DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA XX-XXX

[Sponsor Contact]

Dear [Sponsor Representative]:

Please refer to your new drug application (NDA) for [Insert AED Tradename]® (Insert AED established name) [capsules/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 make safety labeling changes (section 505(o)(4) of the FDCA) and 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. These provisions took effect on March 25, 2008.

Since [Insert AED Tradename] was approved in [Insert year of AED approval], we have become aware of new safety information indicating an increased risk of suicidal thoughts and behavior with antiepileptic drugs (AEDs), including [Insert AED Tradename]. An increased risk of suicidal thoughts and behavior was demonstrated in an FDA meta-analysis (dated May 23, 2008) of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs. 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); the estimated incidence of suicidal behavior or ideation was 0.43% among 27,863 drug-treated patients and 0.24% among 16,029 placebo-treated patients. 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 AEDs regardless of indication of use. We consider this new analysis to be "new safety information" as defined in FDAAA.

The FDA's findings regarding AEDs and suicidal thoughts or behaviors were discussed at a joint Peripheral and Central Nervous System Drugs/Psychopharmacologic Drugs Advisory Committee Meeting on July 10, 2008. The Committee voted in favor of adding a section pertaining to this risk to the *Warnings* section of the prescribing information of all AEDs; the Committee also voted in favor of requiring a Medication Guide for all AEDs to inform patients of this increased risk.

After considering all relevant information, including the new safety information, we believe that the new safety information should be included in the labeling of [Insert AED Tradename], and

we have determined that a REMS is necessary for the drug to ensure that the benefits of [Insert AED Tradename] outweigh the risks. These requirements are described more fully below.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, you must add the following safety-related language to the labeling for [Insert AED Tradename] in the specified sections:

WARNINGS (or WARNINGS and PRECAUTIONS for PLR labels)

Suicidal Behavior and Ideation
Antiepileptic drugs, including [Insert AED Tradename], increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.
Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing [Insert AED Tradename] or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

PRECAUTIONS - Information for Patients
Patients should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking [Insert AED Tradename]. Patients should be instructed to take [Insert AED Tradename] only as prescribed.

Suicidal Thinking and Behavior - Patients, their caregivers, and families should be counseled that AEDs, including [insert AED Tradename], may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

MEDICATION GUIDE

In addition to the changes described above to the labeling, you should submit a proposed Medication Guide for this product. Enclosed is a draft Medication Guide that contains what we

consider to be the necessary information to inform patients of the increased risk for suicidal thoughts and behavior. Pursuant to 21 CFR Part 208 and 505-1(e)(2), FDA has determined that [Insert AED Tradename] poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of [Insert AED Tradename]. FDA has determined that [Insert AED Tradename] has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use this product.

Currently, some AEDs have a Patient Package Insert while others do not. If your AED labeling includes a Patient Package Insert, the information that is contained in the Patient Package Insert should be updated and presented in the Medication Guide format and integrated into the Medication Guide that we are requiring to inform patients of the increased risk for suicidal thoughts and behavior with [Insert AED Tradename].

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior-approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

Include labeling in both Microsoft Word format and content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at: http://www.fda.gov/oc/datacouncil/spl.html.

Use the following designators to prominently label all submissions, including supplements, relating to this safety label change as appropriate:

Safety Labeling Changes under 505(o)(4)

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In accordance with section 505-1(a) of the FDCA, we have determined that a REMS is necessary for [Insert AED Tradename] to ensure that the benefits of the drug outweigh the risks based on the new safety information described above.

Your proposed REMS must contain the following:

- **Medication Guide**: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. The approved Medication Guide submitted as a safety labeling change, noted above, will be considered part of the REMS in accordance with 505-1(a). Under 21 CFR 208 and 505-1(e)(2), you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed [Insert AED Tradename]. Under 21 CFR 208.24(d), you are also responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided.

- **Timetable for Assessment:** The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than at 18 months, 3 years, and 7 years after the REMS is approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

In accordance with section 505-1(a), within 30 days of the date of this letter, you must submit a prior-approval supplement containing your proposed REMS.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information about [Insert AED Tradename] (see Appendix A). Include information in the template that is specific to your proposed REMS for [Insert AED Tradename]. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include the following:

a. An evaluation of patients' understanding of the serious risks of [Insert AED Tradename]
b. A report on periodic assessments 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

Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA [Insert AED NDA number] PROPOSED REMS

OTHER LABELING CHANGES

Although not a part of the safety labeling changes or REMS that we are requiring under sections 505(o)(4) and 505-1(a)(2) of the FDCA as described above, the safety of anticonvulsant exposure during pregnancy is of continuing concern to the FDA. Unfortunately, the quality of data is suboptimal. To help improve these data, and advance our understanding of potential risks, we request that all anticonvulsant labeling contain a statement that informs physicians to advise pregnant patients who are taking anticonvulsants to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

We ask you to examine your labeling; if information on the NAAED Pregnancy Registry is not already present, we request that you add the following language to the Pregnancy and Information for Patients (or Patient Counseling Information, if the labeling is in the new PLR

format) sections. If you already have a single drug registry established that is mentioned in the prescribing information, you should add the information about the NAAED Registry to that information.

For Pregnancy section:

To provide information regarding the effects of in utero exposure to [Insert AED Tradename], physicians are advised to recommend that pregnant patients taking [Insert AED Tradename] enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

For Information for Patients/Patient Counseling Information section:

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see XX section).

If the label is in PLR format, please also include the following statement at the end of the Pregnancy subsection: "Pregnancy registry available."

ADMINISTRATIVE

We note that we have requested you to submit three supplements within this letter. You may submit one prior-approval supplement containing both the safety labeling changes and the proposed REMS. The language advising pregnant patients who are taking anticonvulsants to enroll in the NAAED Pregnancy Registry may be submitted at the same time that you submit the labeling supplement 'Safety Labeling Changes under 505(o)(4)' and the 'NEW SUPPLEMENT FOR NDA [Insert AED NDA Number] PROPOSED REMS'; however, please include another designator prominently labeling that you are also submitting, 'Other Labeling Changes RE: Addition of NAAED Pregnancy Registry information'. Alternatively, you may submit labeling containing the NAAED Pregnancy Registry information within 60 days of the date of this letter, in a separate submission, which should also be prominently labeled to indicate the following: 'Labeling Changes RE: Addition of NAAED Pregnancy Registry information'.

Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made

If you have any questions, call Tamy Kim, PharmD, Safety Regulatory Project Manager, at 301-796-1125.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD

Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Medication Guide
Appendices A and B

Medication Guide

[Insert AED Tradename] (Insert phonetic spelling)

([Insert AED established name])

[Insert AED Tradename] and Suicidal Thoughts or Actions

Read this Medication Guide before you start taking [Insert AED Tradename] and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. This Medication Guide is only about the risk of suicidal thoughts and actions with [Insert AED Tradename]. [Note: If you currently have a PPI and are integrating information from that PPI into the Medication Guide, please delete the last sentence].

What is the most important information I should know about [Insert AED Tradename]?

1. **[Insert AED Tradename] may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

2. **Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**
   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

3. **Do not stop [Insert AED Tradename] without first talking to a healthcare provider.**
   - Stopping [Insert AED Tradename] suddenly can cause serious problems.
   - Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

4. **How can I watch for early symptoms of suicidal thoughts and actions?**
   - Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled.

- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

What else should I know about [Insert AED Tradename]?

- **[Insert AED Tradename] has other side effects.** For more information ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you.

  Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

- **[Insert AED Tradename] can interact with other medicines.** Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Using [Insert AED Tradename] with certain other medicines can affect each other causing side effects.

  Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without first talking with your healthcare provider.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use [Insert AED Tradename] for a condition for which it was not prescribed. Do not give [Insert AED Tradename] to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about [Insert AED Tradename]. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about [Insert AED Tradename] that is written for health professionals.

For more information, go to www. [Insert AED Tradename].com or call 1-800-XXX-XXXX

Issued [Insert Month Year]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

[Insert Sponsor contact information]

Appendix A- REMS Template

<<If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.>>

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:
Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Assessment of the REMS

4. Information Needed for Assessments

5. Other Relevant Information