

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-115**

**ENVIRONMENTAL ASSESSMENT**



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

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**Memorandum**

**Date:** April 26, 2007

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

**To:** Scott N. Goldie  
OPS/ONDQA/DPMA-1

**Through:** Jon Clark  
OPS/PARS

**Subject:** LAMICTAL<sup>®</sup> (lamotrigine) XR 25-200 mg Tablets  
Environmental Assessment Review

NDA # 022-115  
22, 2006

GlaxoSmithKline  
PO Box 13398  
Research Triangle Park  
North Carolina 27709-3398

**Background**

This environmental assessment (EA) dated October 9, 2006, supports new drug application NDA 22-115 for Lamictal<sup>®</sup> (lamotrigine) Extended Release (XR) 25-200 mg Tablets, indicated for the treatment of epilepsy and bipolar disorder.

**Review of the Current Submission**

The EA was prepared in accordance with 21 CFR Part 25 by GlaxoSmithKline, Research Triangle Park, North Carolina. The EA cross references EAs previously submitted and approved for Lamictal<sup>®</sup> Tablets (NDA 20-241) and Lamictal<sup>®</sup> Dispersible Tablets (NDA 20-764). Nomenclature, physical-chemical, and environmental fate, and environmental effects data were previously submitted for lamotrigine in the referenced EAs. No new information, except for a change in estimated predicted sales of lamotrigine and the related EIC, is

provided. This is basically the same EA as was submitted under NDA 20-241/S-027 and 20-764/S-020 (EA date: December 20, 2004). A FONSI was issued for these applications on April 8, 2005.

The sponsor estimates that in the first five years of predicted sales of Lamictal<sup>®</sup>, the highest yearly quantity of lamotrigine marketed in the United States, for all dosage forms and strengths, will be (b) (4). Using this information and the algorithm described in the FDA EA Guidance for Industry document, the Expected Introduction Concentration (EIC) of lamotrigine in the aquatic environment is estimated to be (b) (4). This value is a slight decrease from the (b) (4) value provided in the December 20, 2004, EA.

This estimate assumes that lamotrigine is not metabolized, diluted, or depleted in the environment. Therefore, the EIC equals the Maximum Expected Environmental Concentration (MEEC) at the point of introduction into the aquatic environment. It is assumed that product use is evenly distributed throughout the U.S.

Environmental effects data (EC<sub>50</sub> and NOEC) include toxicological studies in *Ceriodaphnia*, *Daphnia magna*, *Oncorhynchus mykiss* and *Selenastrum capricornutum*. Microbial growth inhibition studies and activated sludge respiration inhibition studies were also conducted. For all three species, the NOEC/MEEC ratios ranged from 5,952 to 47,619. The NOEC/MEEC ratio for activated sludge respiration was 793,650. The MIC for growth inhibition was > 185 mg/L. These ratios were greater than the minimum application factor of 100 as specified in the FDA EA guidance document.

### **Comments and Conclusions**

Based on an evaluation of the information provided in this and previous EAs for Lamictal<sup>®</sup> and in FDA guidance, no further testing is required and no adverse effects are expected from the introduction of lamotrigine into the environment due to the use of Lamictal<sup>®</sup>.

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

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**ENVIRONMENTAL ASSESSMENT**

**and**

**FINDING OF NO SIGNIFICANT IMPACT**

**for**

**LAMICTAL<sup>®</sup> (lamotrigine) XR 25 - 200 mg Tablets**

**NDA 21-115**

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

**April 26, 2007**

## **FINDING OF NO SIGNIFICANT IMPACT**

**for**

**NDA 21-115**

**LAMICTAL<sup>®</sup> (lamotrigine) XR 25-200 mg Tablets**

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 concluded that this action will not have a significant impact on the quality of the human environment. Therefore, an environmental impact statement will not be prepared.

In support of the new drug application, GlaxoSmithKline prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 that evaluates the potential environmental impacts due to use and disposal of this product. The application requests the approval of a new formulation, Lamictal<sup>®</sup> (lamotrigine) Extended Release (XR) 25-200 mg Tablets, for treating patients with epilepsy and bipolar disorders.

Lamotrigine and its metabolites may enter the aquatic environment from patient drug use and disposal. The toxicity of lamotrigine to environmental organisms (*Oncorhynchus mykiss* (rainbow trout), *Daphnia magna* (crustacean) and *Selenastrum capricornutum* (green algae)) was characterized. Activated sludge and microbial growth inhibition studies were also conducted. Results indicate that the compound and its metabolites are not expected to be toxic to aquatic organisms or to inhibit microbial activity at expected environmental introduction concentrations.

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 will be disposed of through community solid waste management systems which typically include landfills, incineration, and recycling. Minimal quantities of unused drug are expected to be disposed of through sanitary sewer systems.

The Center for Drug Evaluation and Research has concluded that this product can be used and disposed of without any expected adverse environmental impacts. 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

## ENVIRONMENTAL ASSESSMENT

LAMICTAL XR 25-200 mg Tablets

Lamotrigine

Author: \_\_\_\_\_

*Jim Ryan*

Date: \_\_\_\_\_

*9 Oct 2006*

Dr Jim J Ryan

Senior Scientist

Chemical Development

Approved: \_\_\_\_\_

*Chris Beels*

Date: \_\_\_\_\_

*9 Oct 2006*

Dr Chris Beels

Director of Developmental Strategy

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**1. DATE**

September 04, 2006

**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 requests approval to manufacture and market Lamictal Extended Release Tablets (lamotrigine) 25-200 mg. Lamictal is currently marketed for the treatment of epilepsy and bipolar disorder. This Environmental Assessment has been submitted pursuant to 21 CFR part 25.

Two environmental assessments have previously been submitted for LAMICTAL Tablets and LAMICTAL® Chewable Dispersible Tablets [GCPV/91/0005/01; GCPV/05/0006/00]. The applicable NDA numbers are NDA 20-241 and NDA 20-764. A Finding of No Significant Impact was issued on 14 December 1998

**4.2. Need for Action**

Lamictal (lamotrigine) is an antiepileptic drug (AED) of the phenyltriazine class, and is chemically unrelated to existing AEDs. It has been approved in combination with other AEDs (called adjunctive therapy) by the U.S. Food and Drug Administration (FDA), as well as for stand-alone medication (also called "monotherapy") for adults. In placebo controlled clinical studies it has been shown to be favorably tolerated and it is highly effective in reducing seizure frequency in patients with partial seizures, primary generalized tonic-clonic seizures, and the generalized seizures of Lennox-Gastaut syndrome.

This NDA, which requests approval of a new formulation, will result in increased use of drug substance. Accordingly this environmental assessment has been prepared to take account of the environmental impact anticipated by this action.

#### **4.3. Locations of Use**

Lamictal XR 25-200 mg Tablets 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. Minimal quantities of unused drug product may be disposed of in the sanitary sewer system.

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

#### **5.1. Nomenclature**

Lamictal contains the active moiety (API) lamotrigine. The environmental studies reported herein were conducted with lamotrigine.

##### **5.1.1. Established Name (U.S.Adopted Name-USAN)**

Lamotrigine

##### **5.1.2. Brand/Proprietary Name/Tradename**

Lamictal

##### **5.1.3. Chemical Names**

###### **5.1.3.1. Chemical Abstracts (CA) Index Name (inverted form)**

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

###### **5.1.3.2. Systematic Chemical Name (uninverted form)**

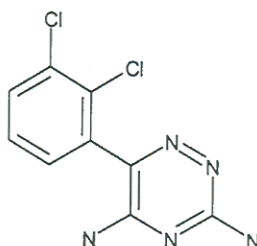
6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine

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

CAS Number: 84057-84-1

**5.3. Molecular Formula** $C_9H_7N_5Cl_2$ **5.4. Molecular Weight**

256.09

**5.5. Structural Formula****6. ENVIRONMENTAL ISSUES****6.1. Metabolism**

Information in this section remains unchanged from the information in Section 7a of the original environmental assessment document provided in previous LAMICTAL® (lamotrigine) Tablets NDA applications 20-241 and 20-764 [GCPV/91/0005/01; GCPV/05/0006/00].

**6.2. Physical/Chemical Properties**

Reference is made to physical/chemistry data provided in Section 7b of the original environmental assessment document provided in previous LAMICTAL® (lamotrigine) Tablets NDA 20-241 and LAMICTAL® Chewable Dispersible Tablets NDA 20-274 [GCPV/91/0005/01; GCPV/05/0006/00]. In addition to these previously existing data, a sorption study onto sludge was conducted and the distribution coefficient ( $K_b$ ) was estimated [SD2004/02163/00].

Based on a low sludge distribution coefficient, lamotrigine has limited affinity for organic material. It is likely that lamotrigine will amass in the aquatic compartment, a conclusion consistent with previous EAs.

**6.2.1. Aqueous Solubility**

Water solubility = 0.17 g/L

**6.2.2. Dissociation Constant(s)**

pKa = 5.7

**6.2.3. Octanol/Water Distribution Constant**

Log Dow (pH 7) = 1.4

**6.2.4. Henry's Law Constant**

Henry Law's Constant (estimate) = 2.2E-11 atm-l/mole

**6.2.5. Activated Sludge Adsorption**

Distribution Coefficient  $K_b$  = 14

**6.3. Environmental Depletion Mechanisms**

Reference is made to environmental depletion data provided in section 7b of the original environmental assessment document provided in previous LAMICTAL® (lamotrigine) Tablets NDA 20-241 and LAMICTAL® Chewable Dispersible Tablets NDA 20-274 applications [GCPV/91/0005/01; GCPV/05/0006/00]. In addition to these previously existing data, an inherent biodegradability study (Zahn-Wellens), under high total suspended solids, was conducted using lamotrigine [SD2004/02162/00]. Lamotrigine does not classify as inherently biodegradable under the conditions of the test. A demonstrable mechanism for environmental depletion has not been identified, although direct exposure to UV radiation may result in photodegradation.

**6.4. Ecotoxicology**

Reference is made to ecotoxicological data provided in section 8 of the environmental assessment documents provided in previous LAMICTAL® (lamotrigine) tablets and LAMICTAL® Chewable Dispersible Tablets NDA applications [GCPV/91/0005/01; GCPV/05/0006/00]. In addition to these previously existing data, aquatic ecotoxicity studies were conducted with lamotrigine using the following test organisms: *Selenastrum capricornutum* (algae), *Daphnia magna* (invertebrate) and *Oncorhynchus mykiss* (fish) [SD2004/02159/00; SD2004/02160/00; SD2004/02161/00]. Results are summarized in Table 1.

**Table 1      Summary of Lamotrigine Acute Ecotoxicity Data**

| Species                                        | Duration | EC <sub>50</sub> |
|------------------------------------------------|----------|------------------|
| <i>Selenastrum capricornutum</i> (green algae) | 72 hours | 39.7 mg/L        |
| <i>Daphnia magna</i> (crustacean)              | 48 hours | 56 mg/L          |
| <i>Oncorhynchus mykiss</i> (rainbow trout)     | 96 hours | 85 mg/L          |

### 6.5.      Environmental Concentrations

Five year forecasts of expected production volumes of lamotrigine have been revised as a result of this new formulation and the calculated expected introductory concentration is greater than 1 part per billion threshold. Calculations of the Expected Introduction Concentration (EIC) and Expected Environmental Concentration (EEC) of lamotrigine are included as confidential information in Confidential Appendix 11.2.1. EIC was calculated based on the revised maximum annual projected amount of drug substance needed to support all Lamictal dosage forms for the next five years [FDA, 1998]. As lamotrigine is expected to persist in the environment, the EIC, conservatively, will be considered equal to the maximum expected environmental concentration MEEC [FDA, 1998].

### 6.6.      Environmental Risk Assessment

The potential risk of adverse environmental effects resulting from the clinical use of all Lamictal dosage forms was re-assessed by comparing the EIC (the greater of EEC and EIC) with experimental ecotoxicity data for lamotrigine. Acute EC<sub>50</sub> and NOEC values were obtained for organisms representing three trophic levels: *Selenastrum capricornutum* (algae), *Daphnia magna* (invertebrate), and *Oncorhynchus mykiss* (fish). Comparisons were made by calculating, conservatively, the ratio of NOEC to MEEC for each of three species (see Confidential Appendix 11.2.2).

For all three species, the NOEC/MEEC ratios for all three species 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 lamotrigine 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 LAMICTAL Extended Release 25-200 mg Tablets for the new formulation 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 GCPV/05/0006/00 Study ID EA. Lamictal (lamotrigine) Dispersible Chewable Tablets Supplemental Environmental Assessment Information, NDA 20-241 and NDA 20-764, FONSI date 14 Dec 1998. Report Date 31-03-1995.

GlaxoSmithKline Document Number GCPV/91/0005/01 Study ID EA. Lamictal Environmental Assessment Information Document, NDA 20-240, FONSI date 14-Dec-1998. Report Date 22-01-1993.

GlaxoSmithKline Document Number SD2004/02159/00 Study ID 03-0200/B (Brixham Environmental laboratory). Lamotrigine: Determination of Acute Toxicity to *Daphnia magna*. Report Date 01-07-2004.

GlaxoSmithKline Document Number SD2004/02160/00 Study ID 03-0200/C (Brixham Environmental laboratory). Lamotrigine: Determination of Toxicity to the Green Algae *Selenastrum capricornutum*. Report Date 01-08-2004.

GlaxoSmithKline Document Number SD2004/02161/00 Study ID 03-0200/D (Brixham Environmental laboratory). Lamotrigine: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*). Report Date 01-08-2004.

GlaxoSmithKline Document Number SD2004/02162/00 Study ID 03-0200/E (Brixham Environmental laboratory). Lamotrigine: Determination of Inherent Biodegradability (Zahn-Wellens test). Report Date 01-10-2004.

GlaxoSmithKline Document Number SD2004/02163/00 Study ID 03-0200/F (Brixham Environmental laboratory). Lamotrigine: Determination of Adsorption onto Activated Sludge (batch test). Report Date 01-10-2004.

## 11. APPENDICES

### 11.1. Non-Confidential Appendices

#### 11.1.1. Data Summary Table

**Table 2 Lamotrigine Data Summary Table**

| Physical/Chemical Properties           |                                                                                          |
|----------------------------------------|------------------------------------------------------------------------------------------|
| Aqueous Solubility                     | Distilled water = 170 mg/L                                                               |
| Dissociation Constant                  | pKa = 5.7                                                                                |
| Octanol/Water Distribution Coefficient | Dow = 25.12, log Dow = 1.4                                                               |
| Henry's Law Constant (estimate)        | VP = 2.2E-11 atm·l/mol                                                                   |
| Sludge Adsorption Biomass              | K <sub>b</sub> = 14                                                                      |
| Depletion Mechanisms                   |                                                                                          |
| Aerobic Biodegradation in water        | Not Readily Biodegradable                                                                |
| Inherent Biodegradation                | Not Inherently Biodegradable                                                             |
| Direct Photolysis                      | Adsorption maximum at 300nm (pH 6)                                                       |
| Hydrolysis                             | t <sub>1/2</sub> > 1 year                                                                |
| Environmental Effects/Ecotoxicity      |                                                                                          |
| Activated Sludge Inhibition            | EC <sub>50</sub> = > 1000 mg/L<br>NOEC = 1000 mg/L                                       |
| Microbial Growth Inhibition Test       | MIC > 185 mg/L                                                                           |
| <i>Daphnia magna</i> , 48 hour acute   | EC <sub>50</sub> = 56 mg/L<br>NOEL = 30 mg/L                                             |
| <i>Ceriodaphnia</i> , 7 day            | EC <sub>50</sub> (immobilisation) > 10 mg/L<br>EC <sub>50</sub> (reproduction) > 10 mg/L |

|                                                  |                                                                                                                              |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
|                                                  | LOEC > 10 mg/L<br>NOEC = 10 mg/L                                                                                             |
| <i>Oncorhynchus mykiss</i> , 96 hour acute       | EC <sub>50</sub> = 85 mg/L<br>NOEC = 60 mg/L                                                                                 |
| <i>Selenastrum capricornutum</i> , 96 hour acute | E <sub>b</sub> C <sub>50</sub> = 39.7 mg/L<br>NOEC = 7.5 mg/L<br>E <sub>r</sub> C <sub>50</sub> = 70.6mg/L<br>NOEC = 15 mg/L |

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/s/

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