CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022399Orig1s000

ENVIRONMENTAL ASSESSMENT

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

Memorandum

Date: September 17, 2009

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

To: Don Henry
OPS/ONDQA

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

Subject: **NDA 22-399:** Solzira™, Gabapentin Enacarbil, Extended Release Tablets, 600 mg

Sponsor: GlaxoSmithKline

Review of Environmental Assessment

A. Background

GlaxoSmithKline seeks approval Solzira™, a prodrug of gabapentin, for the treatment of restless leg syndrome. The approval of this NDA will result in increased use of the active drug substance. Accordingly, an Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

B. Discussion

The Environmental Assessment, dated July 10, 2008, supports this new drug application for Solzira Extended Release Tablets, 600 mg tablets. Solzira is a pro-drug that is enzymatically converted to gabapentin in patients and as a consequence the drug substance of interest entering the environment is gabapentin. Accordingly, the focus of the environmental assessment is the fate and effects of gabapentin in the environment. The EA provides information on the environmental chemistry, fate, and effects of gabapentin residues in the environment.

Calculations of the Expected Introduction Concentration (EIC) and Expected Environmental Concentration (EEC) of gabapentin were provided. The EIC was calculated based on the maximum annual projected amount of drug substance needed to support all Solzirą dosage forms for the next five years. No metabolism or degradation processes for

gabapentin were considered in the calculation of the EIC. An EIC of (b) (4) µg/L was estimated. The EEC was calculated using a 10-fold dilutuin to equal (b) (4) µg/L. 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).

An article by Kasprzyk-Hordern, 2008 (Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. The Occurrence of Pharmaceuticals, Personal Care Products, Endocrine Disruptors and Illicit Drugs in Surface Water in South Wales, UK. *Water Research.* 2008;42:3498-3518) is also cited. Levels of gabapentin in two river systems were reported at varying levels with a highest recorded concentration of 1.89 µg/l.

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 gabapentin was investigated using standard protocols for acute as well as chronic testing. (see below).

Physical/Chemical Properties

Aqueous Solubility	Freely Soluble
Dissociation Constant	pKa = (b) (4)
Octanol/Water Distribution Coefficient	Dow = (b) (4), log Dow = - (b) (4)
ACD clogD (calculation)	**pH logD** (b) (4)
Henry's Law Constant	HL = (b) (4) l
Soil Adsorption (PCKOCwin)	Log Koc = (b) (4) (*calculation*)

Depletion Mechanisms

Porous Pot Test	Primary degradation, 1%, 76 days DOC, 0 %, 76 days
WWTP removal efficiency: Batch Biodegradation Test:	> 99% removal Biotransformation = 90%
WWTP removal efficiency	Poor (data unpublished)
Direct Photolysis	Not expected to be susceptible to direct photolysis by sunlight
Hydrolysis	Hydrolysis in the environment is not expected

Environmental Effects/Ecotoxicity

Activated Sludge Inhibition	EC_{50} > 1,000 mg/l NOEC = 1,000 mg/l
Daphnia magna, 48 hour acute	EC_{50} > 100 mg/l NOEC = 100 mg/l
Oncorhynchus mykiss, 96 hour acute	EC_{50} > 100 mg/l NOEC = 100 mg/l
Desmodesmus subspicatus, 76 hour acute	EC_{50} > 100 mg/l NOEC = 100 mg/l

C. Analysis

Acute NOEC values were obtained for organisms representing three trophic levels: Daphnia magna (invertebrate), Oncorhynchus mykiss (fish), and Desmodesmus subspicatus (algae). An activated sludge respiration inhibition study was also conducted. All NOEC values were > 100 mg/L.

Comparisons of effect versus exposure concentrations were made by calculating the ratio of NOEC to EIC for each of three species.

NOEC/EIC = > 50,000

As discussed in the CDER/CBER EA Guidance, if the EC or LC (or in this case the NOEC) for acute toxicity (base set) testing divided by the EIC is greater than or equal to 100, no further testing should be conducted. 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 Solzira.

D. Comments and Conclusions

Based on an evaluation of the information provided in this EA, 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/

RAANAN A BLOOM
09/21/2009

JON E CLARK
09/22/2009

Environmental Assessment
Finding of No Significant Impact

NDA 22-399
Solzira™, Gabapentin Enacarbil Tablets

Food and Drug Administration
Center for Drug Evaluation and Research

September 17, 2009

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-399

Solzira™, Gabapentin Enacarbil 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 22-399 requests approval for Solzira™, a prodrug of gabapentin, for the treatment of restless leg syndrome. In support of its application, GlaxoSmithKline 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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CONCURRED BY:

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Attachment: July 10, 2008, Environmental Assessment

1. DATE

July 10, 2008

2. NAME OF APPLICANT

GlaxoSmithKline

3. ADDRESS

One Franklin Plaza
P.O. Box 7929
Philadelphia,
PA 19101 USA

4. DESCRIPTION OF PROPOSED ACTION

4.1. Requested Approval

GlaxoSmithKline has filed NDA 20-399 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOLZIRA™ Extended Release Tablets, 600 mg tablets, packaged in (b) (4) bottles. This Environmental Assessment has been submitted pursuant to 21 CFR part 25.

4.2. Need for Action

This NDA requests approval for the use of Solzira™, a prodrug of gabapentin, for the treatment of restless leg syndrome.

The approval of this NDA will result in increased use of drug substance. Accordingly this EA has been prepared to take account of the environmental impact anticipated by this action.

4.3. Locations of Use

Solzira™ will be used in the United States of America, with predominant use coinciding with areas of greatest population density.

4.4. Disposal Sites

At hospitals, pharmacies, and clinics, empty or partially empty packages will be disposed of in accordance with hospital, pharmacy, or clinic procedures. In homes, empty or partially empty packages will be disposed of by the community's solid waste management system; which may include landfills, incineration, and recycling.

5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT THE PROPOSED ACTION

Solzira™ is a pro-drug that is enzymatically converted to gabapentin in patients and as a consequence the drug substance of interest entering the environment is gabapentin and is the focus of interest for this environmental assessment.

5.1. Nomenclature (Gabapentin enacarbil)

Solzira™ tablets contain the active moiety gabapentin enacarbil.

5.1.1. Established Name (International Non-Proprietary Name–INN)

Gabapentin enacarbil.

5.1.2. Brand/Proprietary Name/Tradename

Solzira™

5.1.3. Chemical Names

[1-({[({1-[(2-methylpropanoyl)oxy]ethyl}oxy)carbonyl]amino}methyl)cyclohexyl]acetic acid

5.1.4. Chemical Abstracts Service (CAS) registration number

478296-72-9

5.1.5. Molecular Formula

$C_{16}H_{27}NO_6$

5.1.6. Molecular Weight

329.40

5.1.7. Structural Formula

Gabapentin enacarbil:

5.2. Nomenclature (Gabapentin)

Solzira™ tablets contain the active moiety gabapentin enacarbil which is metabolized and released into the environment as gabapentin.

5.2.1. Established Name (U.S. Adopted Name-USAN)

Gabapentin

5.2.2. Brand/Proprietary Name/Tradename

Active prodrug product of Solzira™

5.2.3. Chemical Names

1-(Aminomethylcyclohexyl) acetic acid.

5.2.4. Chemical Abstracts Service (CAS) registration number

60142-96-3

5.2.5. Molecular Formula

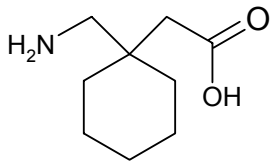
$C_9H_{17}NO_2$

5.2.6. Molecular Weight

171.24

5.2.7. Structural Formula

Gabapentin:



6. ENVIRONMENTAL ISSUES

This Environmental Assessment addresses the environmental impact of gabapentin.

6.1. Metabolism

Gabapentin enacarbil is rapidly converted to gabapentin after adsorption from the intestinal lumen. Gabapentin is not appreciably metabolized in humans and is largely eliminated from systemic circulation by renal excretion.

6.2. Physical/Chemical Properties

Physico-chemical data has been obtained from in-house studies, contracted studies and external sources [FDA, 2005]. Relevant results are summarized below and in the Data Summary Table in the appendices.

6.2.1. Aqueous Solubility

Freely soluble

6.2.2. Dissociation Constant(s)

pKa1 = (b) (4), pKa2 = (b) (4)

6.2.3. Octanol/Water Distribution Constant

Log Pow = (b) (4) (pH 7.4) [FDA, 2005]

6.2.4. Henry's Law Constant

Henry's Law constant was not measured but the calculated value using Henrywin software suggests the atmosphere is not at risk to exposure.

6.2.5. Activated Sludge Adsorption

Gabapentin is freely soluble, a low distribution coefficient and predicted Koc and is therefore unlikely to adsorb to organic matrices (sludge or soil) to a significant extent.

6.3. Environmental Depletion Mechanisms

Biodegradation studies in which the test substance is exposed to aerobic sludge microrganisms in a continuously operated test system simulating the activated sludge process have revealed that gabapentin was subject to little or no primary or ultimate biodegradation [SD2008/01415/00].

The fate and biodegradability of gabapentin has recently been explored in two published papers. One study examined the levels of drug substance in both influent and effluent in a Baltimore WWTP and concluded that gabapentin was subjected to greater than 99% removal efficiency [Yu, 2006]. Furthermore, short-term batch biodegradation tests demonstrated greater than 90% biotransformation and the authors conclude that

gabapentin can be categorized as readily biodegradable. In contrast, a study which investigated aquatic exposure to pharmaceuticals in the South Wales region of the United Kingdom [Kasprzyk-Hordern, 2008], determined levels of gabapentin in two river systems and reported that WWTP removal efficiencies are poor. Gabapentin was detected in river water at varying levels with a highest recorded concentration of 1.89 µg/l. This peak measured environmental concentration (MEC) has been used to inform the environment risk assessment, see Appendix 10.2.3.

The different outcomes in both published studies may be attributable to variation in WWTP technologies and their application in the removal of trace organics. For example, the high biodegradation rates reported for the Baltimore WWTP may be attributable to a plant designed to achieve biological nutrient removal (BNR facility) with a solids residence time between 8 and 10 days for the bioreactors.

6.4. Summary of Environmental Fate

Gabapentin is freely soluble in water, has a low distribution coefficient [FDA, 2005] and is therefore likely to distribute predominantly to the aquatic compartment. Furthermore this substance will not have a tendency to bioaccumulate in the tissue of aquatic organisms. No viable depletion mechanism has been identified for this compound although one academic paper did reported that this substance was significantly removed in a Baltimore WWTP.

6.5. Ecotoxicology

Table 1 Summary of Gabapentin Acute Ecotoxicity Data

Species	Duration	EC_{50}
Desmodesmus subspicatus (green algae)	72 hours	> 100 mg/L
Daphnia magna (crustacean)	48 hours	> 100 mg/L
Oncorhynchus mykiss (rainbow trout)	96 hours	> 100 mg/L

6.6. Environmental Concentrations

Calculations of the Expected Introduction Concentration (EIC) and Expected Environmental Concentration (EEC) of gabapentin are included as confidential information, see Appendix 10.2.1. EIC was calculated based on the maximum annual projected amount of drug substance needed to support all Solzira™ dosage forms for the next five years [FDA, 1998]. EEC was calculated as EIC divided by a surface water dilution factor of 10 [FDA, 1998].

6.7. Environmental Risk Assessment

The potential risk of adverse environmental effects resulting from the clinical use of Solzira™ was assessed by comparing the EIC (the greater of EEC and EIC, [FDA, 1998]) with experimental ecotoxicity data for gabapentin. Acute EC_{50} values were obtained for organisms representing three trophic levels: *Desmodesmus subspicatus* (algae), *Daphnia magna* (invertebrate) and *Oncorhynchus mykiss* (fish) [SD2008/01015/00.; SD2008/01013/00.; SD2008/01014/00.]. Comparisons were made by calculating the ratio of EC_{50} to EIC for each of three species (see Confidential Appendix 10.2.2).

For all three species, the NOEC/EIC ratios for were greater than the minimum application factor of 100, as specified for Tier 2 ecotoxicity data in the FDA Guidance Document [FDA, 1998]. Therefore, it is concluded that clinical use of Solzira™ at predicted production levels will not cause adverse effects to the environment.

The potential risk of adverse environmental effects resulting from the clinical use of Solzira™ was assessed by comparing the MEC [Kasprzyk-Hordern, 2008] with experimental ecotoxicity data for gabapentin. Acute EC_{50} values were obtained for organisms representing three trophic levels: *Desmodesmus subspicatus* (algae), *Daphnia magna* (invertebrate) and *Oncorhynchus mykiss* (fish) [SD2008/01015/00.; SD2008/01013/00.; SD2008/01014/00.]. Comparisons were made by calculating the ratio of EC_{50} to EIC for each of three species (see Confidential Appendix 10.2.3). For all three species, the NOEC/EIC ratios for were greater than the minimum application factor of 100, as specified for Tier 2 ecotoxicity data in the FDA Guidance Document [FDA, 1998]. Therefore, it is concluded that clinical use of Solzira™ at predicted production levels will not cause adverse effects to the environment.

7. MITIGATION MEASURES

No potentially adverse environmental impacts have been identified for the proposed action. Therefore, no mitigation measures are proposed.

8. ALTERNATIVES TO THE PROPOSED ACTION

No potentially adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of Solzira™ for the current indication will provide an important benefit to patients requiring its administration with no known adverse environmental risk.

9. LIST OF PREPARERS

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10. REFERENCES

Food and Drug Administration (FDA). *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Application.* CDER, 5600 Fishers Lane, Rockville, Maryland 20857; 1998. CMC 6, revision 1.

GlaxoSmithKline Document Number SD2008/01011/00. Study ID 1127/1702 (b) (4). Gabapentin: Assessment of the Inhibitory Effect on the Respiration of Activated Sewage Sludge. Report Date 05-Jun-2008.

GlaxoSmithKline Document Number SD2008/01015/00. Study ID 1127/1701 (b) (4). Gabapentin: Algal Growth Inhibition Test. Report Date 28-May-2008.

GlaxoSmithKline Document Number SD2008/01013/00. Study ID 1127/1700 (b) (4). Gabapentin: Acute Toxicity to Daphnia magna. Report Date 28-May-2008.

GlaxoSmithKline Document Number SD2008/01014/00. Study ID 1127/1699 (b) (4). Gabapentin: Actue Toxicity to Rainbow Trout (Oncorhynchus mykiss). Report Date 02-Jun-2008.

Food and Drug Administration (FDA). *FDA Approved Labeling Text: Neurontin (gabapentin) Capsules, Tablets and Oral Solution.* CDER, 5600 Fishers Lane, Rockville, Maryland 20857; 2005. NDA 20-235/S-29; NDA 20-882/S-15; NDA 20-219/S-16.

Yu JT, Bouwer EJ, Coelhan M. Occurrence and Biodegradability Studies of Selected Pharmaceuticals and Personal Care Products in Sewage Effluent. *Agricultural Water Management.* 2006;86:72-80.

Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. The Occurrence of Pharmaceuticals, Personal Care Products, Endocrine Disruptors and Illicit Drugs in Surface Water in South Wales, UK. *Water Research.* 2008;42:3498-3518.

GlaxoSmithKline Document Number SD2008/01415/00 Study ID 1127-1698 (b) (4). Gabapentin: Simulation Test - Aerobic Sewage Treatment: Activated Sludge Units (Porous Pot Test). Report in draft at time of writing.

APPENDICES

10.1. Non-confidential Appendices

10.1.1. Data Summary Table

Table 2 Gabapentin Data Summary Table

Physical/Chemical Properties	
Aqueous Solubility	Freely Soluble
Dissociation Constant	pKa = (b) (4)
Octanol/Water Distribution Coefficient	Dow = (b) (4), log Dow = (b) (4)
ACD clogD (calculation)	pH (b) (4) logD
Henry's Law Constant	HL = (b) (4)
Soil Adsorption (PCKOCwin)	Log Koc = (b) (4) (*calculation*)
Depletion Mechanisms	
Porous Pot Test	Primary degradation, 1%, 76 days DOC, 0 %, 76 days
[Yu, 2006] WWTP removal efficiency: Batch Biodegradation Test:	 > 99% removal Biotransformation = 90%
[Kasprzyk-Hordern, 2008] WWTP removal efficiency	 Poor (data unpublished)
Direct Photolysis	Not expected to be susceptible to direct photolysis by sunlight
Hydrolysis	Hydrolysis in the environment is not expected
Environmental Effects/Ecotoxicity	
Activated Sludge Inhibition	EC_{50} > 1,000 mg/l NOEC = 1,000 mg/l
Daphnia magna, 48 hour acute	EC_{50} > 100 mg/l NOEC = 100 mg/l
Oncorhynchus mykiss, 96 hour acute	EC_{50} > 100 mg/l NOEC = 100 mg/l
Desmodesmus subspicatus, 76 hour acute	EC_{50} > 100 mg/l NOEC = 100 mg/l

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/s/

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