CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s000

REMS

Initial REMS Approval Date: 12/2012

NDA 202155

ELIQUIS® (apixaban) tablets

Factor Xa Inhibitor

Bristol-Myers Squibb Company
Research & Development
777 Scudders Mill Road
Plainsboro, NJ 08536
United States of America

Contact Information:
Phone: 609-897-5854
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

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.

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 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.

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.

[Insert Month DD, YEAR]

IMPORTANT DRUG WARNING

ELIQUIS® (apixaban) tablets

Subject: Discontinuing ELIQUIS without introducing an adequate alternative anticoagulant places nonvalvular atrial fibrillation patients at an increased risk of thrombotic events, including stroke

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information for ELIQUIS (apixaban). ELIQUIS is an oral, reversible factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of ELIQUIS outweigh the potential risks in patients with nonvalvular atrial fibrillation including:

- Increased risk of thrombotic events, including stroke, when discontinuing ELIQUIS without an adequate alternative anticoagulant

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

The ELIQUIS® labeling includes a **BOXED WARNING** to highlight the safety issue of increased risk of thrombotic events following discontinuation of ELIQUIS®.

WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

Increased Risk of Stroke with Discontinuation of ELIQUIS

ELIQUIS has an apparent half-life of 12 hours during repeat dosing, therefore, the anticoagulant effect of ELIQUIS is present when the drug is taken and for at least a day after discontinuation. Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

Patient Counseling

Advise patients to take ELIQUIS only as directed and not to discontinue ELIQUIS without first speaking to you.

Medication Guide

The Medication Guide contains information to support patient counseling regarding the risks and benefits of treatment with ELIQUIS. Additional copies of the ELIQUIS Medication Guide may be obtained from:

- Bristol-Myers Squibb toll-free line at 1-855-354-7847
- the ELIQUIS REMS website at http://www.ELIQUISREMS.com

Reporting Adverse Events

To report all suspected adverse events associated with the use of ELIQUIS, please contact:

- Bristol-Myers Squibb at 1-800-721-5072 and/or
- FDA Medwatch Program at 1-800-FDA-1088 or www.fda.gov/medwatch.

For more information regarding ELIQUIS, please contact the Medical Information department at 1-800-321-1335 or visit the website at www.ELIQUIS.com.

This letter is not intended as a comprehensive description of risks associated with the use of ELIQUIS. Please read the accompanying USPI, including Medication Guide, for a complete description of these risks.

Sincerely,

[Click here to enter names of signatories]

Enclosure: ELIQUIS USPI with Medication Guide

[BMS Corporate logo] [Pfizer Inc logo]

 432US12REMS00101 12/12

IMPORTANT DRUG WARNING

Eliquis® (apixaban) tablets

Distribute this Information to Your Members

[Insert Month DD, YEAR]

Dear Professional Organization:

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Sincerely,

[Click here to enter names of signatories]

Enclosure: ELIQUIS USPI with Medication Guide

[BMS Corporate logo] [Pfizer Inc logo]

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Eliquis® (apixaban) tablets

RISK EVALUATION AND MITIGATION STRATEGY

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 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.

REMS Materials

Dear Healthcare Professional Letter

Dear Professional Organization Letter

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Bristol-Myers Squibb Pfizer

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

/s/

ROBERT TEMPLE
12/28/2012