphnia magna*	48h-EC_{50} = 56 mg/L 48h-NOEC = 30 mg/L	67/548/EEC, Annex V, C.2[4]
Acute Toxicity to zebra fish (*Danio rerio*)	96h-LC_{50} > 100 mg/L 96h-NOEC = 100 mg/L	67/548/EEC, Annex V, C.1[4]

Amlodipine Data Table

Physical / chemical characterization		
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)[2]
Aerobic biodegradation	Not readily biodegradable	source: Pfizer
Metabolism	Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.	Clinical studies
Environmental effects		
Microbial inhibition	**Species** / **MIC (mg/L)** *E. coli* 10mg/l *Pseudomonas putida* 10mg/l *Bacillus spp.* 10 mg/l	Agar plate dilution method. Kumar et al., Acta Microbiol Pol 52:285-92 (2003)[5]
Algae toxicity (green algae)	EC_{50} (72h) = 5.6 mg/L	source: Pfizer
Acute toxicity in *Daphnia magna*	EC_{50} (48h) = 9.9 mg/L	Source: Pfizer
Acute toxicity in *Pimephales promelas* (fathead minnow)	LC_{50} (48h) 2.7 mg/L	source: Pfizer

Environmental Depletion Mechanisms, Fate, and Effects

Aliskiren hemifumarate is not expected to deplete significantly in environmental media, and is only very slowly metabolized within the body. Greater than 90% of the oral dose is fecally excreted, unchanged. For that reason, further bioaccumulation studies were performed for aliskiren, to determine the likelihood of bioaccumulation and persistence in the environment. The noctanol/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 aliskiren hemifumarate 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.

Indeed, the BCF was calculated in two separate ways, based first upon the measured water solubility and next upon the experimentally determined partition coefficient. These results also suggest that aliskiren hemifumarate would not be expected to bioaccumulate:

	pH 5	pH 7	pH 9
Water solubility (mg/L)	> 350 g/L	> 350 g/L	n.a.
BCF [a]	0.46	0.46	n.a.
K_{oc} [b]	3.90	3.90	n.a.

[a] Log (BCF) = 2.791 – 0.564 Log (S), where S = water solubility in mg/L.

[b] Log (K_{oc}) = 3.64 – 0.55 Log (S), where S = water solubility in mg/L.

	Range	
	Low	High
BCF [a]	2.5	111.9
K_{oc} [b]	84.42	1157.18

The highest (3.1) and lowest (1.01) log K_{ow} values were used to calculate the BCF and K_{ow}.

[a] Log (BCF) = (0.79 x log K_{ow}) – 0.40 (Kenaga and Goring, 1980[6])

[b] Log (K_{oc}) = (0.544 x log K_{ow}) + 1.377 (Kenaga and Goring, 1980[6])

As these results indicate it is unlikely for aliskiren hemifumarate to partition to the soil compartment, the environmental toxicity assessments were performed focusing on aquatic organisms. These tests were completed following the tiered testing scheme in the aforementioned Guideline for Industry. The most sensitive EC_{50} from a 48 h acute toxicity test in *Daphnia magna* (56 mg/L) and the calculated EIC of (b) (4) were used to calculate the assessment factor and resulted an assessment factor of (b) (4). Since this factor is greater than 1000, no further testing was performed.

An EIC for amlodipine was determined to be (b) (4), so no further calculations were performed as the EIC is under 1ppb. However, this EIC only accounts for the amlodipine besylate utilized by Novartis, Inc., in their various applications. However, the originator of amlodipine, Pfizer, provided Novartis with ecotoxicity data (see data table above) for acute toxicity to green algae, *Daphnia magna*, and fathead minnow (with EC_{50}s of 5.6 mg/L, 9.9 mg/L and 2.7 mg/L, respectively). All applications involving amlodipine besylate have been excluded from assessment due to EIC under 1ppb.

Cumulative Environmental Fate and Effects

Aliskiren hemifumarate is still under patent with Novartis, so there is no other introduction of aliskiren into the environment, and the effect assessed above is cumulative. Since amilopidine besylated is off-patent, there are greater than fifty generic versions of this drug, as well as the innovator, used in various applications. Proprietary sales data indicate amlodipine besylate sales at under (b) (4) in 2008, suggesting the EEIC is under 1 ppb and the assessment factor would be greater than 1000 for cumulative amlodipine besylate, as well.

7. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed.

8. Literature Reviewed

1. Y. V.; Goncharevskaya, O. A.; Johns, E. J.; Monin, Y. G.; Shakhmatova, E. I., THE INFLUENCE OF AMLODIPINE AND VERAPAMIL ON ION AND WATER TRANSPORT IN THE NEPHRON, SKIN AND URINARY-BLADDER OF AMPHIBIANS. *Comparative Biochemistry and Physiology C-Pharmacology Toxicology & Endocrinology* **1991,** *98* (2-3), 317-322.
2. Pascoe, D.; Karntanut, W.; Muller, C. T., Do pharmaceuticals affect freshwater invertebrates? A study with the cnidarian Hydra vulgaris. *Chemosphere* **2003,** *51* (6), 521-528.

Findings: At very high levels, amlodipine may have an effect on ecological organisms, but not at the levels that would be expected to be found in the aquatic environment.

10. Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs, 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 approval of Tekamlo.

A Finding of No Significant Impact (FONSI) is recommended.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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

/s/

EMILY A MCVEY
06/23/2010

NAKISSA SADRIEH
06/28/2010

Environmental Assessment
Finding of No Significant Impact

NDA 22-545

Tekamlo

Food and Drug Administration
Center for Drug Evaluation and Research
June 23rd, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-545

Tekamlo

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

NDA 22-545 requests approval of Aliskiren/Amlodipine fixed dose combination tablets (150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg) for the treatment of hypertension. In support of its application, Novartis, Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impact from the use and disposal of this product.

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

PREPARED BY:

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CONCURRED BY:

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Associate Director for Research Policy Implementation
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CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science

Attachment: 24 September 2009 Environmental Assessment (confidential appendices removed)

Global Pharma Environment

Aliskiren / Amlodipine (SPA100)

150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg film-coated tablets

Aliskiren / Amlodipine_ABBR_EA

Environmental assessment

Authors: Hoeger B.

Date: 24-Sep-2009

Status: Final

Number of pages: 13

Table of contents

1 Date

22-Sep-2009
Aliskiren / Amlodipine New Drug Application (NDA)

Reference is also made to Environmental Assessment submitted to related aliskiren and amlodipine NDAs:

Tekturna Tablets, NDA 21-985
Original NDA submission: Document dated 24-Jan-2006

Norvasc (amlodipine besylate) Tablets, NDA 19-787
Original NDA submission: approved 5-12-1995

All environmental fate and effects study reports for aliskiren and amlodipine drug substances previously submitted in the Rasilez/Tekturna Tablet NDA 21-985 and Pfizer's Norvasc (amlodipine besylate) Tablets Original NDA 19-787 (approved 5-12-1995), respectively 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 22-545 pursuant to section 505b of the FD&C Act for aliskiren / amlodipine fixed dose combination film-coated tablets. An Environmental Assessment (EA) is submitted pursuant to 21 CFR part 25.

4.2 Need for action

Aliskiren and amlodipine are currently approved separately in various dosage forms and strenghts for the treatment of hypertension. This supplement provides for fixed combinations of aliskiren and amlodipine in the form of 150/5 mg, 150/10 mg, 300/5 and 300/10 mg film-coated tablets, also for the treatment of hypertension. Approval of this submission is expected to benefit patients with hypertension whose blood pressure is not adequately controlled on monotherapy.

4.3 Locations of use

Patients with hypertension will use aliskiren / amlodipine 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

Aliskiren

5.1 Nomenclature

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

Aliskiren hemifumarate

5.1.2 Brand/proprietary name/trade name

Rasilez®/Tekturna®

5.1.3 Chemical names

5.1.3.1 Chemical Abstracts Index name

Benzeneoctanamide, δ-amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)-,(αS,γS,δS,ζS)- (E)-2-butenedioate (2:1) (salt)

5.1.3.2 Systematic chemical name (IUPAC)

(2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-8-methyl-nonanoic acid (2-carbamoyl-2-methyl-propyl)-amide; ½ (E)-but-2-enedioic acid

5.1.4 Other names

SPP100, CGP60536B

5.2 Chemical Abstracts Service (CAS) registration number

173334-58-2 (hemifumarate)

173334-57-1 (free base)

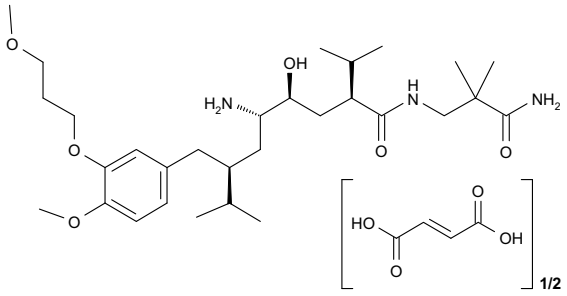
5.3 Molecular formula

$C_{30}H_{53}N_3O_6$. 1/2 C_4 H_4 O_4

5.4 Molecular weight

609.8 g/Mol

5.5 Structural formula



Amlodipine

5.6 Nomenclature

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

Amlodipine besylate

5.6.2 Chemical name

5.6.2.1 Chemical Abstracts Index name

5.6.2.2 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate

5.6.2.3 Systemic chemical name (IUPAC)

Benzenesulfonate2-[4-(2-chloro-phenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro-pyridin-2-ylmethoxy]-ethyl-ammonium

5.6.3 Other names

UK 48340-26

5.7 Chemical Abstract Service (CAS) registration number

111470-99-6

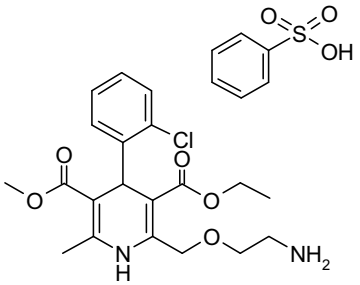
5.8 Molecular formula

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

5.9 Molecular weight

567.06

5.10 Structural formula



6 Environmental issues

6.1 Physical and chemical characterization

Aliskiren hemifumarate

Environmental fate and effects study reports for Rasilez®/Tekturna® drug substance have been initially reported to the agency in aliskiren film-coated tablets Original NDA 21-985 (submitted 13-Feb-2006). 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 1) located at the end of this report.

Aliskiren hemifumarate shows low acute ecotoxicity to microorganism, algae, daphnia and fish. Based on its log P [log K_{ow}] value, aliskiren hemifumarate is not expected to significantly bioconcentrate in living organisms or to sorb onto organic particles. Further, due to the very high water solubility and the resulting low sorption prediction (Table 3, Table 4) no further sorption/desorption properties ($logK_{oc}$) were considered. Henry's Law Constant was not determined, as aliskiren hemifumarate is not expected to be released into air or have a significant vapor pressure, based on its molecular weight and melting point of > 95°C. The aliskiren hemifumarate information is summarized in Data Summary Table (Table 1) at the end of this report.

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.

6.2 Environmental depletion mechanisms

Aliskiren hemifumarate

Aliskiren hemifumarate has been determined to be hydrolytically stable to 83% within forced decomposition testing conducted over a 3-day period in an aqueous medium at 100°C. Based on these results, a half-life of several months up to a year at 25°C was estimated. Aliskiren has not been found to be biodegradable to a significant extent. Based on the UV/VIS absorption spectra [Drug substance elucidation of structure and other characteristics, Module 3], no significant absorption was found above 290 nm for aliskiren. Hence photodegradation is not regarded as a significant source of depletion for this substance. 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 [Module 2.5 Clinical Overview]. According to the original manufacturer, it has a tendency to sorb to sludge and sediments [Pfizer MSDS 2003][1].

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][2].

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 Applications[3], the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D

where:

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

B = 1 / 1.214 x 10^{11} liters per day entering POTWs [1996 Needs Survey, Report to Congress]

C = 1 year / 365 days per year

D = 10^{9} µg/kg (conversion factor)

The EIC of aliskiren hemifumarate and amlodipine besylate has been calculated for the peak production year estimates of the drug substance requirements for all Novartis products containing aliskiren and amlodipine, including the new aliskiren / amlodipine formulations, and for all approved indications. An estimate of drug substance production requirements for the peak year (2011 and 2013, for amlodipine and aliskiren, respectively) is presented in [Confidential Appendix 11.2.1]. The calculated EICs for aliskiren and amlodipine 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 an 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 SPV100 film-coated tablets, for the treatment of hypertension qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the EIC of the active moiety amlodipine will be 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.

6.4 Summary

6.4.1 Aliskiren - aquatic environment

Studies were conducted to accurately determine the water solubility and partition coefficient of aliskiren hemifumarate. The results of the water solubility study indicate that aliskiren hemifumarate would be highly 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 aliskiren hemifumarate 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. The calculated results presented in Table 3 and Table 4 for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) support the conclusion that aliskiren hemifumarate would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

Investigations of environmental depletion mechanisms demonstrated that aliskiren hemifumarate does not biodegrade or hydrolyze rapidly in the aquatic environment.

Five-year production estimates for Rasilez indicate that during the peak year, the EIC of aliskiren hemifumarate at the point of entry into the aquatic environment will be greater than 1 ppb. Novartis is confident that the actual EIC will not exceed these estimates by an order of magnitude.

Based upon these factors, the evaluation of the environmental effects of aliskiren hemifumarate was limited to the aquatic environment.

6.5 Environmental effects of released substances

Aliskiren hemifumarate

The environmental effects of aliskiren hemifumarate were evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA Guidance for Industry[3]). Aliskiren did not show any inhibitory activity in microorganisms which may be found in activated sludge. Acute toxicity in the aquatic species tested was low with daphnia being the most sensitive species with an EC_{50} of 56 mg/L. Results are reported in the Data Summary Table (Table 1).

6.5.1 Aliskiren assessment factor

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications[3], 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.

6.5.1.1 Aliskiren - assessment factor

In the case of aliskiren, by applying the 48-hour EC_{50} from the *Daphnia magna* immobilization study and the EIC from [Confidential Appendix 11.2.2], an assessment factor of 24'669 is obtained. (Calculation of the assessment factor is provided in [Confidential Appendix 11.2.3]). Thus, no additional ecotoxicity testing would be required for aliskiren. Since the assessment factor calculated for aliskiren is a magnitude greater than that reported in the Guidance Document, the results suggest aliskiren 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 anticipated with the packaging, distribution, use or disposal of aliskiren/amlodipine 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 aliskiren/amlodipine film-coated tablets. The use of aliskiren/amlodipine 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. Pfizer MSDS 2003. Official Material Safety Data Sheet for Amlodipine besylate. Last Revision Date: Jan 31 2003.
2. Abdoh, A., Al-Omari, M.M., Badwan, A.A., Jaber, A.M.Y. 2004. Amlodipine Besylate–Excipients Interaction in Solid Dosage Form. Pharmacol Dev Technol 9: 15-24 (2004).
3. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), July 1998. Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications. CMC 6, Revision 1.
4. Annex V to EU Directive 67/548/EEC, Part C. Available online at: http://ecb.jrc.it/testing-methods/ (accessed January 2006).
5. Kumar, K.A., Ganguly, K., Mazumdar, K., Dutta, N.K., Dastidar, S.G., Chakrabarty, A.N. 2003. Amlodipine: a cardiovascular drug with powerful antimicriobial property. Acta Microbiol Pol 52: 285-92 (2003).

6. 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 aliskiren and amlodipine drug substance requirements

[11.2.2] Expected Introduction Concentration (EIC) of aliskiren and amlodipine based upon production estimates

[11.2.3] Calculation of assessment factor for aliskiren and amlodipine

Table 1 Data summary table - aliskiren

Physical / chemical characterization		
ENDPOINT	RESULTS	METHODOLOGY
Water solubility	>800 g/L in buffered water pH7, 22°C >350 g/L @ pH 1, 25°C >350 g/L @ pH 4.7, 25°C >350 g/L @ pH 7.4, 25°C	67/548/EEC, Annex V, A.6[4]
Dissociation constant (pKa)	9.18 (22°C) The undissociated form will only occur at pH >10.5, which is not environmentally relevant.	
Log octanol/water partition coefficient (Log K_{ow})	1.01 (22°C, phosphate buffer pH 7.4) 3.1 (30°C, 0.1 M phosphate buffer pH 7) 3.9-4.5 (estimated) in unbuffered solution	67/548/EEC, Annex V, A.8[4]
Henry's Law Constant (H)	Not determined, as not expected to significantly partition into air, based on molecular weight and melting point > 95°C	
Ultraviolet-visible absorption spectrum	No significant absorption peaks at environmental pH above 290 nm	Drug substance elucidation of structure and other characteristics, Module 3
Depletion mechanisms		
Hydrolysis	Very slow hydrolysis (17%, 3d @100 °C)	
Aerobic biodegradation	5% in 28 days (22 °C)	67/548/EEC, Annex V, C.4-A[4]
Photolysis	No photolysis expected, based on absorption spectrum.	
Metabolism	Very low rate of metabolism. Above 97% of dose remains unabsorbed after oral absorption and is excreted unchanged, mainly through feces. Only about 1% is excreted through urine. Metabolites account for less than 1% of dose.	Module 2.5 Clinical Overview
Environmental effects		
Microbial Inhibition (Activated sludge)	3h-IC_{50} = 4470 mg/L	67/548/EEC, Annex V, C.11[4]
Acute Toxicity to algae (*Scenedesmus spp.*)	72h-EC_{50} > 100 mg/L 72h-NOEC = 100 mg/L	67/548/EEC, Annex V, C.3[4]

Acute Toxicity in *Daphnia magna*	48h-EC_{50} = 56 mg/L 48h-NOEC = 30 mg/L	67/548/EEC, Annex V, C.2[4]
Acute Toxicity to zebra fish (*Danio rerio*)	96h-LC_{50} > 100 mg/L 96h-NOEC = 100 mg/L	67/548/EEC, Annex V, C.1[4]

Table 2 Data summary table - amlodipine

Physical / chemical characterization		
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)[2]
Aerobic biodegradation	Not readily biodegradable	source: Pfizer
Metabolism	Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.	Clinical studies
Environmental effects		
Microbial inhibition	**Species** / **MIC (mg/L)** *E. coli* 10mg/l *Pseudomonas putida* 10mg/l *Bacillus spp*. 10 mg/l	Agar plate dilution method. Kumar et al., Acta Microbiol Pol 52:285-92 (2003)[5]
Algae toxicity (green algae)	EC_{50} (72h) = 5.6 mg/L	source: Pfizer
Acute toxicity in *Daphnia magna*	EC_{50} (48h) = 9.9 mg/L	Source: Pfizer
Acute toxicity in *Pimephales promelas* (fathead minnow)	LC_{50} (48h) 2.7 mg/L	source: Pfizer

12 Calculated environmental fate results

Aliskiren

Table 3 Calculated results for bioconcentration factor (BCF) and soil absorption coefficient (K_{oc}) for aliskiren hemifumarate based upon experimentally determined water solubility.

	pH 5	pH 7	pH 9
Water solubility (mg/L)	> 350 g/L	> 350 g/L	n.a.
BCF [a]	0.46	0.46	n.a.
K_{oc} [b]	3.90	3.90	n.a.

[a] Log (BCF) = 2.791 – 0.564 Log (S), where S = water solubility in mg/L.

[b] Log (K_{oc}) = 3.64 – 0.55 Log (S), where S = water solubility in mg/L.

Table 4 Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient (K_{oc}) for aliskiren hemifumarate based upon experimentally determined partition coefficient (log K_{ow}).

	Range	
	Low	High
BCF [a]	2.5	111.9
K_{oc} [b]	84.42	1157.18

The highest (3.1) and lowest (1.01) log K_{ow} values were used to calculate the BCF and K_{ow}.

[a] Log (BCF) = (0.79 x log K_{ow}) – 0.40 (Kenaga and Goring, 1980[6])

[b] Log (K_{oc}) = (0.544 x log K_{ow}) + 1.377 (Kenaga and Goring, 1980[6])

Appendix 11.1.1
Curriculum vitae of contributor

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)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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