CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-512

REMS

NDA 22-512 PRADAXA (dabigatran etexilate mesylate) Capsules

Class of Product: Direct Thrombin Inhibitor

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)
900 Ridgebury Road, Ridgefield, CT. 06877
Telephone: 1-800-542-6257 and TTY 1-800-459-9906

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

The goal of this REMS is to inform patients about the serious risks associated with the use of PRADAXA (dabigatran etexilate).

II. REMS ELEMENTS:

A. Medication Guide

Boehringer Ingelheim Pharmaceuticals Inc. will ensure that a currently approved Medication Guide will be dispensed with each PRADAXA (dabigatran etexilate) prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

Boehringer Ingelheim Pharmaceuticals Inc. will submit REMS Assessments to the FDA at 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to **prepare** the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Boehringer Ingelheim Pharmaceuticals Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

REMS Assessment Plan Comments

1. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of dabigatran etexilate. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of dabigatran etexilate.
2. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.
   Explain how often you perform non-respondent follow-up or reminders.
   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.
   Explain how you select recruitment sites.
   Submit for review any recruitment advertisements.
3. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
4. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
5. Ensure the sample is demographically representative of the population who use the drug (patients).
6. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
7. List the inclusion criteria. For example, eligible patient respondents must be:
   - Age 18 or older
   - Currently taking dabigatran etexilate or have taken the drug in the past 3 months
   - Not currently participating in a clinical trial involving dabigatran etexilate
   - Not a healthcare provider

   Submit any screener instruments, and describe any quotas of sub-populations used.
8. Explain how you administer surveys and the intended frequency.
   Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.
   Explain how you train surveyors.
9. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
10. Submit for review the introductory text used to inform respondents about the purpose of the survey.
    Tell potential respondents that their answers will not affect their ability to receive or take (patients) the drug, and that their answers and personal information will be kept confidential and anonymous.
11. Clarify in your methodology that respondents are eligible for one wave of the survey only.
12. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.
    According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

13. 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.
14. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.
    Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about dabigatran etexilate?" section of the Medication Guide.
    Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.
    Randomize the order of the multiple choice responses on each survey.
15. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.
    Do not allow respondents 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.
16. 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.
17. 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 dabigatran etexilate. The Medication Guide is a paper handout that contains important information about the risks associated with use of dabigatran etexilate and how to use dabigatran etexilate safely. Medication Guides always include the title "Medication Guide" followed by the word dabigatran etexilate and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about dabigatran etexilate," "What is dabigatran etexilate," and "Who should not take dabigatran etexilate."
18. Use the following (or similar) questions to assess receipt and use of the Medication Guide.
    - Who gave you the Medication Guide for dabigatran etexilate? (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 dabigatran etexilate
    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did you understand what you read in the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did someone offer to explain to you the information in the Medication Guide?
        a) Yes, my doctor or someone in my doctor's office
        b) Yes, my pharmacist or someone at the pharmacy
        c) Yes, someone else – please explain: _____

    d) No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
    a) All,
    b) Most,
    c) Some,
    d) None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

19. Analyze results on an item-by-item or variable-by-variable basis. You may present the date using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.