

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:  
22-512**

**RISK ASSESSMENT and RISK MITIGATION REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**DRISK REMS REVIEW**

**Date:** October 18, 2010  
**To:** Norman Stockbridge, M.D., Ph.D.  
Director, Division of Cardiovascular and Renal Products (DCRP)  
Office of New Drugs (OND)

**Through:** Claudia Karwoski, Pharm.D.  
Director, Division of Risk Management (DRISK)

**From:** **Scientific Lead**  
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**DCRP**  
Mary Ross Southworth, Deputy Director for Safety

**Subject:** Review of Risk Evaluation and Mitigation Strategy (REMS) for  
dabigatran etexilate

**Trade Name:**  
**(Established Name):** Dabigatran etexilate

**Therapeutic Class:** Direct thrombin inhibitor

**Dosage and Route:** Proposed doses - 150 mg and 110 mg oral capsules

**Application Number:** NDA 22-512

**Applicant:** Boehringer-Ingelheim Pharmaceuticals, Inc.

**OSE RCM #:** 2009-2421

## **EXECUTIVE SUMMARY**

This review from the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) evaluates the proposed Risk Evaluation and Mitigation Strategy (REMS) for dabigatran etexilate. The sponsor voluntarily submitted a REMS that included a Medication Guide and a communication plan.

The proposed indication for dabigatran etexilate 110 mg and 150 mg is the prevention of stroke and systemic embolism in patients with atrial fibrillation. When compared to warfarin, dabigatran etexilate 150 mg was superior in preventing stroke and systemic embolism in patients with atrial fibrillation without increasing the risk of major bleeding. The 110 mg dose of dabigatran etexilate was less effective than the 150 mg dose in the prevention of stroke and systemic embolism. Bleeding was a primary safety endpoint in the pivotal trial and the only major safety concern that was observed.

DRISK and Division of Cardiovascular and Renal Products (DCRP) concur that information regarding the risk of bleeding and management could be sufficiently addressed in the labeling. A communication plan did not need to be part of the REMS. Because bleeding is a serious safety concern, patients should be aware of this risk, and therefore Medication Guide-only REMS is recommended.

### **1 INTRODUCTION**

This review is in response to a request from the Division of Cardiovascular and Renal Products (DCRP), to Division of Risk Management (DRISK) to review Boehringer-Ingelheim's voluntary submission of a proposed Risk Evaluation and Mitigation Strategy (REMS) for dabigatran etexilate. The PUDFA goal date is October 19, 2010.

### **2 BACKGROUND**

On December 15, 2009, Boehringer-Ingelheim submitted a new drug application for dabigatran etexilate (NDA 22-512); due to issues with data integrity, a refusal to file letter was issued on February 12, 2010. On April 19, 2010, the sponsor resubmitted their application for dabigatran etexilate, an oral prodrug which is converted to the active metabolite dabigatran. Dabigatran is a direct thrombin-inhibitor that reversibly inhibits fibrin-bound thrombin, free circulating thrombin and thrombin-induced platelet aggregation. The proposed indication for dabigatran etexilate is the prevention of stroke and systemic embolism in patients with atrial fibrillation. The sponsor is seeking approval of two doses, a 150 mg and 110 mg capsules; both dosages are administered twice daily.

### **3 MATERIALS REVIEWED**

#### **3.1 Data and Information Sources**

- Proposed REMS for dabigatran etexilate, submitted 15 December 2009.
- Proposed REMS and supporting documents for dabigatran etexilate, submitted 20 July 2010.

- Combined Efficacy and Safety Review for dabigatran etexilate, Thompson A and Beasley N, dated 25 August 2010.
- Proposed labeling for dabigatran etexilate, submitted 15 December 2009.
- Effient (prasugrel) approved label and REMS, dated 10 July 2009.
- OSE Reviews of proposed REMS for Effient (prasugrel), dated 8 January 2009 and 14 April 2009
- DRISK Review of proposed REMS for Plavix (clopidogrel), dated 14 July 2010.

### **3.2 Analysis Techniques**

The REMS submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA), the REMS notification letter, and consistency with REMS requirements with for other antithrombotics.

## **4 OVERVIEW OF THE PIVOTAL TRIAL**

### **4.1 Overview**

The “**R**andomized **E**valuation of **L**ong- **T**erm Anticoagulant **T**herap**Y**” (RE-LY) was the pivotal trial used in support of the proposed indication. RE-LY was a prospective, multi-centre, non-inferiority study that included approximately 18,000 subjects and compared the safety and efficacy of two blinded doses of dabigatran etexilate (either 110 mg or 150 mg; twice daily) to unblinded warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

### **4.2 Efficacy**

Compared to warfarin, dabigatran etexilate 150 mg twice daily was associated with lower rates of stroke and systemic embolism (HR 0.65 P-value superiority 0.0001) with similar rates of major hemorrhage. Dabigatran etexilate 110 mg twice daily was associated with rates of stroke and systemic embolism similar to warfarin, but was associated with less bleeding.

### **4.3 Safety Concerns**

*Bleeding-* Bleeding was a primary safety endpoint in RE-LY and the only real safety concern that was recognized in the trial. Treatment with dabigatran etexilate 150 mg twice daily had similar rates of major bleeds (HR of 0.93, 95% CI 0.81, 1.07) when compared to warfarin. The risk of bleeding increased with age in all treatment arms; however patients  $\geq 75$  years who received dabigatran etexilate 150 mg had more major bleeds when compared to warfarin. Increased exposure to dabigatran etexilate secondary to moderate renal impairment (CrCl 30-50 mol/min) did not appear to be associated with increased risk of bleeding; analyses suggest that age, independent of renal function, may increase the risk of a major bleed. In addition, there was a dose-related, increased risk of gastrointestinal bleeds for dabigatran etexilate when compared to warfarin. Patients  $\geq 75$  years treated with dabigatran 150 mg had an increased risk for major gastrointestinal bleeds when compared to warfarin (HR 1.79, 95% CI: 1.32, 2.42).

## **5 REVIEW OF THE PROPOSED RISK EVALUATION AND MITIGATION STRATEGY**

### **5.1 Goals of the Proposed REMS**

The goal of the proposed REMS is to mitigate the risk of bleeding associated with the use of dabigatran etexilate.

- The Medication Guide would inform patients of the serious risks associated with dabigatran etexilate, particularly the increased risk of bleeding and how such symptoms should be recognized.
- A communication plan would educate prescribers about the increased risk of bleeding associated with dabigatran etexilate and how to manage them.

### **5.2 REMS Elements**

#### **5.2.1 Medication Guide**

The Medication Guide will be dispensed with each dabigatran etexilate prescription in accordance with Federal law 21 CFR 208.24. Sponsor proposes to make available extra copies so that they can be provided to each patient in the hospital setting.

#### **5.2.2 Communication Plan**

The proposed communication plan includes a Dear Healthcare Provider Letter (Introductory Letter) and a Prescriber Brochure. The sponsor is proposing to educate healthcare providers who manage patients with atrial fibrillation (e.g., cardiologists, emergency medicine physicians, internal medicine physicians, primary care physicians, hospitalist, hematologist, and neurologist) about:

- The associated risk of bleeding with dabigatran etexilate with emphasis on safety experience from the RE-LY study.
- Appropriate usage of dabigatran etexilate (i.e., patient selection, dose selection, how dabigatran etexilate should be taken).
- Relevant precautions, warning, and relevant interactions.

The proposed communication plan would continue for a period of 2 years after launch of the product or at the time of a major labeling change.

#### **5.2.3 Timetable for Submission of Assessments**

The sponsor proposes to submit REMS Assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS.

## **6 DISCUSSION**

The major safety concern for dabigatran etexilate is bleeding. Efficacy and safety for antithrombotics are closely related; an increased risk of bleeding is an expected consequence of antithrombotic therapies and well known to prescribers. Dabigatran etexilate 150 mg was effective in preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation and was not associated with an increase in major bleeds when compared to warfarin, the current standard of care.

If dabigatran etexilate is approved, both DRISK and DCRP believe a communication plan would not be needed to mitigate the risk of bleeding that can occur with dabigatran. This recommendation is based on two assumptions; 1) prescribers understand that bleeding is an expected side effect of antithrombotics and, 2) based on data from RE-LY, major bleeding with dabigatran etexilate is similar to what a patient might experience with warfarin. Information about the risk of bleeding and management can be sufficiently addressed in the labeling.

The sponsor is seeking approval of a slightly lower dose (dabigatran etexilate 110 mg) for the same indication. If the review division decides to approve both the 150 mg and 110 mg doses of dabigatran etexilate, a communication plan may be needed to clearly address concerns about decreased efficacy with the lower dose and appropriate patient selection.

Bleeding associated with dabigatran etexilate is a serious risk; the Medication Guide would provide a means to open dialogue between the healthcare professional and the patient to discuss these risks. In addition, the Medication Guide could convey information on safe and appropriate use, as well as important practical information for the patient (e.g., What Should I do if I miss a dose?) Patient labeling could help stress the importance of patient adherence, which will be essential for the drug to be effective in preventing strokes and systemic embolisms in patients with non-valvular atrial fibrillation.

## **7 CONCLUSION**

Based on the available data, DRISK and DCRP concur that a REMS is necessary for dabigatran etexilate to ensure that the benefits of the drug, for prevention of stroke and systemic embolism in patients with atrial fibrillation, outweigh the risk of bleeding. The REMS should include only a Medication Guide.

DRISK and DCRP believe that a communication plan, as voluntarily submitted by the sponsor, is not needed to mitigate the risk of bleeding associated with dabigatran etexilate. The need for additional risk evaluation and mitigation strategies could arise if other doses (e.g., 110 mg) are approved and/or risks are identified in post marketing studies or safety data that necessitate a change in labeling, such as a boxed warning.

## **8 RECOMMENDATIONS**

At this time, DRISK recommends removing the communication plan from the proposed REMS for dabigatran etexilate and modifying the REMS so that it includes only a Medication Guide and Timetable for Submission of Assessments.

A review of the Medication Guide-only REMS, including comments for the sponsor, is provided under a separate cover (REMS review: Hutchins).

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**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: October 18, 2010

To: Norman Stockbridge, MD, Director  
**Division of Cardiovascular and Renal Products (DCRP)**

Through: Claudia Karwoski PharmD, Director  
**Division of Risk Management (DRISK)**

From: Shawna Hutchins, MPH, BSN RN  
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Melissa Hulett, MSBA, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation  
Strategy (REMS)

Drug Name(s): dabigatran etexilate mesylate

Application  
Type/Number: NDA 22-512

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2009-2421

## **1. INTRODUCTION**

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) for dabigatran etexilate mesylate. Please let us know if DCRP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2. BACKGROUND**

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) submitted the original NDA application for dabigatran etexilate mesylate on December 15, 2009. A Refusal to File (RTF) letter was issued on February 12, 2010 due to data integrity issues. On April 19, 2010 the application was resubmitted. The submission included a Medication Guide.

On August 24, 2010, BIPI submitted an amendment to its 505(b)(1) New Drug Application to address the serious risks of bleeding associated with the use of dabigatran etexilate mesylate found during the RE-LY study. The amendment included a voluntarily submitted Risk Evaluation and Mitigation Strategy (REMS). The REMS elements proposed by the applicant include a Medication Guide and a Communication Plan. This is a priority application with a PDUFA goal date of October 19, 2010. Discussions between DRISK and DCRP lead them to concur that a communication plan was not a necessary component of the REMS and the only component of the REMS would be a Medication Guide.

## **3. MATERIAL REVIEWED**

- Proposed dabigatran etexilate mesylate Risk Evaluation and Mitigation Strategy (REMS), submitted on August 24, 2010 and received by DRISK on August 31, 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**

Based on the available data, DRISK and DCRP concur that a REMS is necessary for dabigatran etexilate mesylate to ensure that the benefits of a drug indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation outweigh the risks of bleeding. The REMS would include only a Medication Guide. Both DRISK and DCRP believe that a communication plan is not needed for dabigatran etexilate mesylate if only one dose is approved. A review of the of DRISK's concurrence with the elements of the REMS and a review of the Medication Guide will each be sent separately.

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 Boehringer Ingelheim Pharmaceutical, Inc.:**

See the appended dabigatran etexilate mesylate 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 of the serious risks associated with the use of dabigatran etexilate mesylate.

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.

- 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 a Medication Guide will be included as part of the Prescribing Information and pharmacists will be instructed to dispense dabigatran etexilate mesylate in the original container. We find your distribution plan acceptable.
- We remind you that under 208.24, you are responsible for ensuring that the that you will include a statement on the dabigatran etexilate mesylate carton or container label stating that the Medication Guide should be dispensed to each patient.
- See our editorial comments on this section of the proposed REMS (see Appendix A).

c. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

We have some editorial comments in this section of the proposed REMS.

d. Regarding your REMS Assessment Plan

1. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of dabigatran etexilate mesylate . 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 mesylate.

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 mesylate or have taken the drug in the past 3 months
  - Not currently participating in a clinical trial involving dabigatran etexilate mesylate
  - 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 mesylate?" 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 mesylate. The Medication Guide

is a paper handout that contains important information about the risks associated with use of dabigatran etexilate mesylate and how to use dabigatran etexilate mesylate safely. Medication Guides always include the title “Medication Guide” followed by the word [Insert tradename] dabigatran etexilate mesylate and its pronunciation. The Medication Guide usually has sections titled “What is the most important information I should know about dabigatran etexilate mesylate,” “What is dabigatran etexilate mesylate,” and “Who should not take dabigatran etexilate mesylate.”

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 mesylate? (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 mesylate
  - 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 data 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.

Please let us know if you have any questions.

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10/18/2010  
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**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation I  
Division of Cardiovascular and Renal Products**

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<b>NDA/BLA #s:</b>	22512
<b>Products:</b>	Pradaxa (dabigatran etexilate) Capsules
<b>APPLICANT:</b>	Boehringer-Ingelheim
<b>DATE:</b>	October 5, 2010

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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 (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for dabigatran etexilate to ensure that the benefits of a drug indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation outweigh the risks of bleeding. In reaching this determination, we have considered the following:

A. Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. An estimated 2.3 million people in North America and 4.5 million people in Europe have AF.<sup>1</sup>

B. The risk of stroke is increased approximately 5-fold in patients with AF.<sup>2</sup> Up to 15% of all strokes are due to AF and strokes in those with AF are more severe than strokes in those without AF.<sup>3</sup> During the past 20 years, hospital admissions for AF have increased by 66% due to the aging of the population and a rising prevalence of chronic heart disease.

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<sup>1</sup> Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Ann Intern Med* 2003;131(12):927-934.

<sup>2</sup> Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N., *et al.* Heart disease and stroke statistics – 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008; 117(4): e25-e146.

<sup>3</sup> Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991; 22: 983-988.

**REMS MEMO**

**NDA 22512**

**p. 2**

For over 50 years, Vitamin K antagonists (VKAs), such as warfarin, have been the only oral anticoagulants available for use as a long-term treatment to prevent strokes in patients with AF. Aspirin (ASA) may be used for patients with AF, but ASA is less effective than warfarin so is currently recommended only for AF patients at low risk of stroke in the American College of Chest Physicians (ACCP) guidelines

- C. Dabigatran etexilate is direct thrombin inhibitor that prevents clot formation.
- D. Dabigatran etexilate would be expected to be lifelong therapy barring permanent conversion of atrial fibrillation to normal sinus rhythm.
- E. Bleeding is an important safety concern associated with dabigatran etexilate use.
- F. Dabigatran etexilate is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for dabigatran etexilate. FDA has determined that dabigatran etexilate 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 dabigatran etexilate. FDA has determined that dabigatran etexilate is a product:

- for which patient labeling could help prevent serious adverse effects
- that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use or continue to use dabigatran etexilate
- for which a Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

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

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10/13/2010

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