

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-512

ENVIRONMENTAL ASSESSMENT

**Environmental Assessment
Finding of No Significant Impact**

NDA 22-512

**Dabigatran Etextilate Capsules
(75 mg, 110 mg, and 150 mg)**

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

July 16, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-512

Dabigatran Etexilate Capsules (75 mg, 110 mg, and 150 mg)

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 22-512 requests approval for dabigatran etexilate capsules (75 mg, 110 mg, and 150 mg). The NDA provides for an indication for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation at moderate to high risk of stroke. In support of its application, Boehringer Ingelheim Pharmaceuticals, Inc. prepared an environmental assessment (EA; attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of dabigatran etexilate.

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: September 2009, Environmental Assessment

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

**(Referenced Confidential Information Has Been Provided
Under Separate Cover)**

DABIGATRAN ETEXILATE

Dabigatran etexilate mesilate capsules(75 mg, 110 mg, and 150 mg)

NDA # 22-512

September 2009

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

ACRONYMS AND ABBREVIATIONS

AF	assessment factor
CAS	chemical abstract service
D	distribution coefficient octanol/water
D.F.	dilution factor
EA	environmental assessment
EEC	expected environmental concentration
EIC	expected introduction concentration
FDA	food & drug administration
K _d	distribution coefficient for adsorption
K _{oc}	organic carbon normalised adsorption coefficient
LOEC	lowest observed effect 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
WWTP	wastewater treatment plants

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ENVIRONMENTAL ASSESSMENT

DABIGATRAN ETEXILATE

75 mg, 110 mg, and 150 mg capsule

SUMMARY:

The Applicant certifies that the Environmental Assessment (EA) provided is in support of Dabigatran etexilate capsules. Ecotoxicity and environmental fate data are provided in this Environmental Assessment to support the L(E)C50 /EIC decision criteria for the active moiety. Boehringer Ingelheim anticipates no adverse effects to humans or environmental organisms as a result of the use of Dabigatran etexilate and the excreted active moiety entering into wastewater treatment plants (WWTP) and subsequent release environments.

1. DATE:

September 2009

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: Approval of Dabigatran etexilate is requested for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation at moderate to high risk of stroke. The subject EA has been submitted to support this supplement, pursuant to 21 CFR & 25.31a(a), following the Center for Drug Evaluation and Research "Guidance for Industry for the Submission of an Environmental Assessment", dated July 1998.

b. Need for the Action: Dabigatran etexilate is the orally active prodrug of dabigatran, a novel, synthetic, non-peptide thrombin inhibitor. Dabigatran etexilate will be administered orally twice daily to patients with non-valvular atrial fibrillation for prevention of stroke and non-CNS systemic embolism.

c. Locations of Use: Dabigatran etexilate 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): Dabigatran etexilate mesilate
(internal code: BIBR 1048 MS)

ii Tradename: Dabigatran etexilate mesilate

iii. Chemical Name: beta-Alanine, N-[[2-[[[4-(((hexyloxy)carbonyl)amino]-iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester, methanesulfate

b. Chemical Abstracts Service (CAS) Registration Number:

593282-20-3 (Dabigatran etexilate mesilate = methane sulfonate)

211915-06-9 (Dabigatran etexilate = free base)

c. Molecular Formula:

C₃₅H₄₅N₇O₈S (Dabigatran etexilate mesilate)

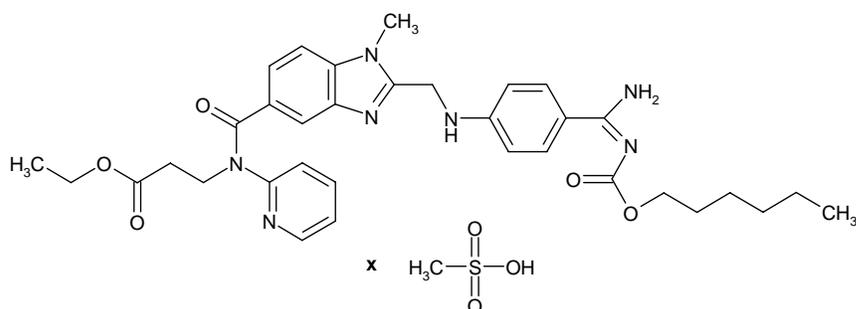
C₃₄H₄₁N₇O₅ (Dabigatran etexilate)

d. Molecular Weight:

723.86 g/mol (Dabigatran etexilate mesilate)

627.75 g/mol (Dabigatran etexilate)

e. Structural Formula:



Active moiety

a. Nomenclature:

i: Established Name: Dabigatran
(internal code: BIBR 953 ZW)

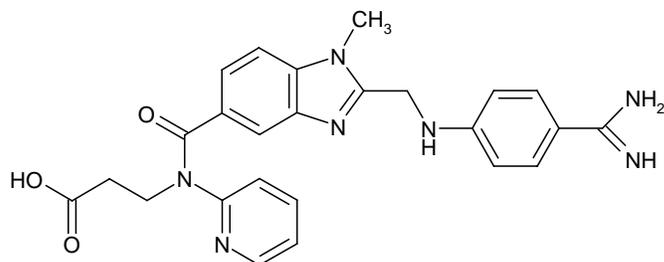
ii: Chemical Name: beta-Alanine, N-[[2-[[[(4-aminoiminomethyl)phenyl] amino]methyl]-1-methyl-1H-benzimidazol-5-yl] carbonyl]-N-2-pyridinyl-

b. Chemical Abstracts Service (CAS) Registration Number: 211914-51-1

c. Molecular Formula: $C_{25}H_{25}N_7O_3$

d. Molecular Weight: 471.51 g/mol

e. Structural Formula:



6. ENVIRONMENTAL ISSUES:

Assessing Toxicity to Environmental Organisms

The physical-chemical, fate and ecotoxicity protocols used in testing Dabigatran 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, 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

Dabigatran etexilate is the orally active prodrug of Dabigatran, a novel, synthetic, non-peptide thrombin inhibitor. Dabigatran etexilate is devoid of any antithrombin activity. The molecular weight of the free base Dabigatran etexilate is 627.75, that of the methanesulfonic acid salt Dabigatran etexilate mesilate 723.86. After oral administration and absorption from the gastrointestinal tract, Dabigatran etexilate is converted by esterases into the active moiety Dabigatran (molecular weight 471.51).

Dabigatran is the primary entity of interest released into the environment through use of Dabigatran etexilate. A human ¹⁴C-ADME study has demonstrated that following oral administration, Dabigatran etexilate (= pro drug) is rapidly and almost completely converted to its active moiety Dabigatran. Most of the radioactivity was excreted in faeces with a small amount excreted in urine. Dabigatran was by far the dominant compound both in faeces and in urine. The pro drug Dabigatran etexilate was not detectable in urine and faeces. Only minor amounts of the administered dose were found as metabolites. Due to the fact that the active moiety, Dabigatran, is by far the dominant compound excreted, the environmental risk assessment will be performed on the basis of data on fate and effect data of Dabigatran.

ii. Physical and Chemical Characterization

Dabigatran has pK values of 12.4, 4.4 and 4.1 respectively, is sparingly soluble in aqueous solutions and its Log_D < -2.2 at the environmentally relevant pH range of 5 to 9. The low Log_D indicates that Dabigatran has no significant potential for bioaccumulation. Refer to Data Summary Table (Appendix 1) for review of physical/chemical data for Dabigatran.

iii. Environmental Depletion Mechanisms

Based on the results of ready biodegradation studies with compounds structural similar to Dabigatran and on the structure of the substance itself, Dabigatran is considered to be not ready biodegradable. Therefore, the study on ready biodegradability was not

conducted. However, a full water/sediment study according to OECD 308 is available (see below).

An adsorption coefficient of $K_{oc} = 5758$ (3 soils) was determined for this substance indicating that no extensive amount of Dabigatran is expected to adsorb onto solids. Transformation in aquatic sediment systems was evaluated using OECD Method 308. Results show rapid disappearance of Dabigatran from the aerobic aquatic systems with a mean DT_{50} of approximately 3 days for the water compartment as well as for the total system. The removal mechanism is mainly via binding to sediment (bound residues) and formation of several minor metabolites. Due to the low amounts of Dabigatran detected in the sediment, a half life could not be calculated for this compartment. Refer to Data Summary Table (Appendix 1) for review of depletion mechanism data for Dabigatran.

iv. Environmental Concentrations

(1) Expected Introduction Concentration (EIC):

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

Where: A= kg/yr produced for direct use (Confidential Appendix 1)
 B= 1/ liters per day entering POTWs*
 C = years/ 365 days
 D =1 X 10⁶ mg/kg (conversion factor)

* 1.274 x 10¹¹ liters per day entering POTW according to the 2006 Need Survey, Report to Congress

The EIC entering into the external aquatic environment ($EIC_{aquatic}$) has been calculated (Confidential Appendix 2). The calculations are based on total expected Pradaxa usage in the peak year during the first five years after introduction, and the corresponding active moiety (Dabigatran) quantities. No adjustments have been made to account for metabolism, other environmental depletion mechanisms, or for the dilution of wastewater effluents into the receiving waters. No seasonal patterns of use are expected.

(2) Expected Environmental Concentration (EEC):

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

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

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

The PEC refines the original EIC estimate by accounting for Dabigatran removal on sludge during wastewater treatment and subsequent dilution into the receiving waters. As a conservative estimate, the PEC was not adjusted for Dabigatran 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

Dabigatran will enter the aquatic environment through effluents discharged by wastewater treatment plants (WWTP). Dabigatran 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 Koc for Dabigatran, sludge applied to land would not result in a high concentration of Dabigatran 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

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

ii. Ecotoxicity Testing

A full set of chronic data on the three aquatic species (daphnids, fish, and algae) are available (prepared for regulatory submission in Europe according to the EMEA guideline).

No toxicity was seen in algae up to the limit of solubility. Chronic testing in daphnids and fish resulted in NOECs of 1.0 mg/l and 3.5 mg/l respectively. Refer to the Data Summary Table (Appendix 1) for review of effects data for Dabigatran.

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

$$\text{PNEC} = \text{L(E)C50 or NOEC} / \text{AF}$$

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.

The PNEC was based on the lowest NOEC result from the chronic base set toxicity tests. The NOEC of 1.0 mg/l from the *Daphnia* reproduction test was chosen as the NOEC. An assessment factor of 10 was applied to calculate the PNEC because the data is obtained from long-term toxicity tests. Therefore, the PNEC is calculated to be 0.10 mg/l.

The PNEC is compared to the PEC (Confidential Appendix 2). The PEC/PNEC ratio is less than one (Confidential Appendix 4) indicating that no significant risk for the aquatic environment is to be expected.

iv. Summary

The ecotoxicity of Dabigatran to three aquatic species was investigated using standard test protocols. The PEC/PNEC ratio is less than one for the most sensitive species (*Daphnia magna*) indicating that no significant risk for the aquatic environment is to be expected.

..

c. SUMMARY

Based on the PEC/PNEC risk assessment, it is unlikely that Dabigatran represents a risk to the aquatic environment. The PEC/PNEC assessment for total Dabigatran entering into the environment was based on a long term daphnia reproduction test as the most sensitive species tested. The PEC calculation is also conservative as it does not take into consideration depletion via biodegradation or photolysis. 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 Dabigatran 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, Health and Safety, Boehringer Ingelheim Pharmaceuticals, Inc. M.S. Environmental Engineering with over 20 years experience in environmental health and safety engineering and management in the pharmaceutical industry.

Wolfgang Weigl Ecotoxicologist, Boehringer Ingelheim GmbH. Dipl Geoecology with concentrations in environmental toxicology and chemistry. Over seven years experience conducting environmental risk assessments.

The contract testing laboratories used for all studies is included in the confidential appendices.

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

3 Pages Withheld in Full Immediately After This Page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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

/s/

RAANAN A BLOOM
07/16/2010

NAKISSA SADRIEH
07/16/2010

MOHEB M NASR
07/25/2010



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

Memorandum

Date: July 16, 2010

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

To: Prafull Shiromani
OPS/ONDQA

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

Subject: **NDA 22-512, Dabigatran Etexilate Capsules (75 mg, 110 mg, and 150 mg)
Review of Environmental Assessment**

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

A. Background

Boehringer Ingelheim Pharmaceuticals, Inc., has filed an original submission pursuant to Section 505 (b) of the Federal Food, Drug, and Cosmetic Act for dabigatran etexilate capsules (75 mg, 110 mg, and 150 mg). The applicant has submitted an environmental assessment (EA) pursuant to 21 CFR part 25 to account for proposed usage of the active ingredient.

B. Discussion

Executive Summary

This EA supports an original submission for the NDA supplement for dabigatran etexilate capsules (75 mg, 110 mg, and 150 mg). Approval of dabigatran etexilate is requested for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation at moderate to high risk of stroke. Dabigatran etexilate is the orally active prodrug of dabigatran, a novel, synthetic, non-peptide thrombin inhibitor. The EA was prepared in accordance with 21 CFR Part 25 by Boehringer Ingelheim Pharmaceuticals, Inc. The EA is compiled in accordance with FDA 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

Dabigatran etexilate is metabolized by esterases into the active moiety dabigatran, which is excreted. Accordingly, the environmental risk assessment was performed on the basis of fate and effect data for dabigatran.

The sponsor uses chronic ecotoxicology data to estimate toxicity parameters in the environment. Specifically, based on the chronic ecotoxicity effects data *Daphnia magna* is the most sensitive species tested. Comparison of the Expected Introductory or Maximum Expected Environmental Concentration (EIC; MEEC) to this value allows the conclusion that dabigatran residues in the environment are not expected to present an environmental risk.

C. Environmental Assessment Review

1. **Date:** September 2009
2. **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc.
3. **Address:**

900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

4. **Proposed Action:** Boehringer Ingelheim Pharmaceuticals, Inc., is requesting approval of dabigatran etexilate capsules (75 mg, 110 mg, and 150 mg) for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation at moderate to high risk of stroke.

5. **Identification of Chemicals:** Dabigatran etexilate is the orally active prodrug of dabigatran, a novel, synthetic, non-peptide thrombin inhibitor.

Prodrug: Dabigatran etexilate

a. Nomenclature

- i. Established Name (USAN): Dabigatran etexilate mesilate
(internal code: BIBR 1048 MS)
- ii Tradename: Dabigatran etexilate mesilate
- iii. Chemical Name: beta-Alanine, N-[[2-[[[4-(((hexyloxy)carbonyl)amino]-iminomethyl]phenyl]amino)methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester, methanesulfate

b. Chemical Abstracts Service (CAS) Registration Number:

593282-20-3 (Dabigatran etexilate mesilate = methane sulfonate)
211915-06-9 (Dabigatran etexilate = free base)

c. Molecular Formula:

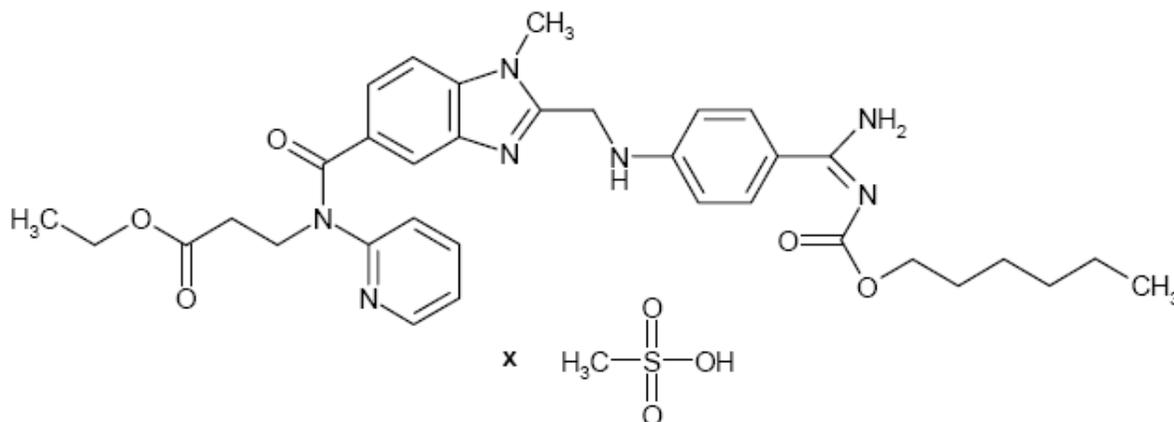
C₃₅H₄₅N₇O₈S (Dabigatran etexilate mesilate)
C₃₄H₄₁N₇O₅ (Dabigatran etexilate)

d. Molecular Weight:

723.86 g/mol (Dabigatran etexilate mesilate)

627.75 g/mol (Dabigatran etexilate)

e. Structural Formula:



Active moiety: Dabigatran

a. Nomenclature:

i: Established Name: Dabigatran

(internal code: BIBR 953 ZW)

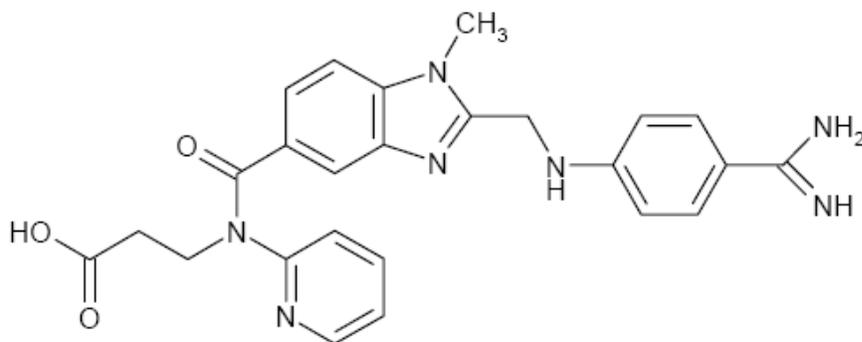
ii: Chemical Name: beta-Alanine, N-[[2-[[[(4-aminoiminomethyl)phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl] carbonyl]-N-2-pyridinyl

b. Chemical Abstracts Service (CAS) Registration Number: 211914-51-1

c. Molecular Formula: C₂₅H₂₅N₇O₃

d. Molecular Weight: 471.51 g/mol

e. Structural Formula:



6. Environmental Characterization

Dabigatran is sparingly soluble in aqueous solutions and is not expected to bioaccumulate.

The following physical and chemical properties of dabigatran are provided.

The following study reports based on OECD guidelines are provided in confidential appendices:

Widmer H. (2005): Determination of the Partition Coefficient (n-Octanol / Water) of BIBR 953 ZW including effect of pH. (b) (4)

Völkel W. (2006): Determination Adsorption/Desorption of [¹⁴C]- BIBR 953 ZW on Soils. (b) (4)

Physical/Chemical Properties

Data Requirement	Guideline	Result
<i>PHYSICAL CHEMICAL PROPERTIES</i>		
Dissociation Constants	Standardized in-house test methods	pKa1 = 12.4 pKa2 = 4.4 pKa3 = 4.1
Partition Coefficient (O/W)	OECD 107	pH 7: log D = < - 2.2 No pH dependency for the range of pH 5 to 9.
Water solubility	Standardized in-house test methods	pH 5.0: 24 mg/L pH 7.0: 17 mg/L pH 8.8: 17 mg/L
Ad-/Desorption (batch method)	OECD 106	Koc = 5758 (mean value for 3 different soils)

Environmental Depletion Mechanisms

According to the applicant, dabigatran is considered not to be ready biodegradable based on results with similar compounds. A ready biodegradability study was not conducted. A water/sediment study conducted according to OECD 308 provides some information on degradation and is provided in a confidential appendix.

Mamouni A. (2006): ¹⁴C-BIBR 953 ZW: Route and Rate of Degradation in Aerobic Aquatic Sediment Systems. (b) (4)

<i>DEGRADATION</i>		
Ready Biodegradability		Based on structural similarities to other compounds, this compound is not expected to readily biodegrade
Aerobic transformation in aquatic sediment systems	OECD 308	<p>The results indicate that Dabigatran will disappear rapidly from aerobic aquatic systems (river and pond, respectively) mainly via binding to sediment (bound residues) and formation of several minor metabolites.</p> <p>Within 14 days, the amount of radioactivity applied in the water phase had decreased to 17.8% and 19.7% for river and pond, respectively. At the end of incubation, the corresponding values were 3.9% and 5.8% of the applied radioactivity.</p> <p>A mean DT50 value of about 3 days was calculated for both the river and pond total systems. Once in the sediment, it slowly degraded to form several minor metabolites. The rate of dissipation of Dabigatran from the water phase was calculated to be also about 3 days (DT50) for both river and pond. Due to the very low amounts of Dabigatran detected in the sediment, its half-life was not calculated for this compartment of the aquatic systems.</p> <p>Mineralisation to ¹⁴CO₂ was insignificant throughout the study, accounting for less than 0.6% and 0.1% of the applied radioactivity for both systems.</p>
Hydrolysis	Standardized in-house test methods	In aqueous solutions at various pH values and at elevated temperatures (60°C) Dabigatran undergoes substantial hydrolytic decomposition. Hydrolysis is pH dependent and occurs in acidic and basic solutions whereas under neutral conditions it is much reduced.
Photolysis	Suntest according ICH	After 22 hours of light irradiation (320-800 nm at 250 W/m ²) the total amount of impurities was (b) (4)

Environmental Concentrations

The sponsor estimates a projected total usage of dabigatran etexilate mesilate at market peak (2015) of (b) (4) kg/yr. This results in an EIC of (b) (4) (ppb) according to the EIC equation (EA Guidance Document) using a POTW effluent value of 1.274 X 10¹¹ liters per day (2006 EPA Need Survey).

A human ¹⁴C-ADME study has demonstrated that following oral administration dabigatran etexilate is converted by esterases into the active moiety dabigatran. Based on a stoichiometric ratio of dabigatran etexilate mesilate to dabigatran of 0.651; the projected total usage of dabigatran at market peak is (b) (4) kg/yr. This results in an EIC of (b) (4)

The expected environmental concentration (EEC) is derived from the EIC by applying a default factor of (b) (4) for dilution in surface waters; EEC = 0.088 ug/L

Environmental Fate and Effects

Environmental Fate

Dabigatran will be excreted and enter the aquatic environment after patient use and disposal through effluents discharged by wastewater treatment plants. Dabigatran is not volatile and is not expected to enter the atmosphere. The low Pow (< -2.2) indicates a low tendency to bioaccumulate. Koc values of (b) (4) indicate some irreversible binding in sediments may occur resulting in bound residues. Additional metabolites may also be formed. The majority of residues are expected to enter the aquatic compartment.

Ecological Toxicity

The following studies conducted according to OECD guidelines are provided in confidential appendices:

Peither A. (2006): BIBR 953 ZW: Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test. (b) (4)

Peither A. (2006): BIBR 953 ZW: Effect on survival and reproduction of *Daphnia magna* in a semi-static test over three weeks. (b) (4)

Peither A. (2006): BIBR 953 ZW: Toxic effects to zebra fish (*Brachydanio rerio*) in an early-life stage toxicity test. (b) (4)

U06-0212 Peither A. (2006): BIBR 953 ZW: Toxicity to activated sludge in a respiration inhibition test. (b) (4)

<i>ECOTOXICITY</i>		
<i>Scenedesmus subspicatus</i> 72 hr algal growth inhibition test	OECD 201	72-hour NOEC: ≥ 10.4 mg/L (= solubility limit)
Daphnia reproduction test, <i>Daphnia magna</i>	OECD 211	21-day NOEC: 1.0 mg/L 21-day LOEC: 3.1 mg/L
Fish early life stage toxicity test, <i>Brachydanio rerio</i>	OECD 210	30-day NOEC: 3.5 mg/L 30-day LOEC: 10.5 mg/L
Activated sludge inhibition	OECD 209	3-hour NOEC: 1000 mg/L

Summary

The sponsor uses chronic ecotoxicology data to estimate toxicity parameters in the environment. Specifically, based on chronic ecotoxicity effects data, *Daphnia magna* are considered the most sensitive species tested. The PNEC is based on a NOEC value of 1.0 mg/L. Comparison of the Expected Introductory or Maximum Expected Environmental Concentration (EIC; MEEC) to this value results in a ratio significantly greater than 10 (NOEC/EIC = ^{(b) (4)}), allowing the conclusion that dabigatran residues in the environment are not expected to present an environmental risk.

Cumulative Environmental Fate and Effects

Dabigatran is an original submission. There are no U.S. marketed generic applications or other NDA applications and dabigatran is not listed in the IMS National Sales data set. Dabigatran etexilate is marketed as Pradaxa in European countries since April 2008 and Pradax in Canada.

7. Mitigation Measures and Alternatives

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

D. Literature Reviewed

No literature on dabigatran as related to environmental occurrences, fate and ecotoxicity were found.

E. Comments and Conclusions

Comparison of the EIC to NOEC values allows for the conclusion that dabigatran residues in the environment are not expected to present an environmental risk.

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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

RAANAN A BLOOM
07/16/2010

NAKISSA SADRIEH
07/16/2010