CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

DATE:	January 28, 2011
NDA #:	NDA 22-544
PRODUCT:	Gralise (gabapentin) Tablets
APPLICANT:	Abbott
FROM:	Ellen Fields, M.D., M.P.H. Clinical Team Leader
THROUGH:	Bob Rappaport, M.D. Division Director, DAAP

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (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.

Gabapentin, the active moiety in Gralise, is a member of the class of antiepileptic drugs (AEDs). AEDs are associated with an increased risk of suicidal thoughts and behavior.

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 Gabapentin, outweigh its serious risks of suicidal thoughts and behavior.

In reaching this determination we considered the following:

A. It is difficult to estimate the size of the population likely to use Gabapentin, however several thousand patients per year suffer from postherpetic neuralgia (PHN).
B. Gabapentin will be used for moderate-to-severe pain resulting from PHN. This is considered serious, as patients with inadequately treated pain are at risk for suicide.
C. The expected benefit of the drug is effective pain relief.
D. The expected duration of treatment is from weeks to months.
E. The most serious known adverse events known be associated with gabapentin include the risk of suicidal thoughts or behaviors and withdrawal precipitated seizures.
F. Gabapentin is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Gabapentin-ER. The Medication Guide is necessary for patients' safe and effective use of Gabapentin-ER. FDA has determined that Gabapentin is a product for which patient labeling could help prevent serious adverse effects and that has 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 Gabapentin.

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

_____
Bob Rappaport, M.D.
Director, Division of Anesthesia and Analgesia Products

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/s/

ELLEN W FIELDS
01/28/2011

BOB A RAPPAPORT
01/28/2011

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:	December 17, 2010
To:	Bob Rappaport, M.D., Director **Division of Analgesic and Anesthetic Products (DAAP)**
Through:	Claudia Karwoski PharmD, Director **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, M.P.H., B.S.N., R.N. Patient Labeling Reviewer **Division of Risk Management (DRISK)** Jodi Duckhorn, M.A. Social Science Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	gabapentin extended release Tablets
Application Type/Number:	NDA 22-544
Applicant/sponsor:	Abbott Products Inc.
OSE RCM #:	2010-1008

1. INTRODUCTION

This review is written in response to a request by the Division of Analgesic and Anesthetic Products (DAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for gabapentin extended release tablets.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

The DRISK review of the Medication Guide will be provided under a separate cover.

2. BACKGROUND

Gabapentin (Neurontin®) was originally approved in December, 1993 (NDA 20-235) as adjunctive therapy in the treatment of partial seizures and was subsequently approved for the management of post-herpetic neuralgia (PHN) in adults (May 2002, NDA 21-424).

On January 31, 2008, the FDA issued an alert to health care professionals that clinical trials of drugs to treat epilepsy showed increased risk of suicidal thoughts or actions. In July 2008, the FDA held a public Advisory Committee meeting (Joint meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee). At this meeting the committee agreed with the FDA's findings that there is an increased risk of suicidality with the analyzed antiepileptic drugs and that this risk was shared by antiepileptic products with varying mechanisms of action and differing indications for use. The specific details and results of the meta-analysis can be found on the FDA website. The panel recommended that appropriate warnings should be added to the labeling and that a Medication Guide be developed for all AEDs.

The FDA officially notified the public on December 16, 2008 that all AED medications would require warnings about the risk of suicidal thoughts or behavior. This notification included a Sponsor Template Letter that was sent to each application holder of an AED medication. This Sponsor Template Letter outlines the required labeling text to address the risk of suicidal thought and behavior. It also requires that a Medication Guide be submitted that contains the necessary information to inform patients of the increased risk for suicidal thoughts or behavior. Finally, this notification outlines that the FDA has determined that a REMS is necessary to ensure that the benefits of the drug outweigh the risks based on the new safety information. Each sponsor of an AED application would be required to submit a REMS.

Abbott Products, Inc., submitted a New Drug Application (NDA) for TRADENAME (gabapentin extended release) Tablets for the treatment of postherpetic neuralgia. This application is submitted under 505 (b)(2) of the FD&C Act and the applicant is relying in the Division's findings of safety and efficacy established for Neurontin (gabapentin).

3. MATERIAL REVIEWED

- Proposed gabapentin extended release tablets Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on March 30, 2010, and received by DRISK on December 13, 2010.

4. RESULTS OF REVIEW

In our review of the proposed REMS, we have:

- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

5. CONCLUSIONS AND RECOMMENDATIONS

The proposed REMS includes the elements in the REMS notification letter (Medication Guide and timetable for submission of assessments) but also includes [redacted] (b) (4) which is not a required element of the REMS and should be removed from the proposed REMS. This is reflected in our comments to the Applicant below.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to Abbott Products Inc.:

See the appended gabapentin extended release REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

a. **GOAL**

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of gabapentin extended release tablets.

b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document. See our editorial comments on this section of the proposed REMS (see Appendix A)

- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. You state that you plan to contract with a third-party fulfillment group responsible for the following activities: identification of all Pharmacies/dispensers in the US, timely printing of Medication Guide tear pads, timely shipment of the tear pads and timely fulfillment of re-ordering of the Medication Guide tear pads in quantities to meet the needs of each

dispenser, as specified by the dispenser. We find this distribution plan acceptable.

- We remind you that under 21 CFR 208.24, you are responsible for ensuring that the gabapentin extended release tablet carton or container label contains a prominent statement that the Medication Guide should be dispensed to each patient. We suggest the following language if the product is enclosed in the carton. "Dispense accompanying Medication Guide to each patient."

c. Your proposed element, (b) (4) is fine for the REMS Supporting Document but is not a required element of the REMS and has been removed. See Appendix.A.

d. Your proposed timetable for submission of assessments (18 months, 3 years and 7 years) is acceptable. We have some editorial comments on this section of the REMS.

e. Regarding your REMS Assessment Plan

The submitted methodology lacks sufficient detail to complete a review.

1. Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of [Tradename]. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." If the plan is to conduct the required assessment using a survey, the submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of [Tradename].
2. We encourage you to recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
   Explain how often non-respondent follow-up or reminders will be completed.
   Explain how an incentive or honorarium will be offered, and the intended amount.
   Explain how recruitment sites will be selected.
   Submit for review any recruitment advertisements.
3. Define the sample size and confidence intervals associated with that sample size.
4. Define the expected number of patients to be surveyed to obtain the final proposed sample size, and how the sample will be determined (selection criteria)
5. The patient sample should be demographically representative of the patients who use [Tradename].
   If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.
6. Explain the inclusion criteria; that is, who is an eligible respondent. For example, *patient* respondents might be:
   - Age 18 or older
   - Currently taking [Tradename] or have taken in past 3 months

- Not currently participating in a clinical trial involving [Tradename]
- Not a healthcare provider

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

7. Explain how surveys will be administered, and the intended frequency.
   We encourage you to offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person.
   Explain how surveyors will be trained.
8. Explain controls used to compensate for the limitations or bias associated with the methodology.
9. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
   Potential respondents should be told that their answers will not affect their ability to receive or take [Tradename], and that their answers and personal information will be kept confidential and anonymous.
10. Respondents should not be eligible for more than one wave of the survey.
11. The assessment is to evaluate the effectiveness of the REMS in achieving the REMS goal by evaluating patients' knowledge of the serious risks associated with use of [Tradename]. The assessment is not to evaluate consumer comprehension of the Medication Guide.
    Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
13. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.
    Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about [Tradename]?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs.
    The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
    The order of the multiple choice responses should be randomized on each survey.
14. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide.

Demographic questions should be collected last or as part of any screener questions.
Respondents should not have the opportunity or ability to go back to previous questions in the survey.
Explain if and when any education will be offered for incorrect responses.

15. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

16. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,
Now we are going to ask you some questions about the Medication Guide you may have received with [Tradename]. The Medication Guide is a paper handout that contains important information about the risks associated with use of [Tradename] and how to use [Tradename] safely. Medication Guides always include the title "Medication Guide" followed by the word [Tradename] and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about [Tradename]," "What is [Tradename]," and "Who should not take [Tradename]."

17. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for [Tradename]? (Select all that apply)
    a) My doctor or someone in my doctor's office
    b) My pharmacist or someone at the pharmacy
    c) Someone else - please explain: _____
    d) I did not get a Medication Guide for [Tradename]

- Did you read the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

- Did you understand what you read in the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

- Did someone offer to explain to you the information in the Medication Guide?
    - Yes, my doctor or someone in my doctor's office
    - Yes, my pharmacist or someone at the pharmacy
    - Yes, someone else please explain:

      _____
    - No

- Did you accept the offer? Yes or No

- Did you understand the explanation that was given to you?

    - All,
    - Most,
    - Some,
    - None
  - Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

18. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
19. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

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/s/

SHAWNA L HUTCHINS
12/17/2010

CLAUDIA B KARWOSKI
12/17/2010
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