CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

	Department of Health and Human Services **Public Health Service** **Food and Drug Administration** **Center for Drug Evaluation and Research** **Office of Surveillance and Epidemiology**
Date:	March 16, 2009
To:	Russell Katz, M.D., Director Division of Neurology Products (DNP)
Through:	Claudia Karwoski, Pharm.D., Director (Acting) Division of Risk Management (DRISK)
From:	**Scientific Lead:** Elizabeth Donohoe, M.D., Drug Risk Management Analyst, DRISK Team: Suzanne Berkman, Pharm.D., Senior Drug Risk Management Analyst and (Acting) Team Leader, DRISK Mary Dempsey, Risk Management Program Coordinator, DRISK LaShawn Griffiths, MSHS-PH, BSN, RN, Patient Labeling Review DRISK Cathy Miller, MPH, BSN, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA) Kellie Taylor, Pharm D., Safety Evaluator Team Leader, DMEPA
Subject:	Review of the Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name:	Lamictal (lamotrigine)
Application Type/Number:	NDA 22-251 (Orally Disintegrating Tablets; ODT); pending approval NDA 22-115 (Extended Release Tablets; XR); pending approval NDA 20-241 (Tablets) NDA 20-764 (Chewable Dispersible Tablets)
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2009-85 (REMS) 2009-131 (Carton and Container Labeling)

1 INTRODUCTION AND BACKGROUND

This review follows a request from the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review and comment on the proposed Risk Evaluation Mitigation Strategy (REMS) of the following:

- Lamictal (lamotrigine) NDA 22-251 (Orally Disintegrating Tablets; ODT); pending approval
- Lamictal (lamotrigine) NDA 22-115 (Extended Release Tablets; XR); pending approval
- Lamictal (lamotrigine) NDA 20-241 (tablets)
- Lamictal (lamotrigine) NDA 20-764 (Chewable Dispersible Tablets)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) (section 505-1(a)(2)) for an approved drug based upon new safety information that becomes available after the approval of the drug.

An FDA meta-analysis of clinical trial data for 11 anti-epileptic drugs (AEDs) demonstrated an increased risk of suicidal thoughts and behavior. The FDA concluded that patients receiving these drugs had "approximately twice the risk of suicidal behavior or ideation compared to patients receiving placebo". In addition, the FDA stated that the results were "generally consistent among the eleven drugs". The FDA considered this new analysis to be "new safety information" under the Food and Drug Administration Amendments Act of 2007 (FDAAA). By letter dated December 16, 2008, FDA advised that this new safety information be included in the labeling of all 11 AEDs.

In addition, the Sponsors were informed that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. The Sponsors were given 30 days to submit a REMS proposal.

The necessary elements of the REMS include a Medication Guide (MG) and a timetable for assessment.

Please note that Lamictal ODT and XR have not been approved. However, because this REMS was required for the entire AED class, once approved, Lamictal ODT and XR will need to comply and have submitted REMS accordingly.

2 MATERIAL REVIEWED

1. Lamictal (lamotrigine) NDA 22-251 (Orally Disintegrating Tablets); pending approval	o Proposed REMS and REMS Supporting Document submitted December 18, 2008
2. Lamictal (lamotrigine) NDA 22-115 (Extended Release Tablets; XR); pending approval	o Proposed REMS and REMS Supporting Document submitted February 4, 2009
3. Lamictal (lamotrigine) NDA 20-241	o Proposed REMS and REMS Supporting

(Tablets)	Document submitted January 15, 2009
4. Lamictal (lamotrigine) NDA 20-764 (Chewable Dispersible Tablets)	○ Proposed REMS and REMS Supporting Document submitted January 15, 2009

3 PROPOSED REMS

3.1 Goal

The Sponsor has proposed the following REMS goal for Lamictal products:

> *The goal of this REMS is to* (b) (4) *of Lamictal [specific formulation].*

The primary purpose for requiring this REMS is to communicate the serious risks associated with anti-epileptic products to patients, specifically increased risk of suicidal thoughts and behavior, through the use of a Medication Guide. Therefore, we recommend a generalized REMS goal to unify the AED REMS, as a class as follows:

> *The goal of the REMS is to inform patients of the serious risks associated with Lamictal, particularly the increased risk of suicidal thoughts and behavior.*

3.2 REMS Elements

The REMS includes a Medication Guide and a timetable for assessment with the information needed for assessment. Each element is described below and a formatted REMS proposal is presented in Appendix A.

3.2.1 Medication Guide

The Lamictal labeling components were reviewed for compliance with 21 CFR 208.24(d) and (e).

Comments on the Medication Guide will be provided in a separate review by DRISK patient labeling reviewer.

Please see DMEPA comments in Appendix B.

3.2.2 Communication Plan

A communication plan is not required as a component of the proposed REMS.

3.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

3.2.4 Implementation System

An implementation system is not a required component of the proposed REMS if there are no elements to assure safe use.

3.3 Assessment of the REMS

The Sponsor will submit a REMS assessment at 18 months, 3 years, and 7 years following REMS approval. The sponsor will submit assessment within 60 days of the noted time intervals.

Information needed for assessment is not a required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS Supporting Document.

The December 16, 2008 letter states that information needed for assessment will include but is not be limited to:

a. A survey of patients' understanding of the serious risks of Lamictal products.

   The sponsor failed to submit a patient survey. The sponsor states in "Information Needed for Assessments" in the Supporting Document that "GSK will provide by separate correspondence our proposed plan to address this requirement."

   We recommend the Sponsor submit a complete description of methodology and the instruments used to measure patient's understanding of the risks and safe use of the Lamictal products to FDA 60 days prior to conducting the survey as outlined in Section 4.

b. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The sponsor states in "Information Needed for Assessments" in the Supporting Document that it is their position that "assessments described in items 'b' and 'c' are legally unfounded [and]….it is also practically unnecessary to conduct…because the products are distributed in unit-of-use packaging to which the Medication Guide will be attached". In the instances that the product is not unit-of-use (Chewable Dispersible Tablets, Tablet), the sponsor proposes to provide a specific number of copies of the Medication Guide with each bottle/container.

The sponsor further states that they propose to be excluded from "b and c" for all the Lamictal products regardless of packaging.

In absence of "unit of use" packaging, we recommend that the sponsor comply with the information needed for assessment as outlined in the REMS Request letter.

4 CONCLUSION AND RECOMMENDATIONS

The Division of Risk Management in the Office of Surveillance and Epidemiology finds the proposed REMS acceptable with the following revisions below and acceptance of the track changes to the REMS template provided in Appendix A. Specifically:

4.1 Recommendations to DNP

1. Goal: We recommend changing the REMS goal as noted above to unify the entire AED class.
2. We recommend DNP incorporate the following language regarding the information needed to assess the effectiveness of the REMS into the approval letter:

    a. A survey of patients' understanding of the serious risks of Lamictal.

    b. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

    c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

4.2 Recommendations to Sponsor

1. Goal: We recommend changing the REMS goal as noted above to unify the entire AED class.
2. Medication Guide

    Please see the tables provided in Appendix B for complete DMEPA comments organized by the specific product.
3. Timetable for Assessment and Information needed for assessment

    The December 16, 2008 letter suggests the following to assess your REMS:

    a. A survey of patients' understanding of the serious risks of Lyrica
    b. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
    c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

    Your submission states that the assessments described in "b" and "c" above are unnecessary because the products are distributed in unit-of-use packaging that contains the Medication Guide. We agree that since the Medication Guide is packaged with the product, you do not need to address distribution and dispensing of the Medication Guide in your REMS assessment.

For the Lamictal products that are not unit of use, you must assess whether patients are receiving the Medication Guide. This requirement stems not from Part 208 of the regulations, but rather from 505-1(d) of FDAAA which requires that the sponsor assess the strategy at designated intervals. When requiring a Medication Guide through a REMS, the strategy is to mitigate the risks of the drug through the use of a Medication Guide that patients both understand and receive. Therefore, each assessment must include information on whether patients understand the information in the Medication Guide as well as the distribution and dispensing of the Medication Guide.

4. Patient Survey

   Submit for review all methodology and instruments used to measure patient's understanding of the risks and safe use of Lamictal. This should include, *but not be limited to*:

   - Sample size and confidence interval associated with that sample size
   - How the sample will be determined (selection criteria)
   - The expected number of patients surveyed
   - How the participants will be recruited
   - How and how often the surveys will be administered
   - Explain controls used to minimize bias
   - Explain controls used to compensate for the limitations associated with their methodology
   - The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.
   - Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.

   We recommend the Sponsor submit a complete description of methodology and the instruments used to measure patient's understanding of the risks and safe use of the Lamictal products to FDA 60 days prior to conducting the survey.

5. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. Please paginate the document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single WORD document.

APPENDICES

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: REMS-_____

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/s/

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3/16/2009 03:34:28 PM
DRUG SAFETY OFFICE REVIEWER

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3/16/2009 04:35:37 PM
DRUG SAFETY OFFICE REVIEWER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF NEUROLOGY PRODUCTS

M E M O R A N D U M

DATE: December 23, 2008

TO: File, NDA 22-251/Lamictal ODT (lamotrigine) Orally Disintegrating Tablets

FROM: Russell Katz, MD, Director, Division of Neurology Products

RE: Risk Evaluation and Mitigation Strategy (REMS)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Lamictal ODT outweigh its risks of increased risk of suicidal thoughts and behavior. In reaching this determination, we considered the following:

A. Lamictal ODT will be approved for the following indications: adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut Syndrome, primary generalized tonic-clonic seizures in adults and pediatric patients ≥2 years of age, and bipolar I disorder. While

it is not possible to estimate the size of the population likely to use Lamictal ODT, the age-adjusted prevalence of epilepsy in developed countries is 4 to 8 per 1,000. It is estimated that approximately three million people in the United States have epilepsy. Lennox-Gastaut Syndrome accounts for approximately 4% of all epilepsy cases in the pediatric population. Although the true prevalence of bipolar disorder is uncertain, the lifetime prevalence of bipolar disorder has traditionally been estimated to be approximately one percent.

B. Seizure disorder and bipolar I disorder are both associated with substantial morbidity and an increased risk of mortality. Both diseases are treatable to some extent with medication, but the underlying disease is chronic and is non-curable.

C. Lamotrigine has been shown to reduce seizure frequency in patients with partial seizures, Lennox-Gastaut Syndrome, and primary generalized tonic-clonic seizures. Lamotrigine has been shown to delay the time to occurrence of a mood episode when used as maintenance treatment in patients with bipolar I disorder. Because it is bioequivalent to Lamictal (lamotrigine), it is expected that Lamictal ODT will confer the same benefits.

D. Lamictal ODT will be used as chronic therapy in patients who obtain a clinical response.

E. A known serious risk of lamotrigine is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The anti-epileptic drugs (AEDs), a class of which Lamictal ODT is a member, have been found (in a meta-analysis of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs) to increase the risk of suicidal thoughts and behavior. In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66). 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use. Lamotrigine had an odds ratio for suicidal behavior or ideation of 2.08 (95% CI: 1.03,4.40) in the meta-analysis.

   The background incidence of suicide in patients with both epilepsy and bipolar disorder is estimated as being higher than the incidence of suicide in the general population. In patients with bipolar disorder, the estimated rate of suicide is 0.40% per year (compared to the international general population average of 0.017% per year); the standardized mortality ratio is estimated to be 22. Estimates of the incidence of suicide in patients with epilepsy vary widely, but studies have consistently indicated a higher incidence of suicide (and suicide attempts) in patients with epilepsy.

F. Lamictal ODT contains lamotrigine and is not a new molecular entity (NME).

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Lamictal ODT, poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for

patients' safe and effective use of Lamictal ODT. FDA has determined that Lamictal ODT is a product that has serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Lamictal ODT.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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/s/

Jackie Ware
12/24/2008 07:37:08 AM
CSO

Russell Katz
12/24/2008 09:15:52 AM
MEDICAL OFFICER