

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-115

**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 25, 2009

To: Russell Katz, M.D. Director
Division of Neurology Products

Through: Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Product Information Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide),

Drug Names;
Application Type and
Number; Applicant:

- Lyrica (pregabalin); NDA 21-446; Pfizer, Inc.
- Keppra (levetiracetam); NDA 21-035; UCB Pharma, Inc.
- Zonegran (zonisamide); NDA 20-789; Eisai Medical Research, Inc.
- Lamictal (lamotrigine); NDA 22-251, NDA 22-115, NDA 20-241, NDA 20-764; GlaxoSmithKline
- Topamax (topiramate); NDA 20-505; Ortho-McNeil-Janssen Pharmaceuticals, Inc.

OSE RCM #: 2009-85

1 INTRODUCTION

- Pfizer, Inc. submitted a New Drug Application (NDA 21-446) for Lyrica (pregabalin) capsules on October 30, 2003.
- UCB Pharma, Inc. submitted a New Drug Application (NDA 21-035) for Keppra (levetiracetam) tablets and oral solution on February 1, 1999.
- Eisai Medical Research, Inc. submitted a New Drug Application (NDA 20-789) for Zonegran (zonisamide) capsules on March 19, 1997.
- GlaxoSmithKline, submitted a New Drug Application
 - (NDA 22-251) for Lamictal (lamotrigine) Orally Disintegrating tablets on November 28, 2007 pending approval.
 - (NDA 22-115) for Lamictal (lamotrigine) Extended Release tablets; XR on November 22, 2006 pending approval.
 - (NDA 20-241) for Lamictal (lamotrigine) tablets on September 16, 2006.
 - (NDA 20-764) for Lamictal (lamotrigine) Chewable Dispersible tablets on September 16, 2006.

FDA has determined that Lyrica (pregabalin), Keppra (levetiracetam), Zonegran (zonisamide), Lamictal (lamotrigine), and Topamax (topiramate) pose 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. FDA has determined that Lyrica (pregabalin), Keppra (levetiracetam), Zonegran (zonisamide), Lamictal (lamotrigine), and Topamax (topiramate) are products with a serious a significant public health concern that meet one of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: these products have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use.

In a letter dated December 16, 2008 the Division of Neurology Products (DNP) informed the sponsors that a REMS is necessary for Lyrica (pregabalin), Keppra (levetiracetam), Zonegran (zonisamide), Lamictal (lamotrigine), and Topamax (topiramate). The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management to review the sponsors' proposed Medication Guides (MG). A review of the sponsors' proposed REMS was completed by DRISK under a separate cover.

2 MATERIAL REVIEWED

- Draft LYRICA (pregabalin) Medication Guide (MG) submitted on January 14, 2009, revised by DNP, and provided to DRISK on March 2, 2009
- Draft KEPPRA (levetiracetam) Medication Guide (MG) submitted on January 15, 2009, revised by DNP, and provided to DRISK on March 3, 2009
- Draft ZONEGRAN (zonisamide) Medication Guide (MG) submitted on January 15, 2009, revised by DNP, and provided to DRISK on March 11, 2009

- Draft LAMICTAL (lamotrigine) Medication Guide (MG) submitted on December 24, 2008, revised by DNP, and provided to DRISK on March 3, 2009
- Draft TOPAMAX (topiramate) Medication Guide (MG) submitted on January 16, 2009, revised by DNP, and provided to DRISK on March 3, 2009

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

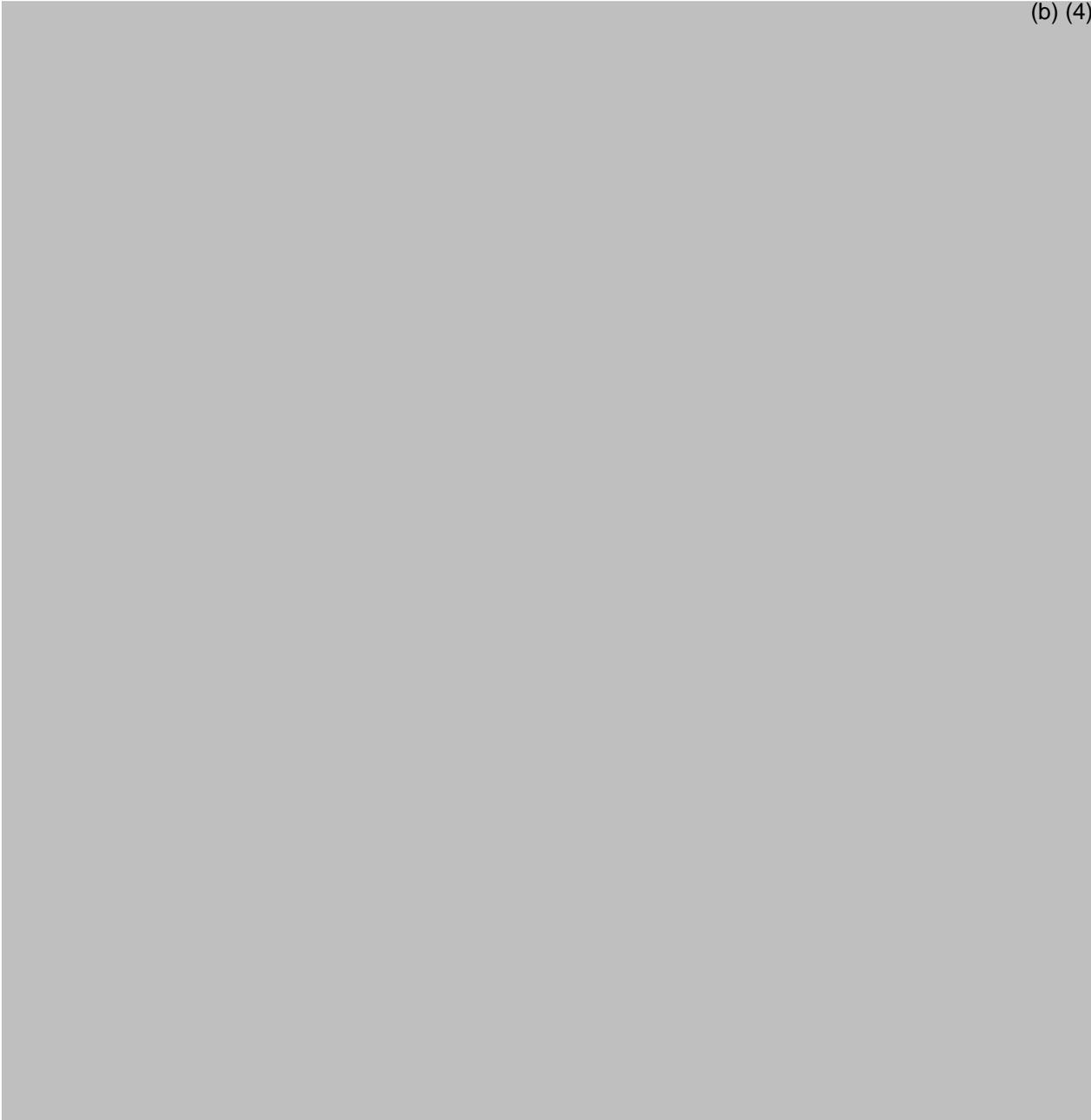
We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

1. In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We recommend that the Sponsor reformat the Medication Guides using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.
2. To enhance patient comprehension, materials should be written at a 6th to 8th grade Flesch Kinkaid reading level, and have a Flesch Reading Ease score of at least 60% (60% corresponds to an 8th grade reading level).

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LAMICTAL (lamotrigine)

DRAFT Lamictal Medication Guide reading scores:

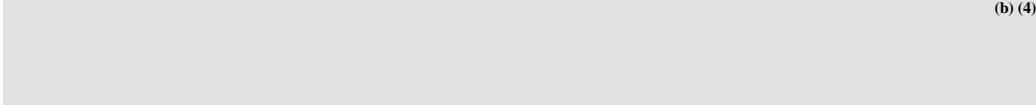
Flesch Reading Ease: 51.0%

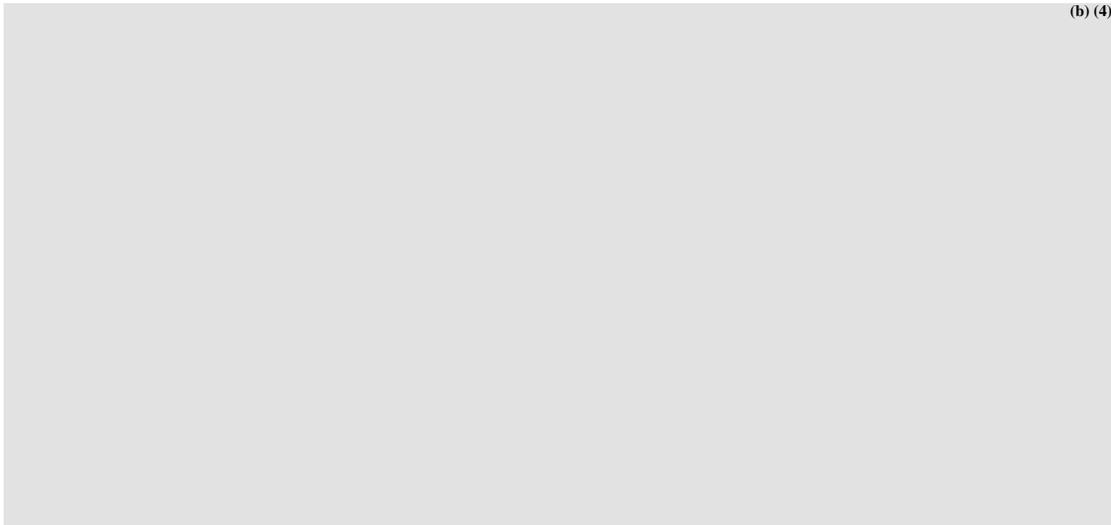
Flesch-Kincaid Grade Level: 9.5

Our revised scores are:

Flesch Reading Ease: 55.6%

Flesch-Kincaid Grade Level: 8.7

- 1) If the Orally Disintegrating Tablets formulation is approved, it should be added to this Medication Guide so that there is one Medication Guide for all formulations of the product. Information should be added to the various sections of the Medication Guide as appropriate, including *but not limited to* the “How should I take” section, and the “ingredients” section.
- 2) The heading “Patients prescribed Lamictal have sometimes been given the wrong medicine because many medicines have names similar to Lamictal, so always check that you receive Lamictal” and the following information regarding tablet pictures, wording, colors, and shapes was removed. The purpose of patient information is to enhance appropriate use and provide important information to patients about medicines. The above information is risk management that should be done at the pharmacy. All pictures have been removed because this information is not information that is usually included in patient information. However, DDMAC feels that this information is important and should be conveyed to the patient. If there is something specific to this medication versus other medications that a patient should know about to prevent medication errors, the Review Division should clarify and change as appropriate, while ensuring that the Medication Guide is consistent with the PI.
- 3)  (b) (4)
- 4) In the section “How should I take Lamictal?” the statement, “Swallow Lamictal tablets whole.  (b) (4) implies that it is alright to chew Lamictal tablets if you can tolerate the taste. The Review Division should clarify if the tablet should be swallowed whole for effectiveness, or if it is simply because of the bitter taste.
- 5) In the section “How should I store Lamictal?” the Review Division should clarify if the storage instructions are the same for all formulations.
- 6) In the section “How should I store Lamictal?” a temperature range was added from the PI.



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/s/

Mary Dempsey
3/31/2009 03:58:02 PM
DRUG SAFETY OFFICE REVIEWER

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4/2/2009 01:40:26 PM
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Jodi Duckhorn
4/2/2009 01:59:30 PM
DRUG SAFETY OFFICE REVIEWER

	<p>Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology</p>
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:	<p>Scientific Lead: Elizabeth Donohoe, M.D., Drug Risk Management Analyst, DRISK</p> <p>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</p>
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	○ Proposed REMS and REMS Supporting Document submitted December 18, 2008
2. Lamictal (lamotrigine) NDA 22-115 (Extended Release Tablets; XR); pending approval	○ Proposed REMS and REMS Supporting Document submitted February 4, 2009
3. Lamictal (lamotrigine) NDA 20-241	○ Proposed REMS and REMS Supporting

(Tablets)	Document submitted January 15, 2009
4. Lamictal (lamotrigine) NDA 20-764 (Chewable Dispersible Tablets)	o 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 communicate the risks 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

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/s/

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

Claudia Karwoski
3/16/2009 04:35:37 PM
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