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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
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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

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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

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