

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-401**

**ENVIRONMENTAL ASSESSMENT**

**Environmental Assessment  
Finding of No Significant Impact**

**NDA 22-401  
Telmisartan/Amlodipine Besylate Tablets**

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

**September 4, 2009**

# **FINDING OF NO SIGNIFICANT IMPACT**

**NDA 22-401**

## **Telmisartan/Amlodipine Besylate Tablets**

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

NDA 22-401 requests approval for a fixed dose combination tablet of telmisartan and amlodipine besylate for the treatment of hypertension. In support of its application, Boehringer Ingelheim Pharmaceuticals, Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impact from the use and disposal of this product.

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

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Office of Pharmaceutical Science

Attachment: December 2008, Environmental Assessment

**ENVIRONMENTAL ASSESSMENT (EA)**  
**NON-CONFIDENTIAL [FREEDOM OF INFORMATION ACT (FOIA)]**  
**SUBMISSION**

**MICARDIS (telmisartan) tablets**  
**Telmisartan/Amlodipine Fixed Dose Combination tablets**

**December 2008**

**Boehringer Ingelheim Pharmaceuticals, Inc.**  
**900 Ridgebury Road**  
**P.O. Box 368**  
**Ridgefield, CT 06877**

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## LIST OF ABBREVIATIONS AND TERMS

AF	assessment factor
BCF	bioconcentration factor
CAS	chemical abstract service
D	distribution coefficient octanol/water
D.F.	dilution factor
EA	environmental assessment
EC50	median effect concentration
EEC	expected environmental concentration
EIC	expected introduction concentration
FDA	food & drug administration
FDC	fixed dose combination
Kd	distribution coefficient for adsorption
Koc	organic carbon normalised adsorption coefficient
LC50	median lethal concentration
LOEC	lowest observed effect concentration
MIC	minimum inhibitory concentration
NOEC	no observed effect concentration
OECD	organisation for economic cooperation and development
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
POTW	publicly owned treatment works
TAD	technical assistance document
USAN	United States adopted names
WWTP	wastewater treatment plants

## ENVIRONMENTAL ASSESSMENT

### MICARDIS (telmisartan) tablets Telmisartan/Amlodipine Fixed Dose Combination (FDC) tablets

#### SUMMARY:

The Applicant certifies that the Environmental Assessment (EA) is provided in support of the applications for:

- MICARDIS (telmisartan) tablets
- Telmisartan/Amlodipine Fixed Dose Combination tablets

These two applications (MICARDIS tablets sNDA for a cardiovascular risk reduction indication, Telmisartan/Amlodipine FDC tablets NDA) are being submitted within only a few weeks of each other, therefore this EA has been prepared covering both applications together.

Ecotoxicity and environmental fate data are provided in this Environmental Assessment to support the L(E)C50 / EIC decision criteria for telmisartan and the fixed dose combination of telmisartan/amlodipine.

As amlodipine is widely used as a generic drug and its use in the FDC of telmisartan/amlodipine will not substantially increase its use, no EA has been prepared. In addition the estimated concentration of amlodipine (as part of the fixed dose combination) from manufacture, patient use and disposal as part of a Boehringer Ingelheim drug product containing amlodipine as the active ingredient is anticipated to be below 1 µg/L (see yearly estimation quantity in Confidential Appendix 1).

Boehringer Ingelheim anticipates no adverse effects to humans or environmental organisms as a result of excreted telmisartan entering into wastewater treatment plants (WWTP) and subsequent release environments.

**1. DATE:** December 2008

**2. NAME OF APPLICANT/PETITIONER:** Boehringer Ingelheim Pharmaceuticals Inc.

**3. ADDRESS:** 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877

#### **4. DESCRIPTION OF PROPOSED ACTION:**

a. Requested Approval: Telmisartan is already approved for the treatment of hypertension and marketed in the US as MICARDIS® tablets and available as 20, 40 and 80 mg strengths. Telmisartan is also marketed as a fixed dose combination with the thiazide diuretic hydrochlorothiazide as a treatment for hypertension. This fixed dose formulation is marketed as MICARDIS® HCT. The subject EA has been submitted pursuant to 21 CFR part 25, following the Center for Drug Evaluation and Research "Guidance for Industry for the Submission of an Environmental Assessment", dated July 1998 for the applications of:

- MICARDIS (telmisartan) tablets, supplement to NDA 20,850
- Telmisartan/Amlodipine Fixed Dose Combination (FDC) tablets in the strengths of T40/A5mg, T40/A10mg, T80/A5mg, and T80/A10mg as part of New Drug Application 22,401.

Since both applications are being submitted within only a few weeks of each other, this EA has been prepared covering both applications together.

**b. Need for the Action:** Telmisartan is currently indicated for the treatment of hypertension. Telmisartan is an orally effective and specific angiotensin II receptor (type AT1) antagonist. The current application seeks to broaden the indication to include cardiovascular risk reduction.

The telmisartan/amlodipine FDC is intended for treatment of hypertension.

**c. Locations of Use:** Telmisartan (as monotherapy, or combined with hydrochlorothiazide or amlodipine) will be used as a prescription agent, in home and hospital environments throughout the US.

**d. Disposal Sites:** End-user disposal at US hospitals, pharmacies or clinics of empty or partially empty packages will follow hospital, pharmacy or clinic procedures. Empty or partially empty containers in residences will typically be disposed of by a community's solid waste management system, which may include landfills, incineration and/or recycling. Minimal quantities of unused drug may be disposed to sewer or septic systems.

## **5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION:**

### **a. Nomenclature**

i. Established Name (USAN): Telmisartan

ii Tradename: MICARDIS

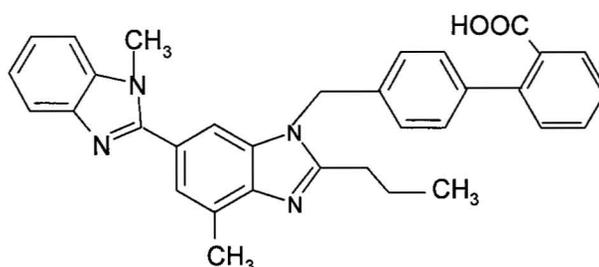
ii. Chemical Name: [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6-bi-1H-benzimidazol]-1'-yl)methyl]-

**b. Chemical Abstracts Service (CAS) Registration Number: 144701-48-4**

**c. Molecular Formula: C<sub>33</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub>**

**d. Molecular Weight: 514.63 g/mol**

e. Structural Formula:



**6. ENVIRONMENTAL ISSUES:**

The physical-chemical, fate and ecotoxicity protocols used in testing telmisartan generally followed the Technical Assistance Documents (TAD) as published in FDA's EA Technical Assistance Handbook and/or Organization for Economic Co-operation and Development (OECD) standard methods. Additional information (pKa values, testing of log D, water solubility, hydrolysis and photolysis) was determined according to standardized in-house methods.

a. Environmental fate of released substances

i. Identification of Substance of Interest

Telmisartan is the primary entity of interest released into the environment through use of MICARDIS (telmisartan) tablets and the telmisartan/amlodipine FDC tablets. Telmisartan is a valid environmental tracer for assessing fate and effects owing that telmisartan is mainly excreted as unchanged drug.

ii. Physical and Chemical Characterization

The pKa values of telmisartan were determined to be 3.5, 4.1 and 6.0. At the environmental relevant pH range of 5 to 9 telmisartan is an ionized molecule. Water solubility and Log D are pH dependent. Based on the low bioconcentration factor (BCF) of 5, telmisartan is not of concern with regard to bioaccumulation. An adsorption coefficient of  $K_{oc} = 895$  for sludge was determined for this substance indicating that no extensive amount of telmisartan is expected to adsorb onto sludge.

Refer to Data Summary Table (Appendix 1) for complete review of physical/chemical data for telmisartan.

iii. Environmental Depletion Mechanisms

Telmisartan is not readily biodegradable. A stability study showed that no significant hydrolytic and photolytic degradation is expected to occur.

Refer to Data Summary Table (Appendix 1) for complete review of depletion mechanism data for telmisartan.

#### iv. Environmental Concentrations

(1) Expected Introduction Concentration (EIC):

$$\text{EIC}_{\text{aquatic}} (\text{ppm}) = A \times B \times C \times D$$

Where: A = kg/yr produced for direct use (Confidential Appendix 1)  
B = 1/ liters per day entering POTWs (publicly owned treatment works)\*  
C = years/ 365 days  
D =  $1 \times 10^6$   $\mu\text{g}/\text{kg}$  (conversion factor)

\*  $1.274 \times 10^{11}$  liters per day entering POTW according to the 2006 Need Survey, Report to Congress

The EIC entering into the external aquatic environment (EIC<sub>aquatic</sub>) has been calculated (Confidential Appendix 2). The calculations are based on total telmisartan usage. No adjustments have been made to account for metabolism, other environmental depletion mechanisms, or for the dilution of wastewater effluents into the receiving waters.

(2) Expected Environmental Concentration (EEC):

The Expected Environmental Concentration (EEC), which is sometimes referred to as the Predicted Environmental Concentration (PEC), was calculated as follows:

$$\text{PEC} = \text{EIC}_{\text{aquatic}} \times [(100 - R) / (100 \times \text{D.F.})]$$

Where: % Removal (R) = 0  
Dilution Factor (D.F.) = 10

The PEC refines the original EIC estimate by accounting for telmisartan's removal on sludge during wastewater treatment and subsequent dilution into the receiving waters. As a conservative estimate, the PEC was not adjusted for telmisartan's removal by biodegradation mechanisms or removal on sludge. A dilution factor of 10 for dilution of wastewater effluents into the receiving waters was applied (Confidential Appendix 3).

#### v. Summary

Telmisartan will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Telmisartan is not volatile and therefore will not enter the air compartment. Generally, only a fraction of sludge from POTWs would be applied to soil. Based on the adsorption/desorption K<sub>oc</sub> for telmisartan, sludge applied to land would not result in a high concentration of telmisartan in the soil compartment.

Based on these considerations, the evaluation of environmental effects was limited to the aquatic environment.

#### b. Environmental effects of released substances

##### i. Activated Sludge Inhibition Testing

Telmisartan presents no significant inhibition to microorganisms and therefore is not expected to disrupt waste water treatment processes. Refer to Data Summary Table (Appendix 1).

##### ii. Ecotoxicity Testing

The full set of acute and chronic data on the three aquatic species (daphnids, fish, and algae) are available. Refer to the Data Summary Table (Appendix 1) for a complete review of available effects data for telmisartan.

##### iii. Predicted No Effect Concentration (PNEC)

The PNEC is calculated by applying an assessment factor (AF) to the effects data developed in the tiered testing; where

$$\text{PNEC} = \text{L(E)C}_{50} / \text{AF}$$

The assessment factor represents the extent of uncertainty in extrapolating test data on a limited number of species to the real environment. In general, the greater number of species tested and the longer duration of tests, the smaller degree of uncertainty and size of the assessment factor (AF).

Based on the chronic ecotoxicity effects data presented in Appendix 1 zebra fish is considered the most sensitive species tested (algal study: the NOEC based on growth rate is considered to be scientifically more reliable than the NOEC based on biomass). Therefore, the PNEC calculated was based on the NOEC value of 1.0 mg/L. An assessment factor of 10 was used. The PNEC for telmisartan is therefore 0.1 mg/l as calculated in Confidential Appendix 4.

##### iv. Summary

The ecotoxicity of telmisartan to three aquatic species was investigated using standard protocols for acute as well as chronic testing. The PNEC for the most sensitive species is therefore 0.1 mg/l

#### c. Summary

Based on the PEC/PNEC risk assessment, it is unlikely that telmisartan represents a risk to the aquatic environment. The PEC/PNEC assessment for total telmisartan usage was based on fish as the most sensitive species tested. No adverse environmental effect was identified in this assessment, as demonstrated by the calculated PEC/PNEC ratio of

<1.0. The PEC/PNEC risk assessment based on total telmisartan usage is provided in Confidential Appendix 4.

Review of current data provides that “**No Further Action**” is required since the PEC/PNEC ratio of <1.0.

#### **7. MITIGATION MEASURES:**

No adverse environmental effects have been identified. No mitigation measures are required.

#### **8. ALTERNATIVES TO THE PROPOSED ACTION:**

No potential effects have been identified for this proposed action. No alternatives to the proposed action are required.

#### **9. LIST OF PREPARERS:**

**David Redalieu**, Associate Director, Environmental Health and Safety at Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT USA.

*Graduate Degree Environmental Engineering with over 20 years experience in environmental and safety engineering and management.*

**Wolfgang Weigl**, Manager Environment, Health & Safety at Corporate Department Environmental Protection & Safety at Boehringer Ingelheim GmbH, Germany

*Graduation as ‘Dipl. Geoökologe’ (Environmental Chemistry and Ecotoxicology)  
Occupational experiences in ecotoxicological risk assessments of plant protection products, chemicals and pharmaceuticals*

#### **10. REFERENCES:**

1. “Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements”, Center for Drug Evaluation and Research (CDER), July 1998.

#### **11. APPENDICES:**

1. Data Summary Table

#### **11A. CONFIDENTIAL APPENDICES:**

1. Projected Total Usage of Telmisartan
2. Basis for Expected Introduction Concentration (EIC) from Use into the External Aquatic Environment.
3. Basis for Predicted Environmental Concentration (PEC) Calculation
4. Basis for PEC/PNEC (Predicted No Effect Concentration) Calculation

## APPENDIX 1

### Data Summary Table

Complete study reports are submitted attached to this document.

Data requirement	Guideline	Result	Report no.
<b>PHYSICAL CHEMICAL PROPERTIES</b>			
Dissociation Constants	in-house	pKa1 = 3.5 pKa2 = 4.1 pKa3 = 6.0	U97-2002
Partition Coefficient (O/W) (HPLC Method)	OECD 117	Log D = 3.5 at pH 4.3	U04-1579
Partition Coefficient (titration)	in-house	Log D = 4.2 at pH 5.0 Log D = 3.5 at pH 7.0 Log D = 3.1 at pH 9.0	U97-2002
Water solubility	OECD 105	in water (pH 4.6): 0.6 mg/L	U04-1577
Water solubility	in-house	pH 5.0: 0.26 mg/L pH 7.0: 0.30 mg/L pH 8.9: 44 mg/L	U97-2002
Ad-/Desorption on sludge	OPPTS 835.1110	Koc = 895 Kd = 297	U07-0047
Ad-/Desorption on soil	OECD 106	Mean of 3 soils: Koc = 11478 Kd = 110	U08-0062-01
Vapor pressure	-	Not determined experimentally, since no significant partition into air is expected based on molecular structure and melting point of ca 267°C.	-
Bioconcentration in fish	OECD 305	BCF (whole body weight): 5	U06-0210
<b>DEGRADATION</b>			
Ready Biodegradability	FDA, TAD 3.11	Not ready biodegradable	U98-3273
Hydrolysis	in-house stability study	In aqueous solutions at various pH values and at elevated temperatures telmisartan undergoes no substantial hydrolytic decomposition.	H003976
Photolysis	in-house stability study	After 24 hours of light irradiation (Xenon lamp) no substantial decomposition was observed.	H003976

Aerobic transformation in aquatic sediment systems	OECD 308	In aerobic aquatic systems, 14C-telmisartan rapidly dissipates from the water phase by adsorption to the sediment. Once in the sediment, its degradation proceeds at a very slow rate, mainly via the formation of bound residues. The dissipation time (DT50) for 14C-telmisartan from the water phase was calculated to be 12.1 and 7.3 days. No half-lives for telmisartan in the river and pond sediments and total systems were calculated since no or only very low dissipation/degradation of telmisartan was observed.	U08-0032-01
<b>ECOTOXICITY</b>			
<i>Desmodesmus subspicatus</i> 72 hr algal growth inhibition test	OECD 201	Based on biomass: 72-hour EC50 = 1.75 mg/L 72-hours NOEC = 0.49 mg/L Based on growth rate: 72-hours EC50 = 9.88 mg/L 72-hours NOEC = 1.03 mg/L	U04-1580
<i>Daphnia magna</i> 48h immobilisation test	FDA, TAD 4.08	EC50 = 18 mg/L NOEC = 5.4 mg/L	U98-3266
<i>Daphnia magna</i> 21d reproduction test	OECD 211	NOEC = 1.2 mg/L LOEC = 3.9 mg/L	U08-0034-01
Rainbow trout 96 hr acute toxicity test	OECD 203	LC50 = 3.74 mg/L NOEC = 1.92 mg/L	U04-1578
Zebra fish 35 d chronic toxicity test	OECD 210	NOEC = 1.0 mg/L LOEC = 3.1 mg/L	U08-0033-01
Microbial growth inhibition	FDA, TAD 4.02	5 different microbial species were tested. For 4 species the MIC was above 1000 mg/L, i.e. growth occurred at 1000 mg/L. For one species ( <i>bactillus subtilis</i> ) the MIC was 20mg/L.	U98-3265
Activated sludge inhibition	OECD 209	NOEC = 1000 mg/L	U08-0200-01

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09/04/2009

JON E CLARK  
09/08/2009

MOHEB M NASR  
09/11/2009



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

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**Memorandum**

**Date:** September 4, 2009

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

**To:** David Claffey  
ONDQA, DPA1

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

**Subject:** **NDA 22-401:** Telmisartan/Amlodipine Besylate Tablets (Proposed trade name: Twynsta)

**Sponsor:** Boehringer Ingelheim Pharmaceuticals, Inc.

**Review of Environmental Assessment**

**A. Background**

Boehringer Ingelheim Pharmaceuticals, Inc. seeks approval of Twynsta: (proposed trade name) ; a fixed dose combination tablet of telmisartan and amlodipine besylate for the treatment of hypertension. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25. The same EA was submitted for NDA 20-850 MICARDIS (telmisartan) tablets.

**B. Discussion**

The Environmental Assessment, dated December, 2008, supports this new drug application for fixed dose combination tablets of telmisartan and amlodipine besylate. The EA provides information on the environmental chemistry, fate, and effects of telmisartan residues in the environment. Information is not required for amlodipine. Amlodipine is widely used as a generic drug and its use in the fixed dose combination of telmisartan/amlodipine will not substantially increase its use. In addition, the estimated concentration of amlodipine (as part of the fixed dose combination) from manufacture, patient use and disposal as part of a Boehringer Ingelheim drug product containing amlodipine as the active ingredient is anticipated to be below 1 µg/L (see yearly estimation quantity in Confidential Appendix 1). Accordingly, amlodipine besylate residues are not expected to pose an environmental risk.

The sponsor estimates an Expected Introduction Concentration (EIC) for telmisartan of (b) (4) based on all Boehringer Ingelheim drug products containing telmisartan as an active ingredient with no metabolism or degradation processes considered in the calculation of the EIC. Since the EIC is greater than 1 ppb, an environmental assessment was submitted and reviewed. The submitted information is as recommended in the CDER/CBER Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998).

Physical/chemical properties were determined. Degradation, activated sludge inhibition, and ecotoxicity tests were performed (see listing, below). The tests were appropriately chosen and conducted, based on the information provided. The ecotoxicity of telmisartan was investigated using standard protocols for acute as well as chronic testing.

See the December, 2008 EA for detailed discussion the environmental chemistry fate, toxicity and estimated environmental concentrations of telmisartan in the environment.

#### **PHYSICAL CHEMICAL PROPERTIES**

<b>Data requirement</b>	<b>Guideline</b>	<b>Result</b>
Dissociation Constants	in-house	pKa1 = 3.5 pKa2 = 4.1 pKa3 = 6.0
Partition Coefficient (O/W) (HPLC Method)	OECD 117	Log D = 3.5 at pH 4.3
Partition Coefficient (titration)	in-house	Log D = 4.2 at pH 5.0 Log D = 3.5 at pH 7.0 Log D = 3.1 at pH 9.0
Water solubility	OECD 105	in water (pH 4.6): 0.6 mg/L
Water solubility	in-house	pH 5.0: 0.26 mg/L pH 7.0: 0.30 mg/L pH 8.9: 44 mg/L
Ad-/Desorption on sludge	OPPTS 835.1110	Koc = 895 Kd = 297
Ad-/Desorption on soil	OECD 106	Mean of 3 soils: Koc = 11478 Kd = 110
Vapor pressure	-	Not determined experimentally, since no significant partition into air is expected based on molecular structure and melting point of ca 267°C.
Bioconcentration in fish	OECD 305	BCF (whole body weight): 5

**DEGRADATION**

Ready Biodegradability	FDA, TAD 3.11	Not ready biodegradable
Hydrolysis	in-house stability study	In aqueous solutions at various pH values and at elevated temperatures telmisartan undergoes no substantial hydrolytic decomposition.
Photolysis	in-house stability study	After 24 hours of light irradiation (Xenon lamp) no substantial decomposition was observed.
Aerobic transformation in aquatic sediment systems	OECD 308	In aerobic aquatic systems, <sup>14</sup> C-telmisartan rapidly dissipates from the water phase by adsorption to the sediment. Once in the sediment, its degradation proceeds at a very slow rate, mainly via the formation of bound residues. The dissipation time (DT50) for <sup>14</sup> C-telmisartan from the water phase was calculated to be 12.1 and 7.3 days. No half-lives for telmisartan in the river and pond sediments and total systems were calculated since no or only very low dissipation/degradation of telmisartan was observed.

**ECOTOXICITY**

<i>Desmodesmus subspicatus</i> 72 hr algal growth inhibition test	OECD 201	Based on biomass: 72-hour EC50 = 1.75 mg/L 72-hours NOEC = 0.49 mg/L Based on growth rate: 72-hours EC50 = 9.88 mg/L 72-hours NOEC = 1.03 mg/L
<i>Daphnia magna</i> 48h immobilisation test	FDA, TAD 4.08	EC50 = 18 mg/L NOEC = 5.4 mg/L
<i>Daphnia magna</i> 21d reproduction test	OECD 211	NOEC = 1.2 mg/L LOEC = 3.9 mg/L
Rainbow trout 96 hr acute toxicity test	OECD 203	LC50 = 3.74 mg/L NOEC = 1.92 mg/L
Zebra fish 35 d chronic toxicity test	OECD 210	NOEC = 1.0 mg/L LOEC = 3.1 mg/L

Microbial growth inhibition	FDA, TAD 4.02	5 different microbial species were tested. For 4 species the MIC was above 1000 mg/L, i.e. growth occurred at 1000 mg/L. For one species (bactillus subtilis) the MIC was 20mg/L.
Activated sludge inhibition	OECD 209	NOEC = 1000 mg/L

### C. Analysis

The most sensitive endpoint (1.0 mg/L; the NOEC for all endpoints in the Zebra fish 35 d chronic toxicity test) and an EIC taking no metabolism into account are used in the risk assessment. The calculated EIC is [REDACTED] (b) (4) based on all Boehringer Ingelheim drug products containing telmisartan as an active ingredient.

$$\text{NOEC/EIC} = \frac{[REDACTED]}{[REDACTED]}$$

The NOEC/EIC ratio as calculated below is greater than 10. As discussed in the CDER/CBER EA Guidance, if the EC or LC (or in this case the NOEC) for chronic toxicity testing divided by the EIC is greater than or equal to 10, no further testing should be conducted unless sublethal effects are observed at the MEEC. Therefore, no additional studies are required.

In conclusion, since the ratio of the LOEC for the most sensitive of the chronic test organisms, to the expected introduction concentration is larger than the assessment factor, no adverse environmental effects are anticipated as a consequence of the use of telmisartan.

### D. Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs, in FDA guidance, and on the scientific validity of the “no effects” conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA.

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

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/s/

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09/04/2009

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