# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 202155Orig1s000

# 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**
**Office of Medication Error Prevention and Risk Management**

# Final Risk Evaluation and Mitigation Strategy (REMS) Review

| | |
|---|---|
| Date: | December 27, 2012 |
| Team Leader: | Reema Mehta, PharmD, MPH<br>Division of Risk Management |
| Division Director | Claudia Manzo, PharmD<br>Division of Risk Management |
| Drug Name(s): | Eliquis® (apixaban) |
| Therapeutic Class: | Factor Xa Inhibitor |
| Dosage and Route: | 2.5 mg and 5 mg oral tablets |
| Application Type/Number: | NDA 202-155 |
| Applicant/sponsor: | Bristol-Myers Squibb |
| OSE RCM #: | 2012-2311 |

# CONTENTS

# 1 INTRODUCTION

This is the Division of Risk Management's (DRISK) final review of Bristol-Myers Squibb (BMS) proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 202-155, Eliquis® (abixiban). This review addressed the proposed REMS received on December 21, 2012.

The REMS proposed by the Sponsor contains a communication plan with a Dear Healthcare Professional (DHCP) letter, letter to Professional Organizations, and REMS website.

## 1.1 BACKGROUND

Eliquis (apixaban), a new molecular entity, is an orally available direct inhibitor of activated Factor Xa (FXa). The proposed indication for Eliquis is the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Eliquis is available as 2.5 mg and 5 mg tablets, and the recommended dose is 5 mg taken twice daily.

The serious risk of concern is that discontinuing Eliquis in the absence of adequate anticoagulation places patients at an increased risk of thrombotic events, including stroke. An increased rate of stroke was observed during the transition from Eliquis to warfarin in clinical trials in atrial fibrillation patients. If Eliquis must be discontinued for a reason other than pathological bleeding, prescribers should consider administering another anticoagulant.

## 1.2 REGULATORY HISTORY

On September 28, 2011, BMS submitted NDA 202-155 for the proposed indication to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation.

In accordance with section 505-1 of the Food, Drug, and Cosmetic Act, the Division of Cardiovascular and Renal Products (DCRP) and the Division of Risk Management (DRISK) determined that a REMS for Eliquis was required to ensure that the benefits of the drug outweigh the increased risk of thrombotic events, including stroke, if Eliquis is discontinued.

On February 3, 2012, the DCRP sent the sponsor a REMS Notification Letter, which included the following requirements for the proposed REMS:

1. **Communication Plan**
   The communication plan must include, at minimum, the following:
   - Dear Healthcare Professional letter distributed to appropriate prescribers
   - Eliquis REMS website
   - Letters to Professional Organizations
2. **Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is initially approved.

On February 13, 2012, the sponsor submitted the proposed REMS (Seq. No. 0040) that included a communication plan with the requirements described in the REMS Notification Letter. No additional risk mitigation strategies for the REMS were proposed by the sponsor.

After review of the application, DCRP found that the sponsor's pivitol trial (ARISTOTLE) demonstrated clinically significant efficacy for Eliquis in the population studied. However, a significant rate (estimated to be approximately 10%) of medication errors (wrong active drug, placebo instead of active, active instead of placebo) was observed in the ARISTOTLE trial. On June 22, 2012, DCRP issued a Complete Response Letter informing the sponsor that the application cannot be reviewed in its present form and requested that the sponsor submit additional information on data management and verification from the ARISTOTLE trial. The REMS was not reviewed during this review cycle.

On September 17, 2012, the sponsor submitted a NDA Resubmission in response to the Complete Response Letter. The resubmission did not include the proposed REMS as a component of the application.

On November 26, 2012, BMS was notified that the resubmission must include a REMS for review by the Agency. On November 29, 2012, the sponsor submitted the proposed REMS (Supplement 81/Sequence 0077). DRISK reviewed the submission and provided BMS with interim comments on December 20, 2012. A summary of the substantive comments is as follows:

- The address on the REMS document must be replaced with the physical address of the location where the REMS will be managed.
- Communication plan: The target audience for the DHCP letter was revised to include emergency medicine physicians, internal medicine physicians, and primary practice physicians. The target audience for the Dear Professional Society letter was revised to include the Association of Emergency Physicians (AEP). Additionally, the requirement to distribute REMS materials via sales representatives and medical science liaisons was removed to align the REMS document with current internal policy.
- DHCP Letter and Letter to Professional Societies: These REMS materials were revised to align with the current proposed label and internal standards regarding content and format.
- REMS website: The REMS document must include the REMS website as a component of the REMS. The landing page for the REMS website is appended to the REMS document. Additionally, comments regarding the content of the website were provided to improve the usability of the site.

BMS sent clarifying questions via email on December 20, 2012 regarding the REMS supporting document, in particular the REMS assessment plan and timetable for submission of assessments, and corrections to the toll-free number on the Medication Guide and REMS letters. On December 20, 2012, the Agency recommended the following revisions: (1) the requirement to report on postmarketing commitments can be removed from the REMS assessment plan; (2) the table accompanying the timetable for

submission of assessments should be removed from the REMS supporting document; and (3) the updates to the toll-free number are acceptable. The sponsor incorporated the recommended revisions and resubmitted the proposed REMS on December 21, 2012.

On December 27, 2012, DCRP sent the Sponsor a revised label, which included clarifying language regarding the apparent half-life of apixiban after repeated administration. These revisions impacted the REMS DHCP letter and Letter to Professional Societies; therefore, the Sponsor was requested to resubmit these materials with the revisions incorporated. The sponsor resubmitted the 2 letters on December 27, 2012 via email.

# 2 MATERIALS REVIEWED

## 2.1 DATA AND INFORMATION SOURCES

- Bristol-Myers Squibb proposed REMS for Eliquis (apixaban) received December 21, 2012 (Sequence 84)
- Division of Risk Management Interim Comments Set #1 for Eliquis (apixaban), dated December 20, 2012.

# 3 RESULTS OF REVIEW OF PROPOSED ELIQUIS RISK EVALUATION AND MITIGATION STRATEGY

## 3.1 OVERVIEW OF CLINICAL PROGRAM

ARISTOTLE is the primary support for the approval of apixaban for its proposed indication, the reduction in risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It was a large (18,201 subjects), double-blind (double dummy), randomized, global, event driven trial comparing apixaban 5 mg bid (with a lower dose for patients with at least 2 of 3 pre-specified risk factors for bleeding) to warfarin titrated to a target INR of 2.0 to 3.0. The primary efficacy endpoint was noninferiority of apixaban to warfarin for time to the composite of stroke or systemic embolism. This endpoint was met. In an additional analysis that was allowed under the study's pre-specified hierarchical analysis plan, apixaban was also superior to warfarin.

## 3.2 SAFETY CONCERNS

The serious risk of concern is that discontinuing Eliquis in the absence of adequate anticoagulation places patients at an increased risk of thrombotic events, including stroke. An increased rate of stroke was observed during the transition from Eliquis to warfarin in clinical trials in atrial fibrillation patients. If Eliquis must be discontinued for a reason other than pathological bleeding, prescribers should consider administering another anticoagulant.

DCRP and DRISK agree that the REMS for Eliquis should be comparable to the currently approved REMS for Xarelto® (rivaroxaban), which is a drug in the same class with similar mechanism of action and safety concern. The currently approved REMS for Xarelto contains a communication plan and informs healthcare providers (HCPs) of the increased risk of thrombotic events without adequate anticoagulation and that Xarelto

should be taken with the evening meal. Food does not affect the bioavailability of Eliquis; therefore, it is not a subject of the proposed REMS.

### 3.3 GOALS

The goal of the ELIQUIS REMS is to inform healthcare providers (HCPs) about:

- the increased risk of thrombotic events, including stroke, in patients with nonvalvular atrial fibrillation when discontinuing ELIQUIS without introducing an adequate alternative anticoagulant
- the importance of following the recommendations in the US Prescribing Information (USPI) on how to convert patients with nonvalvular atrial fibrillation from ELIQUIS to warfarin or other anticoagulants.

### 3.4 REMS ELEMENTS

#### 3.4.1 Communication Plan

Bristol-Myers Squibb will implement a communication plan to HCPs to support implementation of this REMS.

1. Dear Healthcare Professional Letter

A Dear Healthcare Professional (DHCP) Letter will be distributed by direct mail or electronic delivery to HCPs including: cardiologists, neurologists, emergency medicine physicians, internal medicine physicians, primary care physicians, nurse practitioners, physician assistants, and pharmacists. The letter will be distributed within 60 days of approval of ELIQUIS. Annual letters will be sent within 60 days of the anniversary date of approval for ELIQUIS every year for two additional years and within 60 days of FDA approval of any substantial safety update. The DHCP Letter will also be provided to FDA MedWatch at these times. A copy of the USPI and Medication Guide will accompany the DHCP Letter.

In addition, the DHCP Letter, USPI and Medication Guide will also be available on the ELIQUIS REMS website and upon request.

The DHCP letter is part of the REMS and is appended.

2. ELIQUIS REMS Website

Within 30 days of REMS approval, Bristol-Myers Squibb will post information for HCPs and patients on the ELIQUIS REMS website (http://www.ELIQUISREMS.com). This information will remain on the website for a period of 2 years.

The content of the print or web-based material will include the following:

- Goal of the REMS

- Information about the risk
- US Prescribing Information for ELIQUIS
- Medication Guide for ELIQUIS
- DHCP Letter (for a period of 2 years)

The ELIQUIS REMS website is part of the REMS and is appended.

3. Letters to Professional Organizations

A Professional Organization Letter will be distributed by direct mail or electronic delivery within 60 days of the REMS approval date. This communication to professional organizations will include the same information as that contained in the DHCP Letter. Bristol-Myers Squibb will request that these organizations disseminate this information to their members. Bristol-Myers Squibb will communicate the letter to the leadership of the following professional organizations:

- American Heart Association (AHA)
- American College of Cardiologists (ACC)
- Heart Rhythm Society (HRS)
- Society for Cardiovascular Angiography and Interventions (SCAI)
- American Academy of Neurology (AAN)
- American Neurological Association (ANA)
- National Institute of Neurological Disorders and Stroke (NINDS)
- American Stroke Association (ASA)
- National Stroke Association (NSA)
- American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)
- Association of Emergency Physicians (AEP)
- American College of Chest Physicians (ACCP)
- Association of Black Cardiologists (ABC)
- American Academy of Family Physicians (AAFP)
- American College of Physicians (ACP)
- Society of General Internal Medicine (SGIM)

- National Medical Association (NMA)
- American Academy of Nurse Practitioners (AANP)
- American Academy of Physician Assistants (AAPA)
- American College of Clinical Pharmacy (ACCP)
- American Society of Health-System Pharmacists (ASHP)
- American Pharmacists Association (APhA)
- National Association of Chain Drug Stores (NACDS)
- American Association of Critical-Care Nurses (AACN)
- National Association of Clinical Nurse Specialists (NACNS)

The USPI and the Medication Guide will be provided in conjunction with the letter.

The Professional Organization Letter is part of the REMS and is appended.

### 3.4.2 Timetable for Submission of Assessments

Bristol-Myers Squibb will submit REMS Assessments to the FDA at 18 months, 3 years, and 7 years from the date of the REMS approval. 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. Bristol-Myers Squibb will submit each assessment so that it will be received by the FDA on or before the due date.

### 3.5 REMS ASSESSMENT PLAN

The assessment plan must include, but is not limited to, the following components:

1. A report on the distribution of DHCP letters and Professional Organization Letters
2. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with ELIQUIS (for example, through surveys of healthcare providers).
3. With respect to the REMS goals, an assessment of the extent to which the REMS is meeting its goals or whether the goals or other elements should be modified.

## 4 DISCUSSION AND CONCLUSIONS

In conclusion, the amended REMS for Eliquis (abixiban), received December 27, 2012, contains the appropriate and agreed upon revisions on the REMS components as stipulated by the Agency on December 20, 2012, December 21, 2012, and December 27, 2012. The REMS Supporting Document outlines the information and

content that the applicant will use to assess the effectiveness of the Eliquis REMS in achieving the goals.

Therefore, the Eliquis REMS is compliant under FDAAA and acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

## 5 RECOMMENDATIONS

The OSE, DRISK recommends approval of the Eliquis REMS, received December 27, 2012, as appended to this review.

In addition, we recommend the REMS assessment plan described above be included in the REMS Approval Letter.

Any substantive changes to the label that impact the REMS materials should be provided to DRISK for further review.

## ATTACHMENTS

**Attachment A – REMS Document**

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

REEMA J MEHTA
12/27/2012

GARY H SLATKO
12/27/2012

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

**Interim Comments on Risk Evaluation and Mitigation Strategy (REMS)**
**Set # 1**

| | |
|---|---|
| Date: | December 20, 2012 |
| Reviewer(s): | Danielle Smith, PharmD, M.S., Risk Management Analyst<br>DRISK |
| Team Leader | Reema Mehta, PharmD, MPH<br>DRISK |
| Division Director | Claudia Manzo, PharmD<br>DRISK |
| Drug Name(s): | Eliquis (apixaban) |
| Therapeutic Class: | Factor Xa Inhibitor |
| Dosage and Route: | 2.5 mg and 5 mg oral tablets |
| Application Type/Number: | NDA 202-155 |
| Submission Number: | Seq. No. 0077 |
| Applicant/sponsor: | Bristol-Myers Squibb |
| OSE RCM #: | 2012-2311 |

*** This document contains proprietary and confidential information that should not be released to the public. ***

# CONTENTS

## 1 INTRODUCTION

This Division of Risk Management (DRISK) Interim Comments Review evaluates and communicates required revisions to the proposed Risk Evaluation and Mitigation Strategy (REMS) submitted by Bristol-Myers Squibb (BMS) for Eliquis® (apixaban), received on November 29, 2012.

The REMS proposed by the Sponsor contains a communication plan with a Dear Healthcare Professional (DHCP) letter, letter to Professional Organizations, and REMS website.

## 2 BACKGROUND

Eliquis (apixaban), a new molecular entity, is an orally available direct inhibitor of activated Factor X (Factor Xa or FXa). Its proposed indication is the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It is available as 2.5 mg and 5 mg tablets, and the recommended dose is 5 mg taken twice daily.

The serious risk of concern is that discontinuing Eliquis in the absence of adequate anticoagulation places patients at an increased risk of thrombotic events, including stroke. An increased rate of stroke was observed during the transition from Eliquis to warfarin in clinical trials in atrial fibrillation patients. If Eliquis must be discontinued for a reason other than pathological bleeding, prescribers should consider administering another anticoagulant**.**

## 3 REGULATORY HISTORY

On September 28, 2011, BMS submitted NDA 202-155 for the proposed indication to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation.

In accordance with section 505-1 of the Food, Drug, and Cosmetic Act, the Division of Cardiovascular and Renal Products (DCRP) and the Division of Risk Management (DRISK) determined that a REMS for Eliquis was required to ensure that the benefits of the drug outweigh the increased risk of thrombotic events, including stroke, if Eliquis is discontinued.

On February 3, 2012, the DCRP sent the sponsor a REMS Notification Letter, which included the following requirements for the proposed REMS:

1. **Communication Plan**:
   The communication plan must include, at minimum, the following:
   - Dear Healthcare Professional letter distributed to appropriate prescribers
   - Eliquis REMS website
   - Letters to Professional Organizations
2. **Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is initially approved**.**

On February 13, 2012, the sponsor submitted the proposed REMS (Seq. No. 0040) that included a communication plan with the requirements described in the REMS Notification Letter. No additional risk mitigation strategies for the REMS were proposed by the sponsor.

After review of the application, DCRP found that the sponsor's pivitol trial (ARISTOTLE) demonstrated clinically significant efficacy for Eliquis in the population studied. However, a significant rate (estimated to be approximately 10%) of medication errors (wrong active drug, placebo instead of active, active instead of placebo) was observed in the ARISTOTLE trial. On June 22, 2012, DCRP issued a Complete Response Letter (informing the sponsor that the application cannot be reviewed in its present form and requested that the sponsor submit additional information on data management and verification from the ARISTOTLE trial. The REMS was not reviewed during this review cycle.

On September 17, 2012, the sponsor submitted a NDA Resubmission in response to the Complete Response Letter. The resubmission did not include the proposed REMS as a component of the application.

On November 26, 2012, BMS was notified that the resubmission must include a REMS for review by the Agency. On November 29, 2012, the sponsor submitted the proposed REMS (Supplement 81/Sequence 0077), which is the focus of this review.

## 4 MATERIALS REVIEWED

### 4.1 SUBMISSIONS

- Bristol-Myers Squibb proposed REMS (Supplement 81/Sequence 0077) for Eliquis (apixaban), received November 29, 2012

### 4.2 OTHER MATERIALS INFORMING THE REVIEW

- Office of Compliance/REMS Compliance Team Review of the REMS for Eliquis, dated December 18, 2012
- Draft Prescribing Information for Eliquis (apixaban), dated December 19, 2012
- Xarelto (rivaroxaban) REMS, approved July 12, 2012

## 5 SUMMARY OF APPLICANT'S PROPOSED REMS

DCRP and DRISK agree that the REMS for Eliquis should be comparable to the currently approved REMS for Xarelto (rivaroxaban), which is a drug in the same class with similar mechanism of action and safety concern. The currently approved REMS for Xarelto contains a communication plan and informs healthcare providers (HCPs) of the increased risk of thrombotic events without adequate anticoagulation and that Xarelto should be taken with the evening meal. Food does not affect the bioavailability of Eliquis; therefore, it is not a subject of the proposed REMS.

### I. GOAL

The goal of the ELIQUIS REMS is to inform HCPs that discontinuing ELIQUIS in the absence of adequate anticoagulation places patients with nonvalvular atrial fibrillation at an increased risk of thrombotic events, including stroke, and to direct HCPs to follow the

recommendations in the US Prescribing Information (USPI) on how to convert patients with nonvalvular atrial fibrillation from ELIQUIS to warfarin or other anticoagulants.

***Reviewer's Comments:***

*The applicant's goal is not identical to that of Xarelto's REMS due to product labeling differences. However, the applicant's proposed editorial changes do not alter the interpretation of the intended goal. To improve clarity of the message, DRISK recommends presenting the goals as a bulleted list. These revisions are described in Section 7, Comments for the Applicant.*

## II. REMS ELEMENTS

### A. Communication Plan

Bristol-Myers Squibb will implement a communication plan to HCPs to support implementation of this REMS.

1. Dear Healthcare Professional Letter

A DHCP Letter will be distributed by mail to HCPs including: cardiologists, neurologists, internists, family practice physicians, nurse practitioners, physician assistants, and pharmacists. The letter will be distributed within 60 days, 12 months, and 24 months after approval of the REMS, and in the event of any substantial safety update. The DHCP Letter will also be provided to FDA MedWatch at these times. A copy of the USPI and Medication Guide will accompany the DHCP Letter.

(b) (4)

The DHCP letter is part of the REMS and is appended.

***Reviewer's Comments:***

*To ensure the same target audience is addressed with the Eliquis REMS as compared to the Xarelto REMS, the applicant should:*

- *add 'emergency medicine physicians' to the targeted healthcare professionals receiving the letter*
- *replace 'internists' with 'internal medicine physicians' and 'family practice physicians' with 'primary practice physicians'.*

*The section also includes revisions that incorporate comments from the Office of Compliance/REMS Compliance Team to ensure the enforceability of the REMS.*

*Furthermore, the current policy is for REMS to not specifically require that the REMS materials be distributed via sales representatives and medical science liasons. Therefore, this requirement must be removed from the REMS.*

*The aforementioned revisions are described in Section 7, Comments for the Applicant.*

2. ELIQUIS REMS Website

Within 30 days of REMS approval, Bristol-Myers Squibb will post information for HCPs and patients on the ELIQUIS REMS website [redacted] (b) (4). This information will remain on the website for a period of 2 years.

The content of the print or web-based material will include the following:

- Goal of the REMS
- Information about the risk
- US Prescribing Information for ELIQUIS
- Medication Guide for ELIQUIS
- DHCP Letter (for a period of 2 years)

***Reviewer's Comments:***

- *The applicant did not include a statement indicating that the website is a part of the REMS; therefore, the following sentence after the bulleted list must be included:*

  *The ELIQUIS REMS website is part of the REMS and is appended.*

- *Current policy is for the REMS website to have a unique web address from the product website. The applicant must revise the proposed URL address for the REMS website to www.ELIQUISREMS.com, or something similar.*

- *The content of the REMS website is a replicate of the proposed Dear Healthcare Professional Letter. This does not meet the current format and content standards for REMS websites. Therefore, the content of the REMS website must be revised for clarity and consistency with the current standards and practices for REMS websites.*

*The aforementioned revisions are described in Section 7, Comments for the Applicant.*

3. Letters to Professional Organizations

A Professional Organization Letter will be distributed by e-mail within 60 days of the REMS approval date. This communication to professional organizations will include the same information as that contained in the DHCP Letter. Bristol-Myers Squibb will request that these organizations disseminate this information to their members. Bristol-Myers Squibb will communicate the letter to the leadership of the following professional organizations:

- American Heart Association (AHA)
- American College of Cardiologists (ACC)

- Heart Rhythm Society (HRS)
- Society for Cardiovascular Angiography and Interventions (SCAI)
- American Academy of Neurology (AAN)
- American Neurological Association (ANA)
- National Institute of Neurological Disorders and Stroke (NINDS)
- American Stroke Association (ASA)
- National Stroke Association (NSA)
- American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)
- American College of Chest Physicians (ACCP)
- Association of Black Cardiologists (ABC)
- American Academy of Family Physicians (AAFP)
- American College of Physicians (ACP)
- Society of General Internal Medicine (SGIM)
- National Medical Association (NMA)
- American Academy of Nurse Practitioners (AANP)
- American Academy of Physician Assistants (AAPA)
- American College of Clinical Pharmacy (ACCP)
- American Society of Health-System Pharmacists (ASHP)
- American Pharmacists Association (APhA)
- National Association of Chain Drug Stores (NACDS)
- American Association of Critical-Care Nurses (AACN)
- National Association of Clinical Nurse Specialists (NACNS)

The USPI and the Medication Guide will be provided in conjunction with the letter.

The Professional Organization Letter is part of the REMS and is appended.

***Reviewer's Comment:***

*The applicant should add the 'Association of the Emergency Physicians' to the list of professional organizations to remain consistent with list of professional organizations targeted in the Xarelto REMS. The aforementioned revisions are described in Section 7, Comments for the Applicant.*

**B. Timetable for Submission of Assessments**

Bristol-Myers Squibb will submit REMS Assessments to the FDA at 18 months, 3 years, and 7 years from the date of the REMS approval. 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. Bristol-Myers Squibb will submit each assessment so that it will be received by the FDA on or before the due date.

***Reviewer's Comment:***

*The proposed timetable is acceptable; therefore, no further comments are provided on the Timetable for Submission of Assessments.*

## 6 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Eliquis REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Eliquis. Note, DRISK requires the product labeling to be complete prior to finalizing the REMS document to ensure the information is accurate.

Appended to this review is the REMS proposal and appended materials including our track changes (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document. A revised REMS must be submitted by the applicant with the following comments addressed in order for DRISK to proceed with the review.

## 7 COMMENTS FOR THE APPLICANT

The following are required revisions to the proposed REMS received November 29, 2012 that must be incorporated into your REMS proposal. Submit your revised REMS proposal incorporating the Agency's comments as soon as possible to facilitate further review.

Please note that these are interim comments. There may be additional comments on the REMS and REMS materials as edits are made to the product labeling or as comments are routed through the Agency's final clearance process.

**REMS Document**

1. The address on the REMS document must be replaced with the physical address of the location where the REMS will be managed.
2. The target audience for healthcare providers must be revised to add 'emergency medicine physicians', replace 'internists' with 'internal medicine physicians', and replace 'family practice physicians' with 'primary practice physicians'.
3. The REMS document must specify that the REMS website is a component of the REMS; therefore, the following statement must be included "The ELIQUIS REMS website is part of the REMS and is appended." See additional comments under "ELIQUIS REMS Website" below.

See the REMS Document (attached) for suggested track changes.

**Dear Healthcare Professional Letter and Professional Organization Letter**
See the Dear Healthcare Professional Letter (attached) for suggested track changes.
Use the DHCPL as the template for a Professional Organization Letter.

**ELIQUIS REMS Website**
The REMS website landing page has been edited for clarity and to reflect the most recent version of the Prescribing Information.

1. Replace content currently placed on the REMS website landing page with the following:

   *A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. The FDA has required a REMS for ELIQUIS.*

   *The purpose of the ELIQUIS REMS is to inform healthcare providers about:*

   - *the increased risk of thrombotic events, including stroke, in patients with nonvalvular atrial fibrillation when discontinuing ELIQUIS in the absence of adequate anticoagulation*
   - *the importance of following the recommendations in the US Prescribing Information (USPI) on how to convert patients with nonvalvular atrial fibrillation from ELIQUIS to warfarin or other anticoagulants.*

2. In the box to the right of the page titled REMS Support Materials:
   - Change the title from **REMS Support Materials** to **REMS Materials**
   - Change the title of the Dear Healthcare **Provider** Letter to Dear Healthcare **Professional** Letter
   - Include a link to the Dear Professional Organization Letter
   - Remove Full Prescribing Information from the box
3. The Agency requires that the REMS website, ELIQUISREMS.COM, be independent of links to the promotional and/ or commercial website and non-REMS materials about the product.
4. Do not include a link from the REMS website page back to the www.ELIQUIS.com website.
5. Please note the ELIQUIS REMS webpage should also be accessible directly through a search engine.
6. At the bottom of the page, remove "This web page is required and approved by FDA as part of the ELIQUIS REMS.

**REMS Supporting Document**

The REMS Supporting Document must be consistent with all changes made to the REMS document. Please update accordingly.

**Information Needed for Assessments**

The assessment plan must include, but is not limited to, the following components:

1. A report on the distribution of DHCP letters and Professional Organization Letters
2. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with ELIQUIS (for example, through surveys of healthcare providers).
3. With respect to the REMS goals, an assessment of the extent to which the REMS is meeting its goals or whether the goals or other elements should be modified.
4. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Please see additional comments on the assessment are provided in the Supporting Document.

**7.1 GENERAL COMMENTS**

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Eliquis with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents. Additionally, it is preferable that the entire REMS document and attached materials (Dear Healthcare Professional Letter, Professional Organization Letter, and landing page of REMS website) is submitted in both a single PDF document and a single MS Word document.

Format Request: Submit your proposed REMS and other materials in MS 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. 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 be in a single MS Word document.

**ATTACHMENTS**

REMS document (tracked)

Dear Healthcare Professional Letter (tracked)

8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

DANIELLE SMITH
12/20/2012

REEMA J MEHTA
12/20/2012

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review

| | |
|---|---|
| Date: | June 29, 2012 |
| Reviewer(s): | Danielle Smith, PharmD, M.S., Risk Management Analyst<br>DRISK |
| Team Leader | Reema Mehta, PharmD, MPH<br>DRISK |
| Division Director | Claudia Manzo, PharmD<br>DRISK |
| Drug Name(s): | Eliquis (apixaban) |
| Therapeutic Class: | Factor Xa Inhibitor |
| Dosage and Route: | 2.5 mg and 5 mg oral tablets |
| Application Type/Number: | NDA/202155 |
| Submission Number: | Seq. No. 0040 |
| Applicant/sponsor: | Bristol-Myers Squibb |
| OSE RCM #: | 2011-3796 |

*** This document contains proprietary anmd confidential information that should not be released to the public. ***

This document is to defer comment on proposed risk evaluation and mitigation strategy (REMS) submitted by Bristol-Myers Squibb for Eliquis (apixaban).

On September 28, 2011, Bristol-Myers Squibb submitted New Drug Application (NDA) 202-155 for the proposed indication to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation.

On January 20, 2012, the Division of Cardiovascular and Renal Products (DCRP) requested that the Division of Risk Management (DRISK) the review the Pre-Approval REMS Notification letter and REMS Memorandum for alignment. DCRP's decision to require a REMS, in accordance with section 505-1 of the FDCA, was to ensure that the benefits of the drug outweigh the increased risk of thrombotic events, including stroke, if Eliquis is discontinued. DRISK was in agreement with the Division's proposed plan.

On February 3, 2012, Division of Cardiovascular and Renal Products (DCRP) notified the sponsor that a REMS was determined to be necessary for the reason mentioned above. The Division also notified the sponsor that the proposed REMS must include the following:

1. **Communication Plan**:
   The communication plan must include, at minimum, the following:
   - Dear Healthcare Professional letter distributed to appropriate prescribers
   - Eliquis REMS website
   - Letters to Professional Organizations
2. **Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is initially approved.

On February 13, 2012, the sponsor submitted the proposed REMS (Seq. No. 0040).

After review of the application, DCRP found that the ARISTOTLE trial, which was the foundation for obtaining the proposed indication, supported effectiveness of the drug. In addition, there were no issues of approvability relating to CMC, biopharmaceutics, pharmacology, toxicology, or clinical pharmacology. However, the principal concern was what appeared to be a very high rate of medication errors (wrong active drug, placebo instead of active, active instead of placebo) in the ARISTOTLE trial. This medication error rate was thought to be as great as 10%. On June 22, 2012, DCRP issued a Complete Response letter informing the sponsor that the application cannot be reviewed in its present form and requested that the sponsor submit additional information on data management and verification from the ARISTOTLE trial.

DCRP did not address labeling/REMS during this review cycle. It is DCRP's plan to continue discussion of the proposed REMS after the sponsor has submitted a complete response to the action letter. Therefore, DRISK defers comment on the sponsor's risk management proposal at this time.

A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response letter.

Please send DRISK a new consult request at such time. This memo serves to close the existing consult request for Eliquis (apixaban) under NDA 202155 (Seq. No. 0040).

Please notify DRISK if you have any questions.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

DANIELLE SMITH
06/29/2012

CLAUDIA B MANZO
06/29/2012
concur

# 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**

---

**NDA/BLA #s:** 202155
**Products:** Eliquis (apixaban) Tablets
**APPLICANT:** Bristol-Myers Squibb Company
**DATE:** January 17, 2012

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 Eliquis to ensure that the benefits of the drug outweigh the increased risk of thromboembolic events, including stroke, if Eliquis is discontinued. In reaching this determination, we 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[1].

B. The risk of stroke is increased approximately 5-fold in patients with AF[2]. 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[3]. 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.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.

C. Apixaban is direct Factor Xa inhibitor that prevents clot formation.

---

[1] 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.

[2] 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.

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

D. Apixaban would be expected to be lifelong therapy barring permanent conversion of atrial fibrillation to normal sinus rhythm.

E. Thromboembolic events upon cessation of apixaban is an important safety concern associated with apixaban use.

F. Apixaban is a new molecular entity.

The elements of the REMS will be a communication plan and a timetable for submission of assessments of the REMS.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

MARY R SOUTHWORTH
02/03/2012