

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
NDA 21-283/S011**

**ENVIRONMENTAL ASSESSMENT/FONSI**

**ENVIRONMENTAL ASSESSMENT  
AND  
FINDING OF NO SIGNIFICANT IMPACT  
FOR**

**Diovan<sup>®</sup> (valsartan) Tablets**

**NDA 21-283 / S-011**

**Reduction of total mortality after acute myocardial infarction**

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Division of Cardio Renal Drug Products  
(HFD-110)**

**June 30, 2004**

## **FINDING OF NO SIGNIFICANT IMPACT**

### **NDA 21-283 / S-011, Diovan® (valsartan) Tablets**

#### **Reduction of total mortality after acute myocardial infarction**

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

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

This Supplement requests approval of Diovan (valsartan) Tablets for reduction of total mortality after acute myocardial infarction. In support of its supplemental application for Diovan (valsartan) Tablets, Novartis prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Valsartan is a chemically synthesized drug currently approved for use in the treatment of hypertension (alone and in combination with other hypertensive agents) and congestive heart failure.

Valsartan may enter the aquatic environment from patient use and disposal. Although degradation mechanisms were not demonstrated for the aquatic environment, the toxicity of valsartan to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

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

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

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Attachment: Environmental Assessment  
Appended Electronic Signature Page

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## **1 Date**

31-Oct-2003

Diovan Tablets, NDA 21-283

Original NDA submission: Document dated 03-Aug-2000

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

Reference is also made to Environmental Assessments submitted to related Diovan 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 submission: Document dated 18-Mar-1997

Supplement (S-012): Document dated 12-Sept-2001

All environmental fate and effects study reports previously submitted to the Diovan Capsule NDA 20-665 and reviewed by the Agency have not been included in this Assessment.

## **2 Name of applicant/petitioner**

Novartis

## **3 Address**

One Health Plaza

East Hanover, NJ 07936-1080

## **4 Description of proposed action**

### **4.1 Requested approval**

Novartis has filed a supplement to NDA 21-283 pursuant to section 505b of the FD&C Act for Diovan (valsartan) 40mg film-coated tablet, packaged in HDPE bottles and triplex blisters. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

### **4.2 Need for action**

Diovan film-coated tablets are indicated for the treatment of hypertension, and may be used alone or in combination with other antihypertensive agents. In addition, Diovan film-coated tablets are indicated for use in congestive heart failure. This current submission supports the use of Diovan film-coated tablets in the reduction of total mortality after acute myocardial infarction (post-MI).

### 4.3 Locations of use

Patients with hypertension, congestive heart failure and post acute myocardial infarction will use Diovan 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.

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)

Valsartan

#### 5.1.2 Trade name

Diovan®

#### 5.1.3 Chemical names

##### Chemical Abstracts Index name

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

##### Systematic chemical name (IUPAC)

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

#### 5.1.4 Other names

CGP 48933 (research code)

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

137862-53-4

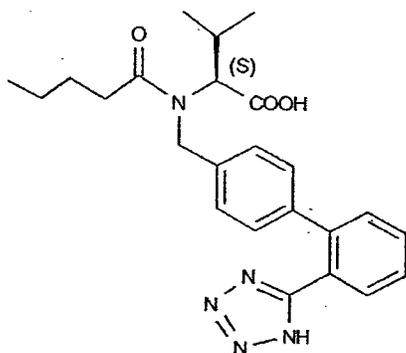
### 5.3 Molecular formula

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

## 5.4 Molecular weight

435.5

## 5.5 Structural formula



## 6 Environmental issues

### 6.1 Physical and chemical characterization

Physical and chemical properties and constants were determined for Diovan drug substance, valsartan, and initially reported in Diovan 80 and 160mg Capsules, Original NDA 20-665 (submitted 28-Dec-1995; approved by FDA on 23-Dec-1996). For the convenience of the reviewer, this information is presented again in the present Environmental Assessment.

Studies to determine water solubility, dissociation constant, octanol/water partition coefficient, vapor pressure, and ultraviolet-visible absorption were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA Environmental Assessment Technical Assistance Handbook as a guide.

The values obtained for each of these studies are presented in the Data Summary Table (Table 1) located at the end of this report.

#### 6.1.1 Water solubility (TAD Section 3.01)

The solubility of valsartan was determined at  $25 \pm 2$  °C in aqueous buffers at pH 5, 7 and 9. Valsartan was determined to have a pH-dependent solubility in water. Due to the solubility and strong acidity of valsartan, the pH 7 and 9 buffer capacities were exceeded and the final values for pH were between 5.2 and 5.6. The mean solubility (N = 6) at each pH is reported in the following table.

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### Mean water solubility

	pH 5	pH 7	pH 9
Mean solubility (mg/L)	2990	8210	1470
Standard deviation	196	430	186
Final pH range	5.2-5.6	5.2-5.6	5.2-5.6

The mean solubility of valsartan (mg/L and M) at each pH level is reported in the Data Summary Table (Table 1).

#### 6.1.2 Dissociation constant (TAD Section 3.04)

The pK<sub>a</sub> value of valsartan was determined in CO<sub>2</sub>-free reagent water at 25°C. Under the conditions of this study, two pK<sub>a</sub>'s were determined: 3.76 (carboxylic group) and 5.60 (tetrazole group). Since valsartan has been shown to dissociate, water solubility and octanol/water partition coefficient were determined at pH 5, 7 and 9.

Dissociation constants are reported in the Data Summary Table (Table 1).

#### 6.1.3 n-Octanol/water partition coefficient (TAD Section 3.02)

The n-octanol/water partition coefficient (K<sub>ow</sub>) for valsartan was determined by the shake flask method using <sup>14</sup>C-labeled material. Partitioning testing was conducted in triplicate at pH 5, 7 and 9 aqueous buffers at 25 ± 2 °C using nominal concentrations of 0.001 and 0.0001 M in n-octanol-saturated buffer at each pH. The following mean values were observed:

#### Mean partition coefficients

pH	Initial Buffer Concentration		mean K <sub>ow</sub>	Log P
	moles/L			
5	9.85 x 10 <sup>-4</sup>		32.2	1.51
	1.07 x 10 <sup>-4</sup>		31.8	1.50
7	1.04 x 10 <sup>-3</sup>		6.78 x 10 <sup>-2</sup>	-1.17
	1.09 x 10 <sup>-4</sup>		9.83 x 10 <sup>-2</sup>	-1.01
9	1.04 x 10 <sup>-3</sup>		1.43 x 10 <sup>-2</sup>	-1.84
	1.10 x 10 <sup>-4</sup>		1.82 x 10 <sup>-2</sup>	-1.74

Based upon the mean K<sub>ow</sub> and the log P [log K<sub>ow</sub>] values obtained in this study, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb onto organic particles. Further, since the log K<sub>ow</sub> was less than 3 at all pH levels tested, no further sorption/desorption properties (log K<sub>ow</sub>) were considered.

The mean log n-octanol/water partition coefficient (log K<sub>ow</sub>) of valsartan at each pH level is reported in the Data Summary Table (Table 1).

#### **6.1.4 Vapor pressure (TAD Section 3.03)**

The vapor pressure of valsartan was determined in triplicate by the gas saturation method at 25°C using nitrogen flow rates of 5, 10 and 20 ml/min over a period of 16 days. No valsartan was detected in the sorbent material at any of the flow rates. The detection limit of the instrumentation was therefore used to determine the vapor pressure of valsartan. The equilibrium vapor pressure of valsartan at 25°C was determined to be less than  $1.33 \times 10^{-3}$  Pa at the nitrogen flow rate of 20 ml/min, or less than  $1.0 \times 10^{-3}$  torr. This corresponds to a Henry's Law Constant (H) less than  $1.30 \times 10^{-3}$ .

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 Henry's Law Constant for valsartan is reported in the Data Summary Table (Table 1).

#### **6.1.5 Ultraviolet-visible absorption spectrum (TAD 3.05)**

Ultraviolet/visible spectra were obtained for valsartan at pH 5, 7 and 9. Valsartan in pH 5.00 buffer exhibited no absorption peaks. Absorption spectra in pH 7.01 buffer consisted of one major peak at 209 nm and two shoulders at 250 nm and 229 nm. Absorption spectra of valsartan in buffer at pH 8.96 consisted of one major peak at 207 nm and two shoulders at 229 nm and 251 nm.

The absorption maxima for valsartan are reported in the Data Summary Table (Table 1).

### **6.2 Environmental depletion mechanisms**

Environmental depletion mechanisms were investigated for valsartan. Studies to determine hydrolysis and aerobic biodegradation were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA Environmental Assessment Technical Assistance Handbook as a guide.

#### **6.2.1 Hydrolysis (TAD Section 3.09)**

The first environmental depletion mechanism investigated was hydrolysis. Preliminary testing of  $^{14}\text{C}$ -labeled valsartan was conducted over a 5-day period as per TAD, Section 3.09. Under the test conditions employed (50°C and all solutions removed from light), valsartan was determined to be hydrolytically stable at pH 5, 7 and 9 at 50°C. Based on these results, a half-life equal to or greater than one year at 25 °C was estimated using the criteria established in TAD, Section 3.09.

Hydrolysis results are reported in the Data Summary Table (Table 1).

#### **6.2.2 Aerobic biodegradation (TAD Section 3.11, modified)**

Since valsartan was considered to be hydrolytically stable, aerobic biodegradation was investigated as a potential depletion mechanism. The aerobic biodegradation of valsartan was determined in a batch-activated sludge (BAS) system. The method followed FDA TAD 3.11, with some modifications. Labeled test article was added to sludge obtained from a municipal

wastewater treatment plant and aerobically incubated in the dark for 28 days at  $22 \pm 2$  °C. Since only slight transformation of the test article occurred with essentially no mineralization, the test was continued for another 10 days under these conditions. After 38 days, aeration to the system was discontinued, and the test system was incubated anaerobically for one month. At the end of one month, the systems were again sampled and assayed. Again, no significant degradation of the test article or mineralization occurred during the anaerobic portion of the study. The BAS test system was validated by the reference test article, [<sup>14</sup>C]sodium benzoate, which resulted in approximately 80% evolved <sup>14</sup>CO<sub>2</sub> over the 28-day study.

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

The results of the biodegradation study are reported in the Data Summary Table (Table 1).

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

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

where:

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

B =  $1 / 1.214 \times 10^{11}$  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 valsartan has been calculated for the peak production year estimates of the drug substance requirements for all products containing valsartan and for all approved indications as well as the currently proposed indication ([Confidential Appendix 11.2.1]). The calculated EIC is 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 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 accurately determine the water solubility and partition coefficient of valsartan at pH 5.0, 7.0 and 9.0 at  $25 \pm 2$  °C. The results of the water solubility study indicate that valsartan would be relatively soluble in water over the environmental pH range. The n-octanol/water partition coefficient, which indicates the tendency of a non-ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that valsartan would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.) The calculated results presented in Table 2 for the bioconcentration factor (BCF) and in Table 3 for the soil adsorption coefficient ( $K_{oc}$ ) further support the conclusion that valsartan would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

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

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

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

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). With no rapid, complete environmental depletion mechanism identified, microbial

inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02. Additionally, since the Log  $K_{ow}$  was less than 3.5, acute toxicity testing was conducted in *Daphnia magna* utilizing TAD 4.08 from the US FDA Environmental Assessment Technical Assistance Handbook. Both studies were conducted under FDA Good Laboratory Practices (GLPs).

### 6.5.1 Microbial inhibition test (TAD section 4.02)

The agar plate dilution method was used to evaluate the toxicity of valsartan to pure cultures of molds, ascomycetes, free-living nitrogen-fixing and soil bacteria, and blue-green algae. The minimum inhibitory concentrations (MIC) established for valsartan for these five representative cultures are:

Species	MIC (mg/L)
<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

Results indicate valsartan is non-inhibitory to microorganisms which may be found in activated sludge.

Results are reported in the Data Summary Table (Table 1).

### 6.5.2 Acute toxicity in *Daphnia magna* (TAD 4.08)

With no depletion mechanism identified and with a Log  $K_{ow}$  < 3.5, a forty-eight hour acute toxicity study was conducted on one suitable test organism (an aquatic invertebrate) to further evaluate the ecotoxicity of valsartan, as described in the "Tiered Approach to Fate and Effects Testing"<sup>3</sup>.

Acute toxicity testing was conducted in *Daphnia magna* under static conditions following the protocol described in FDA Environmental Assessment Technical Assistance Handbook, Document 4.08. Based on the results of this study, the 48-hour median effect concentration ( $EC_{50}$ ) for valsartan was estimated to be 580 mg/L, and the No-Observed-Effect-Concentration (NOEC) was determined to be 280 mg/L.

Results are reported in the Data Summary Table (Table 1).

### 6.5.3 Assessment factor

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications, an Assessment Factor is a toxicity ratio which provides a consistent regulatory basis for determining if and when additional ecotoxicity testing should be performed, using a tiered approach. The Assessment Factor may be calculated by dividing an appropriate acute toxicity test endpoint by the MEEC (Maximum Expected Environmental

Concentration). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of valsartan, by applying the 48-hour EC<sub>50</sub> from the Daphnia magna study and the EIC from [Confidential Appendix 11.2.2], an Assessment Factor of [ $\gg 10,000$ ] 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 significantly more than one order of magnitude greater than that reported in the Guidance Document, the results suggest valsartan would be nontoxic in the aquatic environment.

## 7 Mitigation measures

Based upon the information and data presented in this environmental assessment, Novartis has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of Diovan 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 Diovan film-coated tablets. The use of Diovan film-coated tablets will directly benefit patients with hypertension, congestive heart failure and after acute myocardial infarction.

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

## 9 List of preparers

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

## 10 References

1. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.
2. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09 and 3.11 (modified).
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. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 4.02 and 4.08.

## **11 Appendices**

### **11.1 Non-confidential appendices**

[11.1.1] Curriculum vitae of contributors

### **11.2 Confidential appendices**

[11.2.1] Production estimates of valsartan drug substance requirements

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

[11.2.3] Calculation of assessment factor

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**Table 1 Data Summary Table**

DATA SUMMARY TABLE		
Water Solubility – mean (mg/L)	2990 @ pH 5 8210 @ pH 7 1470 @ pH 9	
Dissociation Constants (mean pKa's)	3.76 (carboxylic group) and 5.60 (tetrazole group)	
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	
Henry's Law Constant (H)	< 1.30 x 10 <sup>3</sup>	
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.	
DEPLETION MECHANISMS		
Hydrolysis	t <sub>1/2</sub> ≥ 1 year at 25 °C	
Aerobic Biodegradation	0.02 % <sup>14</sup> C evolved over 28-day aerobic study	
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 urine.	
ENVIRONMENTAL EFFECTS		
Microbial Inhibition	<b>Species</b>	<b>MIC (mg/L)</b>
	<i>Aspergillus niger</i>	> 1000
	<i>Trichoderma viride</i>	> 1000
	<i>Clostridium perfringens</i>	> 1000
	<i>Bacillus subtilis</i>	1000
	<i>Nostoc sp.</i>	200
Acute Toxicity in <i>Daphnia magna</i>	EC <sub>50</sub> = 580 mg/L NOEC = 280 mg/L	

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### Calculated environmental fate results

**Table 2** 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 3** Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient ( $K_{oc}$ ) for Valsartan based upon experimentally determined partition coefficient ( $\text{log } K_{ow}$ ).

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

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

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

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

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