CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-985

ENVIRONMENTAL ASSESSMENT

NOVARTIS

Global Pharma Environment

Aliskiren (SPP100)

Alikiren_EA_1

Environmental assessment

Author:	Andreas Hartmann
Document type:	Full environmental assessment
Document status:	Final
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1 Date

Original submission: 13-Feb-2006

2 Name of applicant/petitioner

Novartis Pharmaceuticals Corporation

3 Address

One Health Plaza
East Hanover, NJ 07936

4 Description of proposed action

4.1 Requested approval

Novartis is filing NDA 21-985 pursuant to section 505b of the FD&C Act for Rasilez (aliskiren), 150 mg and 300 mg film-coated tablets. An Environmental assessment (EA) is being submitted pursuant to 21 CFR part 25.

4.2 Need for action

Rasilez is indicated for the indication of hypertension.

4.3 Locations of use

Patients with hypertension will use Rasilez drug products 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.

Rejected materials from the Novartis facility at Suffern, NY are incinerated at the American Ref-Fuel (Hempstead) Facility, 600 Avenue C, Westbury, NY 11590.

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

5.1 Nomenclature

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

Aliskiren hemifumarate

5.1.2 Brand/proprietary name/trade name

Rasilez

5.1.3 Chemical names

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)

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)

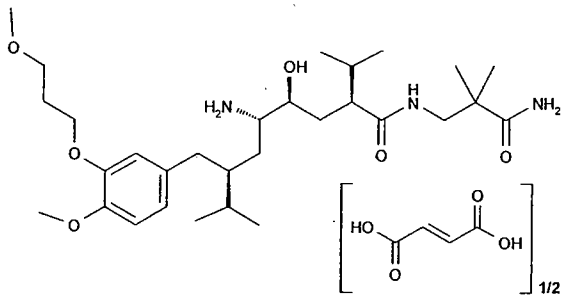
5.3 Molecular formula

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

5.4 Molecular weight

609.8 g/Mol

5.5 Structural formula



Environmental issues

5.6 Physical and chemical characterization

Physical and chemical properties and constants were determined for Rasilez drug substance, aliskiren hemifumarate. Studies to determine water solubility and octanol/water partition coefficient were conducted under Good Laboratory Practice (GLP) protocols utilizing OECD guidelines[3] as a guide. The dissociation constant was taken from Module 2 of the CTD, Drug substance general properties.

5.6.1 Water solubility (OECD 105)

The solubility of aliskiren hemifumarate was determined at 22 ± 2 °C in aqueous buffers at pH 1, 4.7 and 7.4. Aliskiren hemifumarate was determined to have a very high water solubility of at least 350 g/L in buffered solutions at the above pHs.

The mean solubility of aliskiren hemifumarate (mg/L) at each pH level is reported in the Data summary table (Table 1). Please refer to Confidential Appendix 10.2.1 for the complete study report.

5.6.2 Dissociation constant

The pK_a value of the aliskiren hemifumarate was determined during drug development activities and was estimated using the SPARC/Marvin prediction method[1]. The pK_a was predicted to be 8.77 (SPARC) and was determined to be 9.18 at 22°C (see CTD Module 2. Drug substance general properties). Since aliskiren hemifumarate has been shown to be fully dissociated at environmentally relevant pH values, water solubility and octanol/water partition coefficient were determined with the dissociated species only.

Dissociation constants are reported in the Data summary table (Table 1). Please refer to CTD module 2, Drug Substance general properties, for full results.

5.6.3 n-Octanol/water partition coefficient (OECD 117)

The n-octanol/water partition coefficient (K_{ow}) was determined for aliskiren hemifumarate by the shake flask method according to OECD guideline 117. Partition testing was conducted in at pH 7 in n-octanol-saturated aqueous buffers at 30 °C.

Based upon the K_{ow} and the log K_{ow} values obtained, 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 predictions (Table 2, Table 3) no further sorption/desorption properties (log K_{oc}) were considered.

The mean log n-octanol/water partition coefficient (log K_{ow}) of aliskiren hemifumarate at environmentally relevant pH levels is reported in the Data summary table (Table 1). Please refer to Confidential Appendix 10.2.2 for the complete study report.

5.6.4 Vapor pressure

Henry's Law Constant was not determined, as aliskiren hemifumarate is not expected to be released into the air or have a significant vapor pressure, based on its molecular weight and melting point of >95°C..

5.6.5 Ultraviolet-visible absorption spectrum

UV absorption spectra for aliskiren hemifumarate were obtained from Module 2, Drug substance Elucidation of structure and other characteristics, and are reported in the Data summary table (Table 1). No significant absorption was found above 290nm. Hence, photodegradation is not regarded a significant source of depletion for this substance.

5.7 Environmental depletion mechanisms

Environmental depletion mechanisms were investigated for aliskiren hemifumarate. Studies to determine hydrolysis and aerobic biodegradation were either taken from Module 2, Drug Substance properties or were conducted under Good Laboratory Practice (GLP) protocols utilizing OECD guidelines as a guide.

5.7.1 Hydrolysis

The first environmental depletion mechanism investigated was hydrolysis. Forced decomposition testing of aliskiren hemifumarate was conducted over a 3-day period in an aqueous medium at 100°C (see Module 2, Drug Substance properties). Under the test conditions employed, aliskiren hemifumarate was determined to be hydrolytically stable to 83%. Based on these results, a half-life of several months up to a year at 25 °C was estimated using the criteria in TAD Section 3.09 [2].

Hydrolysis results are reported in the Data summary table (Table 1). Please refer to Module 2, Drug Substance properties for the complete study report.

5.7.2 Aerobic biodegradation (OECD 301A)

Since aliskiren hemifumarate was considered to be hydrolytically stable, aerobic biodegradation was investigated as a potential depletion mechanism. The aerobic biodegradation of aliskiren hemifumarate was determined according to OECD guideline 301A (DOC die-away test) for 28 days. Under these conditions, aliskiren hemifumarate biodegraded to 5%.

Aerobic biodegradation in the wastewater treatment process may not be considered an important environmental depletion mechanism for aliskiren hemifumarate.

The results of the biodegradation study are reported in the Data summary table (Table 1). Please refer to Confidential Appendix 10.2.3 for the complete study report.

5.8 Environmental concentration

5.8.1 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 has been calculated for the peak production year using estimates of Rasilez drug substance requirements (Confidential Appendix 10.2.4). The calculated EIC is provided in Confidential Appendix 10.2.5.

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

5.9 Summary

5.9.1 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 2 and Table 3 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.

5.10 Environmental effects of released substances

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]). Microbial inhibition was evaluated in accordance with OECD Guideline Number 209. Additionally, acute toxicity testing was conducted in Green Algae, Daphnia magna and Zebra fish under Good Laboratory Practice (GLP) protocols utilizing OECD guidelines.

5.10.1 Microbial inhibition test (OECD 209)

Microbial inhibition was evaluated by means of an activated sludge inhibition test according to OECD guideline 209. Results indicate aliskiren hemifumarate is non-inhibitory to activated sludge microorganisms.

Results are reported in the Data summary table (Table 1). Please refer to Confidential Appendix 10.2.4 for the complete study report.

With no rapid depletion mechanism identified and with a non-inhibitory effect on the respiration rate of activated sludge, aliskiren hemifumarate would be expected to persist in the environment but not to disrupt waste treatment processes. According to the "Tiered Approach to Fate and Effects Testing", additional acute ecotoxicity data were considered. Two acute and one subchronic toxicity study in dapnia, fish and algae were available to further evaluate the ecotoxicity of the compound.

5.10.2 Acute toxicity in *Daphnia magna* (OECD 202)

Acute toxicity testing was conducted in *Daphnia magna* under static conditions following OECD guideline 202. Based on the results of this study, the 48-hour median effect concentration (EC_{50}) for aliskiren hemifumarate was estimated to be 56 mg/L and the No-Observed-Effect-Concentration (NOEC) was determined to be 30 mg/L.

Results are reported in the Data summary table (Table 1). Please refer to Confidential Appendix 10.2.7 for the complete study report.

5.10.3 Acute toxicity in green algae (OECD 201)

Subchronic toxicity testing was conducted in *Scenedesmus spp.* under static conditions following OECD guideline 201. Based on the results of this study, the 72-hour median effect

concentration (EC_{50}) for aliskiren hemifumarate was found to above 100 mg/L and the No-Observed-Effect-Concentration (NOEC) was determined to be 100 mg/L.

Results are reported in the Data summary table (Table 1). Please refer to Confidential Appendix 11.2.8 for the complete study report.

5.10.4 Acute toxicity in Zebra fish (OECD 203)

Acute toxicity testing was conducted in Zebra fish (*D. rerio*)under static conditions following OECD guideline 203. Based on the results of this study, the 96-hour median lethal concentration (LC_{50}) for aliskiren hemifumarate was found to be above 100 mg/L and the No-Observed-Effect-Concentration (NOEC) was determined to be 100 mg/L.

Results are reported in the Data summary table (Table 1). Please refer to Confidential Appendix 11.2.9 for the complete study report.

5.10.5 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 Maximum Expected Environmental Concentration (MEEC). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of aliskiren hemifumarate, by applying the 48-hour EC_{50} from the *Daphnia magna* study and the EIC from Confidential Appendix 10.2.5, an Assessment Factor of >>1000 is obtained. (Calculation of the Assessment Factor is provided in Confidential Appendix 10.2.10). Thus, no additional ecotoxicity testing would be required for aliskiren hemifumarate. Since the Assessment Factor calculated for aliskiren hemifumarate is more than one order of magnitude greater than that reported in the Guidance Document, the results suggest aliskiren hemifumarate would be nontoxic in the aquatic environment.

6 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 Rasilez within the United States. No mitigation measures are considered necessary.

7 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 Rasilez. The use of Rasilez will directly benefit patients suffering from hypertension.

It is the conclusion of Novartis that approval of this Application is therefore preferable to non-approval.

8 List of preparers

Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in Non-confidential Appendix 10.1.1.

9 References

1 SPARC online calculator of physico-chemical properties, pKa calculation. http://ibmlc2.chem.uga.edu/sparc/ , accessed Jan 2006.

2 US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09.

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 OECD Guidelines for Testing of Chemicals, PDF Edition (ISSN 1607-310X), update November 2004.

10 Appendices

10.1 Non-confidential appendices

10.1.1 Curriculum vitae of contributor

10.2 Confidential appendices

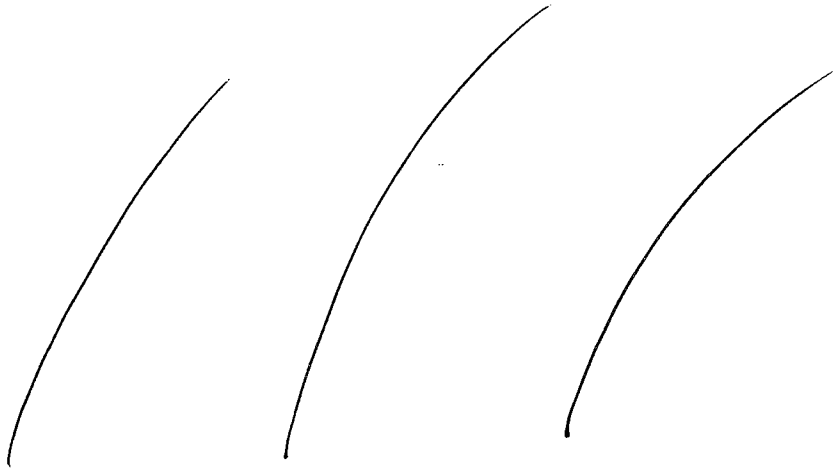


Table 1 Data summary table

Physical / chemical characterization	
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
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
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
Depletion mechanisms	
Hydrolysis	Very slow hydrolysis (17%, 3d @100 °C)
Aerobic biodegradation	5% in 28 days (22 °C)
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.
Environmental effects	
Microbial Inhibition (Activated sludge)	3h-IC_{50} = 4470 mg/L
Acute Toxicity to algae (*Scenedesmus spp.*)	72h-EC_{50} > 100 mg/L 72h-NOEC = 100 mg/L
Acute Toxicity in *Daphnia magna*	48h-EC_{50} = 56 mg/L 48h-NOEC = 30 mg/L
Acute Toxicity to zebra fish (*D. rerio*)	96h-LC_{50} > 100 mg/L 96h-NOEC = 100 mg/L

Calculated environmental fate results

Table 2 **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]	- 0.95	- 0.95	n.a.
K_{oc} [b]	0.59	0.59	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 3 **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]	1.93	3.1

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)

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

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

Memorandum

Date: May 10, 2006

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

To: Administrative Files: NDA 21-985

Subject: Review of Environmental Assessment for Rasilez Tablets 150 mg and 300 mg

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

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

Rasilez Tablets

150 mg & 300 mg

NDA 21-985

Treatment of Hypertension

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Pre-Marketing Assessment I

April 27, 2006

Environmental Assessment Review, NDA 21-985
Rasilez Tablets
(Treatment of hypertension)

EXECUTIVE SUMMARY

A FONSI is recommended

The environmental assessment (EA) dated February 13, 2006 supports the new drug application for Rasilez (Aliskiren hemifumarate) Tablets which are indicated for treatment of hypertension. The EA was prepared in accordance with 21 CFR Part 25 by Novartis Pharmaceutical Corporation.

Aliskiren hemifumarate is the salt of a weak organic base and a weak organic acid and is dissociated in water at environmentally relevant pH. The pK_a is 9.18 at 22°C. Aliskiren hemifumarate is soluble in water (>350 g/L at 25°C at pH 1, 4.7, 7.4). The log K_{ow} is 3.1 at pH 7. Aliskiren hemifumarate is expected to enter the aquatic environment from patient use and disposal.

Aliskiren hemifumarate has a very slow rate of metabolism, with the majority of the dose excreted unchanged and metabolites accounting for less than 1% of the dose. Aliskiren hemifumarate has a very slow rate of hydrolysis, and no photolysis is expected. Aliskiren hemifumarate is subject to aerobic biodegradation.

The EIC of aliskiren hemifumarate is — ppb.

The toxicity of aliskiren hemifumarate to environmental organisms was characterized. The results indicate that aliskiren hemifumarate is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

REVIEW OF EA SUBMITTED IN NDA 21-985

I. DATE: February 13, 2006
II APPLICANT: Novartis Pharmaceuticals Corporation

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

IV DESCRIPTION OF PROPOSED ACTION:

a. Requested Approval: Novartis Pharmaceutical Corporation has filed an NDA for Rasilez (aliskiren), 150 mg and 300 mg film-coated tablets. An EA has been submitted pursuant to 21 CFR part 25.
b. Need for Action: Rasilez is indicated for the treatment of hypertension.
c. Locations of Use: Hospitals, clinics and patient homes.
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. Rejected product will be incinerated per Novartis procedures.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

USAN Name: Aliskiren hemifumarate

Brand Name: Rasilez

CAS 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)

IUPAC Name: (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

CAS Number: 173334-58-2 (hemifumarate)
173334-57-1 (free base)

Molecular Formula: $C_{30}H_{53}N_3O_6 \cdot 1/2\ C_4H_4O_4$

Molecular Weight: 609.8

The molecular structure of aliskiren hemifumarate is provided in the EA dated February 13, 2006, page 4.

ADEQUATE

VI ENVIRONMENTAL ISSUES / Assessing Toxicity to Environmental Organisms

Information about environmental fate and effects are included in the EA. The test reports from the contract laboratories are provided in the confidential appendices. GLP protocols and OECD test methods are used.

Environmental Fate:

Identification of Substances of Interest:

Aliskiren hemifumarate enters the aquatic environment from patient use and disposal. Above 97% of the dose remains unabsorbed after oral absorption and is excreted unchanged, mainly through feces. Only 1% is excreted through urine. Metabolites account for less than 1% of the dose. Based on the pharmacokinetics information, the applicant focused its evaluation on aliskiren hemifumarate.

Physical and Chemical Characterization of aliskiren hemifumarate:

Aliskiren hemifumarate has a very high solubility in water, which was determined to be >350 g/L at pH 1, 4.7, and 7.4 at 25°C. Solubility is >800 g/L in pH 7 buffered water at 22°C. The pK_a is 9.18 at 22°C. Therefore, aliskiren hemifumarate is fully dissociated at environmentally relevant pH values. The undissociated form will only occur at pH >10.5, which is not environmentally relevant.

The log K_{ow} of aliskiren is 1.01 at pH 7.4 and 25°C, and 3.1 at pH 7 and 30°C. The acid of the test substance is an existing chemical, and experimental log K_{ow} values in the literature range from -0.48 to 0.46. The firm estimates a log K_{ow} value of 3.9-4.5 in unbuffered solution; this value, however, is not relevant because completely salt free solutions do not occur in the environment. Based upon the log K_{ow} values obtained, aliskiren hemifumarate is not expected to significantly bioconcentrate in living organisms or to sorb to organic particles.

In addition, the firm calculates predictive values for the bioconcentration factor (BCF) and absorption coefficient (K_{oc}), which support the firm's conclusion that aliskiren hemifumarate is not expected to bioconcentrate or bioaccumulate. Using the experimentally determined water solubility and partition coefficient (log K_{ow}), the firm calculated the BCF value to be in the range of -0.95 to 111.9, and the K_{oc} to be 0.59 to 3.1. K_{oc} values greater than 1000 indicate that the substance of interest will significantly adsorb to biosolids. BCF values less than 250 suggest a low bioaccumulation potential. Based on the log Kow values, the high solubility of the drug substance, and the above discussed low sorption predictions, further sorption/desorption studies (experimental K_{oc}) were not pursued.

Vapor Pressure:
Aliskiren hemifumarate is not expected to be released into the air or have a significant vapor pressure, based on the molecular weight and the melting point (>95°C). Henry's Law constant was not determined.

Environmental Depletion Mechanisms:
Forced degradation by hydrolysis was conducted over a three day period at 100°C (the firm references data presented in Module 2). Under these conditions, aliskiren hemifumarate was determined to be hydrolytically stable to 83%. Using the criteria described in TAD 3.09, a half-life of degradation by hydrolysis was estimated to be several months to a year.

The aerobic biodegradation of aliskiren hemifumarate was tested according to OECD guidelines for 28 days. Under these conditions, aliskiren hemifumarate degraded to 5%.

Significant photodegradation of aliskiren hemifumarate is not expected, since the UV absorption spectra showed no significant absorption peaks at environmental pH above 290 nm (the firm references data presented in Module 2).

Environmental Concentrations:
The total quantity of aliskiren hemifumarate (drug substance) required for peak production in the next 5 years (2011) is expected to be NMT [redacted] (Confidential Appendix 10.2.4). This corresponds to an Expected Introduction Concentration (EIC) of [redacted] ppb.

Summary of the Environmental Fate:
Based upon the water solubility and partition coefficient of the drug substance, aliskiren hemifumarate is expected to enter the aquatic environment. Investigations of environmental depletion mechanisms demonstrate that aliskiren hemifumarate does not biodegrade or hydrolyze rapidly in the aquatic environment.

Environmental Effects:
The toxicity of aliskiren hemifumarate to environmental organisms was characterized. The results indicate that aliskiren hemifumarate is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

All tests were performed according to OECD guidelines. Test reports from the contract laboratories are provided in the confidential appendices.

Microbial Inhibition Test
The activated sludge respiration inhibition test results showed that the 3 hour EC_{50} concentration is [redacted] This result suggests that aliskiren hemifumarate is not expected to disrupt the waste treatment process.

Daphnia:
A 48-hour toxicity test was conducted according to OECD guideline 202.
The 48-hour EC_{50} for *Daphnia magna* is 56 mg/L. The 48-hour NOEC for *Daphnia magna* is

30 mg/L.

Algae:
A 72 hour toxicity test was conducted on *Scenedesmus subspicatus* under static conditions following OECD guideline 201. The 72-hour EC_{50} for algae is >100 mg/L. The 72-hour NOEC for algae is 100 mg/L.

Zebra Fish
A 96 hour toxicity test was conducted on zebra fish (*Brachydanio rerio*) under static conditions following OECD guideline 203. The 96-hour LC_{50} for zebra fish is >100 mg/L. The 96-hour NOEC for zebra fish is 100 mg/L.

Summary of Environmental Effects

Test	Result
Microbial Inhibition (activated sludge)	EC_{50} (3 hours) = —— ng/L
Toxicity to algae (*Scenedesmus spp.*)	EC_{50} >100 mg/L (72 hours) NOEC = 100 mg/L (72 hours)
Toxicity to *Daphia magna*	EC_{50} = 56 mg/L (48 hours) NOEC = 30 mg/L (48 hours)
Toxicity to Zebra fish (*D. rerio*)	LC_{50} >100 mg/L (96 hours) NOEC = 100 mg/L (96 hours)

Assessment Factor
The assessment factor was determined for the most sensitive species *Daphnia magna*. The calculation is provided in Confidential Appendix 10.2.10. The assessment factor is equal to the EC_{50} (*Daphnia magna*)/EIC (aquatic), which is 56 mg/L / —— ppm = —— Since —— is significantly greater than 1000, no further testing is required. In addition, the NOEC level for each species tested is significantly greater than the EIC. The results suggest that aliskiren hemifumarate would be nontoxic in the aquatic environment.

ADEQUATE

VII MITIGATION MEASURES

Since no potential adverse environmental impacts are foreseen, no mitigation measures are considered necessary.

ADEQUATE

VIII ALTERNATIVES

Since no potential adverse environmental impacts are identified, no alternatives to the proposed action are suggested.

ADEQUATE

IX PREPARER

Name, job title and qualifications were provided.

ADEQUATE

X REFERENCES

The firm references the FDA Environmental Assessment Technical Assistance Handbook, the FDA Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications, the OECD Guidelines and the SPARC online calculator of physical-chemical properties, pKa calculation.

ADEQUATE

XI APPENDICES

Non-confidential appendix 10.1.1 is the CV for the preparer of the EA.

The maximum production estimate and the EIC calculation are provided in Confidential Appendices 10.2.4 and 10.2.5. The calculation of the Assessment Factor is provided in Confidential Appendix 10.2.10.

The detailed laboratory reports are also provided in confidential appendices.

ADEQUATE

Review by: Ruth Ganunis on April 27, 2006
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