

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-217**

**ENVIRONMENTAL ASSESSMENT**

**Environmental Assessment  
Finding of No Significant Impact**

**NDA 22-217**

**Aliskiren/Valsartan Film-Coated Tablets**

**Food and Drug Administration  
Center for Drug Evaluation and Research  
May 18, 2009**

## **FINDING OF NO SIGNIFICANT IMPACT**

**NDA 22-217**

### **Aliskiren/Valsartan Film-Coated Tablets**

The National Environmental Policy Act of 1969 (NEPA) requires 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.

NDA 22-217 requests approval of Aliskiren/Valsartan 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. In support of its application, Novartis Pharmaceuticals Corporation prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impact from 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.

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Attachment: Sept. 12, 2008, Environmental Assessment (confidential appendices removed)

Global Pharma Environment

Aliskiren / Valsartan  
(SPV100)

150/160 mg and 300/320 mg  
film-coated tablets

Aliskiren / Valsartan\_ABBR\_EA\_1

## **Environmental assessment**

Authors: Hoeger B.  
Date: 12-Sep-2008  
Status: Final  
Number of pages: 15

Property of Novartis

## **1 Date**

12-Sep-2008

Aliskiren / Valsartan NDA 22-217

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

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

Tekturna Tablets, NDA 21-985

Original NDA submission: Document dated 24-Jan-2006

All environmental fate and effects study reports for aliskiren and valsartan drug substances previously submitted in the Rasilez/Tekturna Tablet NDA 21-985 and Diovan Capsule NDA 20-665, 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 22-217 pursuant to section 505b of the FD&C Act for aliskiren / valsartan 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 valsartan are currently approved separately in various dosage forms and strengths for the treatment of hypertension. This supplement provides for fixed combinations of aliskiren and valsartan in the form of 150/160 mg and 300/320 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 / valsartan 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<sup>®</sup>/Tekturna<sup>®</sup>

### 5.1.3 Chemical names

#### 5.1.3.1 Chemical Abstracts Index name

Benzeneoctanamide,  $\delta$ -amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)- $\gamma$ -hydroxy-4-methoxy-3-(3-methoxypropoxy)- $\alpha,\zeta$ -bis(1-methylethyl)-, ( $\alpha S,\gamma S,\delta S,\zeta S$ )- (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;  $\frac{1}{2}$  (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)

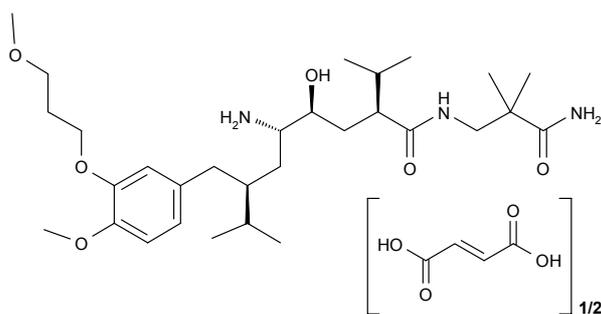
### 5.3 Molecular formula

$C_{30}H_{53}N_3O_6 \cdot \frac{1}{2} C_4 H_4 O_4$

### 5.4 Molecular weight

609.8 g/Mol

### 5.5 Structural formula



## Valsartan

### 5.6 Nomenclature

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

Valsartan

#### 5.6.2 Trade name

Diovan<sup>®</sup>

#### 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-butanoic acid

#### 5.6.4 Other names

VAL489, CGP 48933 (research code)

### 5.7 Chemical Abstracts Service (CAS) registration number

137862-53-4

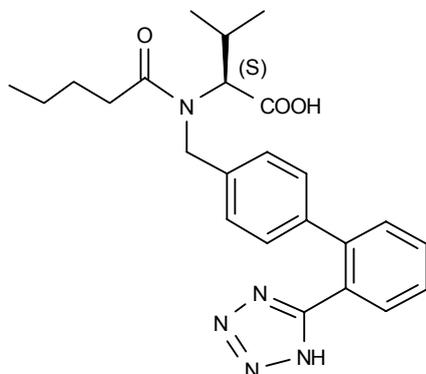
### 5.8 Molecular formula

C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>

### 5.9 Molecular weight

435.5

### 5.10 Structural formula



## 6 Environmental issues

### 6.1 Physical and chemical characterization

#### Aliskiren hemifumarate

Environmental fate and effects study reports for Rasilez<sup>®</sup>/Tekturna<sup>®</sup> 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 ( $\log K_{oc}$ ) 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  $> 95^{\circ}\text{C}$ . The aliskiren hemifumarate information is summarized in Data Summary Table (Table 1) at the end of this report.

#### 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 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 2) located at the end of this report.

Valsartan shows very low acute ecotoxicity to microorganisms, algae, daphnia and fish. Based on its low log P [ $\log K_{ow}$ ] value, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb onto 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. The valsartan information is summarized in Data Summary Table (Table 2) located at the end of this report.

## 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](#)).

### 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 as a relevant environmental depletion mechanism. Results are reported in the Data Summary Table ([Table 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<sup>1</sup>, 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 10<sup>11</sup> liters per day entering POTWs [1996 Needs Survey, Report to Congress]

C = 1 year / 365 days per year

D = 10<sup>9</sup> µg/kg (conversion factor)

The EIC of aliskiren hemifumarate and valsartan has been calculated for the peak production year estimates of the drug substance requirements for all Novartis products containing aliskiren and valsartan, including the new aliskiren / valsartan formulations, and for all approved indications. An estimate of drug substance production requirements for the peak year (2010 and 2013, for valsartan and aliskiren, respectively) is presented in [[Confidential](#)

[Appendix 11.2.1](#). The calculated EICs for aliskiren and valsartan are provided in [\[Confidential Appendix 11.2.2\]](#).

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

## 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.

### 6.4.2 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  $25 \pm 2$  °C (Data Summary [Table 2](#)). 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 for the bioconcentration factor (BCF) and the soil adsorption coefficient ( $K_{oc}$ ) presented in [Table 5](#) and [Table 6](#) 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. 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 the pharmacologically active parent compound, valsartan, 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<sup>1</sup>). 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. 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](#)).

## Valsartan

The environmental effects of valsartan was evaluated in the aquatic environment following the “Tiered Approach to Fate and Effects Testing” (Figure 1, July 1998 EA Guidance for Industry<sup>1</sup>). With no rapid, complete environmental depletion mechanism identified, microbial inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02<sup>2</sup>. Additionally, acute toxicity testing was conducted in algae, daphnia and fish, utilizing standard methods according to either TAD 4.08<sup>2</sup>, EU standard methodology<sup>3</sup> or OECD guidelines. 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<sub>50</sub> of 90 mg/L. Results are reported in the Data Summary Table ([Table 2](#)).

### 6.5.1 Aliskiren and Valsartan assessment factors

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications<sup>1</sup>, 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<sub>50</sub> from the *Daphnia magna* immobilization study and the EIC from [[Confidential Appendix 11.2.2](#)], an assessment factor of 23’333 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.

#### 6.5.1.2 Valsartan - assessment factor

In the case of valsartan, by applying the 72-hour EC<sub>50</sub> from the green algae study and the EIC from [[Confidential Appendix 11.2.2](#)], an assessment factor of 10,588 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 more than ten times higher 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 anticipated with the packaging,

distribution, use or disposal of aliskiren/valsartan 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/valsartan film-coated tablets. The use of aliskiren/valsartan 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 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.
2. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 4.02 and 4.08.
3. Annex V to EU Directive 67/548/EEC, Part C. Available online at: <http://ecb.jrc.it/testing-methods/> (accessed January 2006).
4. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.
5. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09 and 3.11 (modified).

## 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 valsartan drug substance requirements

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

[11.2.3] Calculation of assessment factor for aliskiren and valsartan

**Table 1**                      **Data summary table - aliskiren**

<b>Physical / chemical characterization</b>	
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 <sub>ow</sub> )	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
<b>Depletion mechanisms</b>	
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.
<b>Environmental effects</b>	
Microbial Inhibition (Activated sludge)	3h-IC <sub>50</sub> = 4470 mg/L
Acute Toxicity to algae ( <i>Scenedesmus spp.</i> )	72h-EC <sub>50</sub> > 100 mg/L 72h-NOEC = 100 mg/L
Acute Toxicity in <i>Daphnia magna</i>	48h-EC <sub>50</sub> = 56 mg/L 48h-NOEC = 30 mg/L
Acute Toxicity to zebra fish ( <i>D. rerio</i> )	96h-LC <sub>50</sub> > 100 mg/L 96h-NOEC = 100 mg/L

**Table 2**      **Data summary table - valsartan**

<b>Physical / chemical characterization</b>		
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 <sub>ow</sub> )	1.51 @ pH 5 in 9.85 x 10 <sup>-4</sup> moles/L buffer 1.50 @ pH 5 in 1.07 x 10 <sup>-4</sup> moles/L buffer -1.17 @ pH 7 in 1.04 x 10 <sup>-3</sup> moles/L buffer -1.01 @ pH 7 in 1.09 x 10 <sup>-4</sup> moles/L buffer -1.84 @ pH 9 in 1.04 x 10 <sup>-3</sup> moles/L buffer -1.74 @ pH 9 in 1.10 x 10 <sup>-4</sup> moles/L buffer	TAD Section 3.02
Henry's Law Constant (H)	< 1.30 x 10 <sup>-8</sup>	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
<b>Depletion mechanisms</b>		
Hydrolysis	t <sub>½</sub> ≥ 1 year at 25 °C	TAD Section 3.09
Aerobic biodegradation	0.02 % <sup>14</sup> 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	<b>Species</b>	<b>MIC (mg/L)</b>	TAD section 4.02
	<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	
Algae toxicity (green algae)	EC <sub>50</sub> (72h) = 90 mg/L NOEC = 58 mg/L		EU standard method 92/69/EC (L383) C.3 * Algal inhibition test.
Acute toxicity in <i>Daphnia magna</i>	EC <sub>50</sub> (48h) = 580 mg/L NOEC = 280 mg/L		TAD 4.08
Acute toxicity in <i>Salmo gairdneri</i> (rainbow trout)	LC <sub>50</sub> (96h) >100 mg/L NOEC = 100 mg/L		OECD 203, Fish, acute toxicity test (1992)

## 12 Calculated environmental fate results

### Aliskiren

**Table 3** Calculated results for bioconcentration factor (BCF) and soil absorption coefficient (K<sub>oc</sub>) 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 <sup>a</sup>	0.46	0.46	n.a.
K <sub>oc</sub> <sup>b</sup>	3.90	3.90	n.a.

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

<sup>b</sup>  $\text{Log (K}_{oc}) = 3.64 - 0.55 \text{ Log (S)}$ , where S = water solubility in mg/L.

**Table 4** Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient (K<sub>oc</sub>) for aliskiren hemifumarate based upon experimentally determined partition coefficient (log K<sub>ow</sub>).

	Range	
	Low	High
BCF <sup>a</sup>	2.5	111.9
K <sub>oc</sub> <sup>b</sup>	84.42	1157.18

The highest (3.1) and lowest (1.01) log K<sub>ow</sub> values were used to calculate the BCF and K<sub>ow</sub>.

<sup>a</sup>  $\text{Log (BCF)} = (0.79 \times \text{log K}_{ow}) - 0.40$  (Kenaga and Goring, 1980)

<sup>b</sup>  $\text{Log (K}_{oc}) = (0.544 \times \text{log K}_{ow}) + 1.377$  (Kenaga and Goring, 1980)

## Valsartan

**Table 5** 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 <sup>a</sup>	6.77	3.83	2.76
$K_{oc}$ <sup>b</sup>	53.5	30.7	22.3

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

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

**Table 6** Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient ( $K_{oc}$ ) for valsartan based upon experimentally determined partition coefficient ( $\log K_{ow}$ )

	Range	
	Low	High
BCF <sup>a</sup>	0.0135	6.32
$K_{oc}$ <sup>b</sup>	2.32	160

The highest (-1.86) and lowest (1.52)  $\log K_{ow}$  values were used to calculate the BCF and  $K_{oc}$ .

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

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

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/s/

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Jon E. Clark  
5/18/2009 02:32:51 PM

Moheb Nasr  
5/19/2009 09:42:14 AM



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

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**Memorandum**

**Date:** May 18, 2009  
**From:** Raanan A. Bloom, Ph.D.  
OPS/IO/PARS  
**To:** Ramesh Sood  
OPS/ONDQA/DPA1  
**Through:** Jon Clark, M.S.  
OPS/IO/PARS  
**Subject:** **Review of Environmental Assessment**

**NDA 022-217**

**Aliskiren/Valsartan 150/160 mg and 300/320 mg film-coated tablets.**

**Sponsor:** Novartis Pharmaceutical Corporation

**A. Background**

Novartis is requesting approval for Aliskiren/Valsartan 150/160 mg and 300/320 mg film-coated tablets for the treatment of hypertension. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

**B. Discussion**

The following review was conducted by [REDACTED] (b) (4) under contract to CDER/OPS on February 22, 2009, and approved by Raanan A. Bloom, Ph.D., OPS/IO/PARS, Senior Environmental Officer.

**Executive Summary**

NDA 22-217 requests approval of aliskiren/valsartan 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, and NDAs 21-985 and 22-107 for aliskiren. For convenience, the firm provided summaries of the results in this submission.

Novartis provided updated peak production requirements covering all Novartis products on the US market for the year 2013 in Confidential Appendix 11.2.1. The peak production year requirements for aliskiren hemifumarate for all Novartis products containing aliskiren hemifumarate for all indications are expected to be NMT (b) (4) kg. Assuming no metabolism or degradation, this peak production estimate corresponds to EIC = (b) (4) ppb in the aquatic environment (Confidential Appendix 11.2.2). The peak production year requirements for valsartan for all Novartis products containing valsartan for all indications are expected to be NMT (b) (4) kg. Assuming no metabolism or degradation, this peak production estimate corresponds to EIC = (b) (4) ppb in the aquatic environment (Confidential Appendix 11.2.2).

In the case of aliskiren hemifumarate, by using the 48-hour EC<sub>50</sub> from the *Daphnia magna* study and the calculated EIC, an assessment factor of 23,333 is obtained (Confidential Appendix 11.2.3). Since the assessment factor calculated for aliskiren hemifumarate is greater than the tier 1 assessment factor of 1000, the results suggest aliskiren hemifumarate would be nontoxic in the aquatic environment.

Aliskiren hemifumarate may enter the aquatic environment from patient use and disposal. The toxicity of aliskiren hemifumarate 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.

In the case of valsartan, by using the 72-hour EC<sub>50</sub> from the green algae study and the calculated EIC, an assessment factor of 10,588 is obtained (Confidential Appendix 11.2.3). Since the assessment factor calculated for valsartan is greater than the tier 1 assessment factor of 1000, the results suggest valsartan would be nontoxic in the aquatic environment.

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 September 12, 2008, Environmental Assessment

### BACKGROUND:

**I. DATE:** 12-SEP-2008

Reference is also made to related aliskiren and valsartan NDAs:

Diovan<sup>®</sup> (Valsartan) Capsules, NDA 20-665

Original submission:	20-NOV-1995
Amendment	30-MAY-1996
Amendment	22-OCT-1996

Diovan HCT<sup>®</sup> (Valsartan/ Hydrochlorothiazide) Tablets, NDA 20-818

Original approval	06-MAR-1998
Supplement (S-012)	12-SEP-2001

Diovan<sup>®</sup> (Valsartan) Tablets, NDA 21-283

Original submission	03-AUG-2000
Supplement (S-001)	05-JUL-2001
Supplement (S-011)	31-OCT-2003

Rasilez<sup>®</sup>/Tekturna<sup>®</sup> (Aliskiren) Tablets, NDA 21-985 24-JAN-2006

Tekturna HCT<sup>®</sup> (Aliskiren/ Hydrochlorothiazide) Tablets, NDA 22-107

Original Submission	20-MAR-2007
Supplement (S-002)	12-NOV-2008

All environmental fate and effects study reports for aliskiren and valsartan drug substance were previously reported in the above referenced NDAs. The studies were previously reviewed by the Agency and FONSI's were issued. No new environmental fate and effects data are included in this Environmental 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 Aliskiren/Valsartan 150/160 mg and 300/320 mg film-coated tablets. This EA has been submitted pursuant to 21 CFR part 25.
- b. Need for Action: Aliskiren and valsartan are currently approved separately, as well as in combinations in various dosage forms and strengths for the treatment of hypertension. This

application provides for fixed combinations of aliskiren and valsartan 150/160 mg and 300/320 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 aliskiren and valsartan are provided on pages 3-6 of the EA. This information was the subject of previous reviews.

ADEQUATE

## VI. ENVIRONMENTAL ISSUES

### Aliskiren

Physical and chemical properties, and environmental fate and effects data were determined for aliskiren hemifumarate and were previously submitted in the EA for Tekturna<sup>®</sup> NDA 21-985 (submitted February 10, 2006, a FONSI issued April 27, 2006). Updated data on sorption and desorption studies were submitted in the EA for Tekturna HCT<sup>®</sup> NDA 22-107 (submitted Nov-12-2008, FONSI issued February 21, 2009). No new data is provided in this submission. For convenience, the previously submitted data is summarized below.

#### Physical and Chemical Characterization

With a pK<sub>a</sub> of 9.18 at 22°C, aliskiren hemifumarate is fully dissociated at environmentally relevant pH values. Aliskiren hemifumarate has a very high solubility in water and a low log K<sub>ow</sub> value. Aliskiren hemifumarate has low to moderate sorption (<45.6%) and moderate to high desorption (>28.3%). Based on these results aliskiren hemifumarate is not likely to significantly bioconcentrate in living organisms or to sorb to organic particles. 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).

#### Depletion mechanisms

Aliskiren hemifumarate is not metabolized significantly. Aliskiren hemifumarate is subject to very slow hydrolysis, with a half-life of several months up to a year at 25°C. Aliskiren is not biodegradable to a significant extent under environmental conditions. Significant photodegradation of aliskiren hemifumarate is not expected, since the UV absorption spectra showed no significant absorption peaks at environmental pH above 290 nm. No environmentally relevant rapid depletion mechanism is identified.

Expected Introduction Concentration

Novartis provided updated peak production requirements covering all Novartis products on the US market for the year 2013 in Confidential Appendix 11.2.1. The peak production year requirements for aliskiren hemifumarate for all Novartis products containing aliskiren hemifumarate for all indications are expected to be NMT (b) (4) kg. This peak production estimate corresponds to EIC = (b) (4) ppb in the aquatic environment (Confidential Appendix 11.2.2).

Environmental Effects:

For convenience, the previously reviewed environmental effects data is summarized in this submission.

## Summary of Environmental Effects

Test	Result
Microbial Inhibition (activated sludge)	IC <sub>50</sub> = 4470 mg/L (3 hours)
Toxicity to algae ( <i>Scenedesmus spp.</i> )	EC <sub>50</sub> >100 mg/L (72 hours) NOEC = 100 mg/L (72 hours)
Toxicity to <i>Daphnia magna</i>	EC <sub>50</sub> = 56 mg/L (48 hours) NOEC = 30 mg/L (48 hours)
Toxicity to Zebra fish ( <i>D. rerio</i> )	LC <sub>50</sub> >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 11.2.3. The assessment factor is equal to the EC<sub>50</sub> (*Daphnia magna*)/EIC (aquatic), which is 56 mg/L / 0.0024 ppm = 23,333. Since 23,333 is significantly greater than the tier 1 assessment factor of 1000, no further testing is required (It is noted that based on the data provided, the firm qualifies for use of the tier 2 assessment factor of 100). The results indicate that aliskiren hemifumarate is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

**Valsartan**

Physical and chemical properties, and environmental fate and effects data were determined for valsartan and were previously submitted in the EA for Diovan Capsules NDA 20-665 (submitted November 20, 1995, a FONSI issued December 3, 1996). No new data is provided in this submission. For convenience, the previously submitted data is summarized below.

Physical and Chemical Characterization

Valsartan is relatively soluble in water over the environmental pH range. Based on its low log K<sub>ow</sub> value, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb to organic particles. Since the log K<sub>ow</sub> was less than 3 at all pH levels tested, no further

sorption/desorption properties (log  $K_{oc}$ ) were considered. Valsartan is not expected to be released into the air or have a significant vapor pressure.

#### Depletion mechanisms

Valsartan is not metabolized significantly. Valsartan is hydrolytically stable, and does not biodegrade aerobically or anaerobically to any significant extent. Significant photodegradation of valsartan is not expected, since the UV absorption spectra showed no significant absorption peaks at environmental pH above 290 nm. No environmentally relevant rapid depletion mechanism is identified.

#### Expected Introduction Concentration

Novartis provided updated peak production requirements covering all Novartis products on the US market for the year 2013 in Confidential Appendix 11.2.1. The peak production year requirements for valsartan for all Novartis products containing valsartan for all indications are expected to be NMT (b) (4) kg. This peak production estimate corresponds to EIC = (b) (4) ppb in the aquatic environment (Confidential Appendix 11.2.2).

#### Environmental Effects

For convenience, the previously reviewed environmental effects data is summarized in this submission.

<b>Test</b>	<b>Result</b>
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 <sub>50</sub> = 90 mg/L (72 hours) NOEC = 58 mg/L
Acute toxicity in <i>Daphnia Magna</i>	EC <sub>50</sub> = 580 ppm (48 hours) NOEC = 280 mg/L
Acute toxicity in <i>Salmo gairdneri</i> (= <i>Onocorhynchus mykiss</i> , rainbow trout)	LC <sub>50</sub> > 100 mg/L (96 hours) NOEC = 100 ppm

#### Assessment factor

The assessment factor was determined for the most sensitive species, green algae, with an EC<sub>50</sub> of 90 mg/L. The calculation is provided in Confidential Appendix 11.2.3. The assessment factor is equal to the EC<sub>50</sub> (green algae)/EIC (aquatic) = 90 mg/L / 0.0085 ppm = 10,588. Since 10,588 is significantly greater than the tier 1 assessment factor of 1000, no further testing is required (It is noted that based on the data provided, the firm qualifies for use of the tier 2 assessment factor of 100). The results indicate that valsartan is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

#### Conclusion

No significant environmental impact is expected from use or disposal of Aliskiren/Valsartan film-coated tablets. A FONSI is recommended.

ADEQUATE

**VII. MITIGATION MEASURES**

Information not required because no potential adverse environmental effects were identified.

ADEQUATE

**VIII. ALTERNATIVES**

Information not required because no potential adverse environmental effects were 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 aliskiren and valsartan drug substance requirements

11.2.2 Expected Introduction Concentration (EIC) of aliskiren and valsartan based upon production estimates

11.2.3 Calculation of assessment factor for aliskiren and valsartan

ADEQUATE

**C. 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 introduction of aliskiren and valsartan residues into the environment due approval of this NDA for the treatment of hypertension.

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

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/s/

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Raanan Bloom  
5/18/2009 01:27:09 PM  
ENV ASSESSMENT

Jon E. Clark  
5/18/2009 02:33:27 PM  
CHEMIST