

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202439Orig1s000**

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

## 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:** 202439  
**Products:** Xarelto (rivaroxaban) 15 mg and 20 mg Tablets  
**APPLICANT:** Janssen Pharmaceuticals  
**DATE:** October 27, 2011

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 rivaroxaban to ensure that the benefits of the drug outweigh the risks of a thromboembolic event upon cessation of Xarelto or when drug absorption is decreased by not taking the tablet daily with the evening meal.

- 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.

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. Rivaroxaban is direct Factor Xa inhibitor that prevents clot formation.
- D. Rivaroxaban would be expected to be lifelong therapy barring permanent conversion of atrial fibrillation to normal sinus rhythm.
- E. Thromboembolic events upon cessation of rivaroxaban or when drug absorption is decreased by not taking the tablet daily with the evening meal are important safety concern associated with rivaroxaban use.
- F. Rivaroxaban 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 Xarelto. FDA has determined that Xarelto 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 Xarelto. FDA has determined that Xarelto is a product:

- for which patient labeling could help prevent serious adverse effects
- 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, a Communication Plan, and a timetable for submission of assessments of the REMS.

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/s/  
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ALISON L BLAUS  
10/31/2011

MARY R SOUTHWORTH  
10/31/2011

**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:** November 4, 2011

**Reviewer(s):** Danielle Smith, Pharm.D, M.S., Risk Management Analyst  
Division of Risk Management (DRISK)

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DRISK

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**Drug Name:** XARELTO® (rivaroxaban)

**Therapeutic Class:** Factor Xa Inhibitor

**Dosage and Route:** 15 mg and 20 mg oral tablets

**Application Type/Number:** NDA 202-439

**Submission Number:** Sequence Number 0116

**Applicant/Sponsor:** Janssen Pharmaceuticals Inc.

**OSE RCM #:** 2011-271

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

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## **EXECUTIVE SUMMARY**

This review responds to a request from the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Xarelto (rivaroxaban). Xarelto is an orally bioavailable, reversible, direct inhibitor of Factor Xa. Its proposed indication is to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

An increased rate of thrombotic events, including stroke, was observed following Xarelto discontinuation in clinical trials. Additionally, in the absence of taking Xarelto with an evening meal or in a fasting state, the bioavailability of Xarelto is significantly reduced, potentially resulting in inadequate anticoagulation and decreased efficacy. Because of the potential risks, the Sponsor was requested by the Agency to address this risk in their voluntarily submitted proposed REMS.

DRISK agrees that the risk of thrombotic events upon Xarelto discontinuation, if an adequate alternative anticoagulant is not administered, and potential decreased efficacy of Xarelto therapy if not taken with the evening meal, warrants a REMS because the risks are both life-threatening and preventable. The Sponsor's proposed REMS includes a Medication Guide and Communication Plan that entails the distribution of a Dear Healthcare Professional Letter and a Dear Professional Organization Letter, and establishing and maintaining a Xarelto REMS website. We find the proposed REMS submitted on November 1, 2011 to be acceptable and recommend approval.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

On December 30, 2010, Janssen Pharmaceuticals, Inc. submitted a New Drug Application (NDA), identified as NDA 202-439, for Xarelto (rivaroxaban) proposing a new indication for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AFib). Rivaroxaban is an orally bioavailable, reversible, direct inhibitor of Factor Xa. In support of this indication, Janssen conducted the global ROCKET trial, a large (>14,000 subjects) randomized, double-blind (double dummy) event-driven non-inferiority trial in adults with nonvalvular AFib at high risk for thrombotic events. ROCKET compared rivaroxaban 20 mg once daily (15 mg in patients with CrCl 30-49 mL/min) to warfarin, which was to be titrated to a target range of 2.0 to 3.0. The primary endpoint was time to a composite of stroke and systemic embolism. During the clinical review and clinical pharmacology review, issues for concern were identified. The most notable concern was discovered in exploratory analysis of the data in the post-treatment phase which showed a significant rise in ischemic stroke events in patients who were on rivaroxaban compared to those on warfarin. From day 3 to day 30 after the last dose of study medication, 18/4587 (0.39%) ischemic stroke events occurred among completers in rivaroxaban compared to 4/4652 (0.09%) events in warfarin treated patients. Clinical reviewers and clinical pharmacology reviewers in DCRP believe the likely cause for this increased risk is that there was inadequate anticoagulation during the transition from rivaroxaban to warfarin therapy due to the absence of an appropriate bridging strategy.

The additional safety concern identified was that the 20 mg tablet (and similarly the 15 mg tablet) had an absolute bioavailability of approximately 66% under fasting conditions, which could result in a potential risk of inadequate anticoagulation with XARELTO therapy.

On July 1, 2011, rivaroxaban (10 mg once daily) was approved for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery. This indication was approved without a REMS.

On September 8, 2011, the Cardiovascular and Renal Drugs Advisory Committee met to discuss the efficacy and safety concerns expressed by DCRP and the approvability of the drug. Members of the committee felt that rivaroxaban is not superior to warfarin, nor is an effective alternative to warfarin. However, the majority of members felt that it was effective vs. placebo and should be an available alternative for patients failing other anticoagulant therapies.

Because of the risk of increased stroke due to the absence of an appropriate bridging strategy, and decreased bioavailability under fasting conditions, DCRP believes that the implementation of a REMS is necessary to ensure that the benefits of rivaroxaban treatment outweigh the potential risks of rivaroxaban treatment.

## **1.2 REGULATORY HISTORY**

Following are highlights of key regulatory actions and communications for Xarelto, following the NDA submission:

**30 December 2010:** Original Submission with REMS (Sequence Number 000)

**8 September 2011:** Cardiovascular and Renal Drugs Advisory Committee met to discuss the efficacy and safety concerns expressed by DCRP and the approvability of Xarelto

**29 September 2011:** REMS submission (Seq No. 0108)

**13 October 2011:** Interim Comments Set # 1 (requesting website landing page submission)

**14 October 2011:** REMS submission; website screenshots provided [via email]

**19 October 2011:** Teleconference with Sponsor

**25 October 2011:** Interim Comments Set # 2; first set of full comments on the REMS document, Supporting Document, and REMS website [via email]

**27 October 2011:** Interim Comments Set # 3 [via email]

**31 October 2011:** Interim Comment Set # 4 [via email]

**1 November 2011:** Interim Comment Set # 5 [via email]

**1 November 2011:** Submission of final agreed-upon REMS (Seq No. 0116)

## **2 METHODS AND MATERIALS**

### **2.1 DATA AND INFORMATION SOURCES**

The following data and information sources were reviewed:

Xarelto (NDA 202-439) REMS submitted December 30, 2010 (Seq No. 0000)

- REMS Amendment submitted September 29, 2011 (Seq No. 0108)
- REMS Amendment received October 20, 2011 (Seq No. 0113)
- REMS Amendment received October 26, 2011 (e-mail)
- REMS Amendment received October 28, 2011 (e-mail)
- REMS Amendments received October 31, 2011 (e-mail)
- REMS Amendment submitted November 1, 2011 (email)
- REMS Amendment submitted November 1, 2011; final agreed-upon REMS (Seq No. 0116)

The following data and information sources were referenced:

- Xarelto Prescribing Information [substantially completed labeling], dated October 28, 2011
- Office of Prescription Drug Promotion (OPDP) Internal Consult, Comments on Draft REMS Materials. Reviewer: Emily Baker, dated October 26, 2011
- Cross-Discipline Team Leader Review. Reviewer: A. Thompson, dated October 6, 2011
- Clinical Review of Xarelto. Reviewers: N. Beasley, P. Dunnmon and M. Rose, dated August 10, 2011
- Clinical Pharmacology Review of Xarelto. Reviewers: S.N. Sabarinath and TY McDowell, dated August 10, 2011

## **2.2 ANALYSIS TECHNIQUES**

The REMS proposal was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA) and consistency with the requirements communicated during a teleconference between Alison Blaus, regulatory project manager, and Sponsor representatives on September 22, 2011.

## **3 RESULTS OF REVIEW OF PROPOSED REMS**

### **3.1 SAFETY CONCERNS**

A REMS has been determined to be necessary to ensure that the benefits of XARELTO outweigh the potential risks in patients with nonvalvular AFib, including:

- Increased risk of thrombotic events, including stroke, if XARELTO is discontinued without introducing an adequate alternative anticoagulant
- Potential decreased efficacy of XARELTO (15 mg and 20 mg) if not taken with the evening meal

### **3.2 GOALS**

The goals of the XARELTO<sup>®</sup> REMS are:

1. To inform healthcare professionals (HCPs) that discontinuing XARELTO without introducing an adequate alternative anticoagulant places non-valvular atrial fibrillation

patients at an increased risk of thrombotic events, including stroke, and to follow recommendations in the US Prescribing Information (USPI) on how to convert atrial fibrillation patients from XARELTO to warfarin or other anticoagulants.

2. To inform non-valvular atrial fibrillation patients that XARELTO should not be stopped without first informing their healthcare professional as to minimize the risks of post-discontinuation thrombotic events.
3. To inform healthcare professionals and non-valvular atrial fibrillation patients that XARELTO (15 or 20 mg tablets) should be taken with the evening meal.

### **3.3 REMS ELEMENTS**

#### **3.3.1 Medication Guide**

A Medication Guide will be dispensed with each XARELTO prescription in accordance with 21 CFR 208.24.

#### **3.3.2 Communication Plan**

Janssen Pharmaceuticals Inc. will implement a communication plan to HCPs to support the implementation of this REMS. This communication plan will include the following:

##### **3.3.2.1 Dear Healthcare Professional Letter**

A Dear Healthcare Professional (DHCP) Letter will be distributed by mail to: interventional cardiologists; clinical cardiologists; neurologists; emergency medicine physicians; internal medicine physicians; primary care physicians; nurse practitioners; physician assistants; pharmacists; critical care nurses, and cardiac nurse specialists. The letter will be distributed within 60 days, 12 months, and 24 months after the approval of the REMS, and in the event of any substantial safety update. A copy of the USPI and Medication Guide will accompany the DHCP Letter.

In addition, upon request, the DHCP Letter, USPI and Medication Guide will also be distributed to HCPs via sales representatives and medical science liaisons at the time of initial contact, when inquired about the risks outlined in the REMS.

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

##### **3.3.2.1 XARELTO REMS website**

Within 30 days of REMS approval, Janssen Pharmaceuticals Inc. will post printed or web-based information for HCPs and patients on the XARELTO REMS website ([www.xarelto.rems.com](http://www.xarelto.rems.com)). This information will remain on the website for a period of 2 years. The USPI and the Medication Guide will be provided in conjunction with the letter.

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

- Goals of the REMS
- Information about the risk
- Prescribing information for XARELTO

- Medication Guide for XARELTO
- DHCP Letter (for a period of 2 years)

The web-based material is part of the REMS and is appended.

### **3.3.2.2 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. Janssen Pharmaceuticals Inc. will request that these organizations disseminate this information to their members. Janssen Pharmaceuticals Inc. will communicate the letter to the leadership of the following professional organizations:

- The American Heart Association (AHA)
- The American College of Cardiologists (ACC)
- The Society for Cardiovascular Angiography and Interventions (SCAI)
- The American Academy of Neurology (AAN)
- The American Neurological Association (ANA)
- The National Institute of Neurological Disorders and Stroke (NINDS)
- The American Stroke Association (ASA)
- The National Stroke Association (NSA)
- The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)
- The Association of Emergency Physicians (AEP)
- The American College of Chest Physicians (ACCP)
- The Association of Black Cardiologists (ABC)
- The American Academy of Family Physicians (AAFP)
- The American College of Physicians (ACP)
- The National Medical Association (NMA)
- The American Academy of Nurse Practitioners (AANP)
- The American Academy of Physician Assistants (AAPA)
- The American College of Clinical Pharmacy (ACCP)
- The American Society of Health-System Pharmacists (ASHP)
- The American Pharmacists Association (APhA)
- The American Association of Critical-Care Nurses (AACCN)
- The 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.

### **3.3.2.3 Timetable for Submission of Assessments**

Janssen Pharmaceuticals Inc. will submit REMS assessments to FDA 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 will conclude no earlier than 60 days before the submission date for that assessment. Janssen Pharmaceuticals Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

### **3.4 REMS ASSESSMENT PLAN**

The evaluation for the effectiveness of the XARELTO<sup>®</sup> REMS will include the following:

- 1) An evaluation of patients' understanding of the serious risks of XARELTO.
- 2) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- 3) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- 4) A report on the distribution of DHCP letters.
- 5) An evaluation of healthcare providers' awareness and understanding of the serious risks associated with XARELTO (for example, through surveys of healthcare providers).
- 6) 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**

The proposed REMS for Xarelto, submitted on November 1, 2011, addresses all the necessary revisions and reflects the Sponsor's acceptance of the FDA recommendations from previous interim reviews.

## **5 CONCLUSION**

In conclusion, the amended proposed REMS for Xarelto (rivaroxaban), tablets 15 and 20 mg, dated November 1, 2011, contains the appropriate and agreed upon revisions on the REMS components (Medication Guide and communication plan) as stipulated by the Agency on September 22, 2011. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of Xarelto in achieving the goals.

Therefore, the Xarelto REMS acceptable to the Division of Risk Management.

## **6 RECOMMENDATIONS**

The DRISK recommends approval of the Xarelto REMS as submitted on November 1, 2011.

## **APPENDICES**

REMS Document

Dear Healthcare Professional (DHCP) Letter

Dear Professional Organization Letter

Medication Guide

Xarelto REMS Website

16 Pages have been Withheld in Full as duplicate REMS located in the "REMS Section".

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/s/  
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DANIELLE SMITH  
11/04/2011

CLAUDIA B KARWOSKI  
11/04/2011  
concur