

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202439Orig1s000**

**OTHER REVIEW(S)**



## DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

### *Regulatory Project Manager Review*

**NDA:** 202439  
**Drug:** XARELTO (rivaroxaban) 15 and 20 mg Tablets  
**Class:** Factor Xa Inhibitor  
**Sponsor:** Johnson & Johnson PRD (on behalf of Janssen Pharmaceuticals)  
**Initial Indication:** “XARELTO® is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.”  
**Final Indication:** XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled [*see Clinical Studies (14.1)*].

**Date of submission:** 5 January 2011  
**Approval date:** 4 November 2011  
**PDUFA date:** 5 November 2011

#### ❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Cross Discipline Team Leader (CDTL)
    - Aliza Thompson, M.D.
  - Medical Reviewers
    - Preston Dunnmon, M.D. (Safety)
    - Martin Rose, M.D., JD (Efficacy)
  - Pharmacology & Toxicology
    - Pat Harlow, Ph.D.
  - Regulatory Health Project Manager
    - Alison Blaus
- Office of New Drug Quality Assessment (ONDQA), Branch I
  - Pei-I Chu, Ph.D. (Drug Product)
- Office of Clinical Pharmacology
  - Sabarinath, Sreedharan, Ph.D.
  - Tzu-Yun McDowell, Ph.D.
- Office of Biostatistics, Division of Biometrics I
  - John Lawrence, Ph.D.
- Office of Surveillance and Epidemiology
  - John Senior, M.D. (Liver Review)
  - Denise Baugh (DMEPA)
  - Latonia Ford (Medication Guide)
  - Danielle Smith (Risk Evaluation and Mitigation Strategy - REMS)

- Office of Medical Policy, Division of Drug Marketing, Advertising and Communications (DDMAC)
  - Emily Baker – Full Product Labeling
  - Zarna Patel – Patient Labeling
- Office of Compliance, Division of Scientific Investigations (DSI)
  - Susan Thompson, M.D. (Clinical Studies)

❖ **BACKGROUND**

Rivaroxaban (BAY 59-7939) is an oral Factor Xa inhibitor that was being co-developed by Johnson & Johnson Pharmaceuticals (J&J) and Bayer HealthCare Pharmaceuticals (Bayer) under IND 75,238 for the prevention of stroke and non-central nervous system (non-CNS) systemic embolism in patients with non-valvular atrial fibrillation (AFib). Rivaroxaban is also being developed under [REDACTED] (b) (4) and under IND 64,892 (managed by the Division of Hematology Products) for prevention and treatment of venous thromboembolism (VTE) and Deep Vein Thrombosis (DVT). Bayer and J&J submitted NDA 22-406 to market rivaroxaban for the prevention of DVT after major orthopedic surgery based on the data from the RECORD studies but the sponsor was issued a Complete Response letter on 27 May 2009. NDA 22-406 was resubmitted on 3 January 2011 and later approved on 3 July 2011.

The sponsors completed two Phase 3 trials under IND 75,238, ROCKET-AF and J-ROCKET-AF.

- ROCKET-AF (**R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared with **V**itamin **K** Antagonism for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation) was a randomized, double-blind, double-dummy, noninferiority study evaluating the efficacy and safety of administering rivaroxaban 20 mg once daily (15 mg for renal impaired) compared to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. The dose studied was 20 mg once daily (15 mg for those with Cr CL 30-49). ROCKET-AF enrolled approximately 12000 patients.
- J-ROCKET-AF was essentially the same as ROCKET-AF with respect to study design, but was specifically conducted for the Japanese NDA and was not powered as a stand-alone pivotal study. This study was designed to demonstrate non-inferiority of rivaroxaban to warfarin in terms of bleeding events and enrolled approximately 1200 patients. The doses studied were 15 mg once daily (10 mg for those with Cr CL 30-49)

In the initial submission, the sponsor sought the following indication:

“XARELTO<sup>®</sup> is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.”

The review of this application proceeded relatively smoothly, meeting all 21<sup>st</sup> century review timelines, with approximately 126 information requests since 5 January 2011.

❖ **REGULATORY TIMELINE and GENERAL APPLICATION POINTS (for the atrial fibrillation indication only)**

- IND received: 13 June 2006
- End of Phase 2 Meeting: 12 September 2006 (minutes dated 25 September 2006)
- ROCKET-AF Monitoring Meeting: 29 September 2009 (minutes dated 19 October 2009)
- Pre-NDA Meeting: 27 October 2009 (minutes dated 6 November 2009)
- ROCKET-AF data presented to FDA on 8 November 2010 (minutes dated 7 December 2010)
- NDA submission Received on 5 January 2011

- Filing Meeting: 3 February 2011
- 74-day Issues Letter with Comments: 17 March 2011
- Executive Carcinogenicity Assessment Committee (CAC) Meeting: 15 April 2011
- Mid-cycle Meeting: 2 June 2011
- Advisory Committee: 8 September 2011
- PDUFA Date: 5 November 2011
- Approval Date: 4 November 2011

### **User Fee**

The user fee for this application was paid in full on 12 November 2010, prior to the submission of the application (ID 3010832).

### **Pediatric Review Committee (PeRC)**

The PeRC meeting to discuss this application was held on 28 September 2011. The PeRC and the Division agreed with the sponsor that, “Atrial fibrillation is a relatively rare form of arrhythmia in the pediatric population. When it is seen in an infant or child, it is often associated with a structural heart abnormality, particularly after surgical repair or palliation of congenital heart disease. Other episodes may be associated with metabolic derangements.” A full pediatric waiver was granted for this application.

### **Advisory Committee**

The rivaroxaban ADCOM was held on 8 September 2011 (please see quick minutes in the action package). The members of the committee voted 9 (Yes) to 2 (No) (with 1 abstain) in favor of approval. When asked, however, about the claim that rivaroxaban should be given, some members felt the drug was not superior to warfarin, nor was it an effective alternative to warfarin. Members felt it was effective vs. placebo and in some members opinions should be deemed a second line therapy. Rivaroxaban was considered to merit a claim for patients failing other anticoagulant therapies. Failure of other anticoagulant therapies was defined as issues such as warfarin-induced skin necrosis or gastrointestinal upset with dabigatran.

### **Trade name**

XARELTO was deemed fully acceptable for use on 12 May 2011.

### **Review Status**

The sponsor proposed a priority review for this application. Upon discussion at the 3 February 2011 filing meeting, the Division disagreed and instead designated a standard review timeline. The rationale for denying a priority review was outlined in Dr. Rose’s memorandum dated 4 February 2011.

### **❖ LABELING REVIEW**

Labeling discussions began in late September with an internal labeling planning meeting. At that meeting, we agreed that we would work with the Study Endpoints and Labeling Division (SEALD) to ensure that our sections of the label would comply with the Code of Federal Regulations (21 CFR 201.56 and 201.57) and the Selected Requirements for Prescribing Information (SRPI). Although SEALD had a number of comments regarding the sections of the PI pertaining to the Hematology, the Division decided that those comments would be provided to Hematology for their consideration. If they came to an agreement on the changes, we would make those changes for them as part of this application.

In the overall presentation of the information in the label, the Agency agreed that all of the information in the label should be presented in each section, first by information that applied to both indications and then information pertaining to atrial fibrillation followed by Prophylaxis of Deep Vein Thrombosis.

The Agency and the sponsor had negotiations regarding several aspects of the labeling. The most notable sections, some of the discussion that took place regarding wording, and the final outcome are documented below:

**Boxed Warning**

The Agency had a teleconference with Johnson & Johnson and Bayer on 12 October 2011 to discuss various aspects of labeling. The sponsor thought the below proposed boxed warning (b) (4)

Although we acknowledged the point made by the sponsor that line one of the Boxed Warning was not unique to XARELTO and was a risk for all antithrombotics, the Division disagreed that (b) (4) The Division agreed to review alternative language proposed by the sponsor, but said that due to the clinical data/events observed post discontinuation in ROCKET, the overall need for a box was warranted:

(b) (4)

On 14 October 2011, the sponsor again proposed (b) (4)

(b) (4)

(b) (4)

The Division did not agree with the removal of the box but was open to the sponsor slightly rewording the box language and to propose language on 21 October 2011. After multiple discussions, the sponsor and the Agency agreed on the following box language (for the AFIB indication only – the DVT portion of the box was amended slightly after agreement from the Division of Hematology and appears in the final labeling attached to the action letter):

**WARNINGS: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA**

**A. DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION**

**Discontinuing XARELTO places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant [see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Clinical Studies (14.1)].**

**Section 1 – Indication**

The sponsor proposed an indication similar to the first paragraph of the below (that proposal can be found in the Background section of this review). During the labelling meetings, the Division had discussed possible options for the indication such as describing XARELTO as a second line therapy to PRADAXA (dabigatran) and warfarin (b) (4)

After much discussion and several iterations, the Division proposed the following indication.

“XARELTO® (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

(b) (4)

Although the sponsor agreed to the first paragraph of the Division’s proposal at our 12 October 2011 teleconference, they did not agree with the second paragraph (b) (4)

The Division disagreed and said that this information was unique to this application and that it needs to be prominently described. The Division added that the increase in events in the rivaroxaban arm when transitioning to warfarin was important enough to place in a box and thus important enough to place in Indication section. In their 14 October version of the label, the sponsor proposed the following:

“XARELTO (rivaroxaban) Tablets are indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

(b) (4)

After considering the sponsor’s proposal, we suggested the following indication. The Division felt that simply noting (b) (4) would leave the decision to the sponsor on what (b) (4) meant and did not think it was appropriate to include a (b) (4) as the number was subjective and the concept a (b) (4) rather than one used commonly in clinical practice:

“XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the

risk of stroke and systemic embolism when warfarin therapy is (b) (4) [see *Clinical Studies (14.1)*].”

After consideration from the sponsor, the Agency and sponsor came to agreement on the final indication, by changing (b) (4) to “well-controlled”:

XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled [see *Clinical Studies (14.1)*].

## **Section 2 – Dosage and Administration**

Under subsection 2.1 (Atrial Fibrillation), the Agency proposed the following instructions to describe how patients should be transitioned from XARELTO to warfarin. It is important to note that no transition strategy was formally studied in ROCKET and that this strategy was based on Clinical Pharmacology data.

(b) (4) *from or to Warfarin* - When switching patients from warfarin to XARELTO, discontinue warfarin and start XARELTO as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.”

The sponsor pointed out that although investigators tended to target an INR of 2.0 after discontinuing XARELTO, in actuality, the INR at the time tended to be much lower than 2.0 at the actual time of transition. The risk of thrombotic stroke rose more quickly for INR < 2 than the risk of hemorrhagic stroke for INR > 3. With that in mind, the sponsor proposed that the target INR of 2.0 be higher. The Division did not object with the sponsor’s rationale that waiting until INR was < 2 placed patients at higher risk than if they were above 3, thus noting a target transitioning INR of “below 3.0”.

## **Section 5 – Warning and Precautions**

Upon suggestion by Dr. Ford, the Medication Guide reviewer, section 5 was reordered to place 5.1 (Risk of Bleeding) in 5.2 and move 5.2 (Increased Risk of Stroke After Discontinuation in Atrial Fibrillation) to the first warning. This reordering of the warnings was to be consistent with the warning placed in the box. The Agency’s policy is that information in section 5 should be ordered by importance of the information and since risk of stroke was placed in a box, it should appear first.

## **Section 8 - Use in Specific Populations**

Dr. Harlow had the following labeling recommendations that were also included in the label approved by the Division of Hematology products, NDA 22406, on 1 July 2011:

### **8.1 Pregnancy**

#### **Pregnancy Category C**

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing.

Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus. Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown

pronounced maternal hemorrhagic complications in rats and an increased incidence of postimplantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of 10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 11 times the human exposure of unbound drug, based on AUC comparisons to the maximum recommended human dose of 10 (20) mg/day. Fetal body weight decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 40 (14) times the human exposure of unbound drug.

## **8.2 Labor and Delivery**

Safety and effectiveness of rivaroxaban during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 17 times maximum human exposure of the unbound drug at the human dose of 10 (20) mg/day).

## **8.3 Nursing Mothers**

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

## **Section 13 – Non-Clinical Toxicology**

### **13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 3- and 5-times (1 and 1.6 times), respectively, the human exposure of unbound drug at the human dose of 10 (20) mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 4- and 10-times (2- and 4-times), respectively the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells in vitro or in the mouse micronucleus test in vivo.

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 33 (13) times the exposure in humans given 10 (20) mg rivaroxaban daily

There was no useful information to present under **Section 13.2 (Animal Toxicology and/or Pharmacology)**.

## **Section 14 – Clinical Studies**

A number of items were a point of discussion in section 14.

- On 19 October, the following geographical distribution and the TTR from ROCKET was added to Section 14 right before Table 6 (it had previously been placed after Figure 1 – and the Division placed the word “only” prior to the percentage):

“Subjects were enrolled in Eastern Europe (39%), North America (19%), Asia Pacific (15%), Western Europe (15%), and Latin America (13%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of only 55%, worse during the first few months of the study.”

In a 19 October teleconference, we agreed that the sponsor could propose alternative wording, but that the TTR would definitely need to be included in the trial and not be buried at the end of the section.

- Table 6 – The sponsor proposed [REDACTED] (b) (4)  
[REDACTED] the Division disagreed and noted that it would only be appropriate to include hazard ratios for the composite. [REDACTED] (b) (4)  
[REDACTED]
- Figure 1 - Kaplan-Meier (KM) Curves of Adjudicated Primary Composite Endpoint of Stroke and Non-CNS Systemic Embolism by Treatment Group (All Randomized Patients Followed to Site Notification) – On 12 October, the Division asked the sponsor to rework their original KM curve to include a Y axis that is the cumulative event rate, [REDACTED] (b) (4)  
[REDACTED] The sponsor provided a curve on 14 October, but needs to provide another curve that would be clear enough for printing (it was suggested to crop the time to 2.5 years if that provides a clearer curve).

#### ❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the XARELTO team members, organized by role or discipline.

##### **Divisional Memorandum** (4 November 2011)

Dr. Grant authored the Division memo noting the rationale behind the approval of XARELTO for atrial fibrillation.

##### **Cross-Discipline Team Leader (CDTL) Review** (6 October 2011)

In Dr. Thompson's review, dated 6 October 2011, she recommended approval of this application. She noted, however, a number of reasons for this decision as well as some suggestions for potential post-marketing commitments/requirements and risk evaluation and management strategies.

##### *Recommendation for other Postmarketing Requirements and Commitments*

Per Dr. Thompson, bleeding is an important toxicity of anticoagulants and at this time, there is no established antidote for rivaroxaban. GI bleeding was more common on rivaroxaban and in the U.S., rates of major bleeding were high. Dr. Thompson believed that a postmarketing study was needed to address methods for reversing rivaroxaban's anticoagulant activity and hence ensure that rivaroxaban's risks do not exceed its benefits. The following options could be explored per Dr. Thompson's review:

- (1) preclinical studies (there would need to be confidence that findings from such studies could be easily translated into humans)
- (2) an enhanced pharmacovigilance plan (this could be linked to the pre-existing postmarketing requirement under NDA 022406)
- (3) a clinical study testing the effects of a promising agent/intervention on bleeding in patients experiencing a clinically significant bleed or in patients who require urgent invasive or surgical procedures.

##### *Recommendation for Postmarketing Risk Evaluation and Management Strategies*

Dr. Thompson noted that rivaroxaban's atrial fibrillation communication plan should address events seen in the post-treatment period (with emphasis on the risk of embolic events if rivaroxaban is stopped and adequate anticoagulation is not provided by another agent) and

bleeding risk. It should possibly also address the need to administer rivaroxaban with the evening meal.

**Clinical Review** (dated 10 August 2011)

Drs. Dunnmon and Rose reviewed the rivaroxaban NDA from a safety and efficacy standpoint respectively. Upon review of the clinical data, submitted up to and including 1 August 2011, both clinical reviewers recommend a complete response. The justification for their complete response recommendation was as follows:

1. Rivaroxaban's Relative Effectiveness to Warfarin - There is a lack of substantial evidence that rivaroxaban will have its desired effect when used as recommended in labeling. (21 CFR 314.125(b)(5)). The data from ROCKET is not adequate to determine whether rivaroxaban is as effective for its proposed indication in comparison to warfarin when the latter is used skillfully (e.g., TTR >~68%, near the midpoint of center based TTR in the RE-LY study (trial comparing dabigatran vs. warfarin), and the US median TTR of 65% in ROCKET). In order for atrial fibrillation (AFib) patients to be protected from the risk of thrombotic events, a new drug for this indication should be demonstrated to be as effective as warfarin when it is used skillfully. This requirement is based on an FDA policy that requires drugs for conditions that are "life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack)..." to be shown to as effective as approved agents. This issue also implicates 21 CFR 314.125(b)(4), described in the next paragraph, because of the potential risk of additional strokes in patients who might receive rivaroxaban instead of approved treatment should rivaroxaban be approved. The FDA policy cited above and other aspects of this issue were discussed in detail in Section 6.1.10.2 of the complete clinical review.
2. Transition from Rivaroxaban - There is insufficient information about the drug to determine whether it is safe for use with its proposed labeling (21 CFR 314.125(b)(4)). In ROCKET there was an excess of strokes in the rivaroxaban arm during the transition from blinded study drug to open label warfarin at the end of the study. The Sponsor's proposed instructions for the transition from rivaroxaban to warfarin, developed *after* ROCKET was completed, have not been evaluated or shown to be safe in terms of bleeding risk or embolic risk in a clinical study. Such a study must be performed prior to approval in this case (see Section 6.1.10.3.7 of the clinical review for a discussion of this issue). The study of the transition regimen could be performed as part of the study needed to satisfy the deficiency cited in paragraph 1, above. There are no additional or novel issues that would preclude rivaroxaban's US approval from a safety perspective.

**Biostatistics Review** (dated 28 July 2011)

Upon review of the rivaroxaban NDA, Dr. Lawrence confirmed that rivaroxaban was non-inferior to warfarin, as warfarin was used in the study, on the primary endpoint (time to a composite of stroke and systemic embolism). When analyzing the data up to 2 days after last dose, the confidence interval for the hazard ratio is entirely below 1 (point estimate = 0.79, 95% CI = (0.66, 0.96)). There is a question about whether warfarin was used optimally in the study (the median TTR across sites was 59). For superiority, the ITT analysis is preferred. In the ITT analysis, the confidence interval does not exclude 1 (point estimate = 0.91, 95% CI = (0.77, 1.08)). Rivaroxaban was not superior on all-cause mortality by either the on-treatment or ITT analysis.

**Clinical Pharmacology Review** (dated 10 August 2011)

Dr. Sabarinath and McDowell reviewed the pending application and had the following recommendations:

- Recommended Dosing Regimen - Rivaroxaban should be administered daily at the recommended dose with the evening meal.
- Specific Populations:

- Patients with moderate (CrCl 30-49 mL/min) and severe (CrCl 15-29 mL/min) renal impairment should receive 15 mg rivaroxaban once daily.
- Patients with moderate hepatic impairment (Child-Pugh B) should receive 10 mg rivaroxaban once daily.
- **Aspirin Concomitant Use** - The concurrent use of aspirin is a major risk factor for bleeding. This increase in bleeding risk is similar between rivaroxaban and warfarin. However, concomitant aspirin use does not seem to provide an additional benefit for the stroke prevention. Patients should be advised about the increased bleeding risk with concomitant aspirin use while on rivaroxaban therapy.
- **Transitioning from Rivaroxaban to Warfarin** - A reasonable transition strategy for switching patients from rivaroxaban to warfarin, considering the time course of their PD effects, is concomitant administration of rivaroxaban and warfarin for 2 days or more. The strategy ensures an INR  $\geq 2$  during the transition period. Rivaroxaban should be stopped once the observed pre-dose INR is  $\geq 2$  and the INR should be maintained within the target range of 2-3 with warfarin. Since rivaroxaban is recommended to be dosed with the evening meal, for the purpose of monitoring the INR during the transition period, the INR measurement on the next day (i.e., after 16 hours post dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured daily during the transition until the INR  $\geq 2$ .

**Pharmacometrics Review** (10 August 2011)

Dr. McDowell conducted a combined review with Dr. Sreedharan. Please see the summary under Clinical Pharmacology which is inclusive of both Clinical Pharmacology and Pharmacometrics.

**Pharmacology & Toxicology Review** (1 August 2011)

Dr. Patricia Harlow reviewed the rivaroxaban atrial fibrillation NDA and found from a non-clinical perspective, the application was approvable. Most of the toxicities she identified in the non-clinical studies were either attributable to the pharmacodynamic effect of rivaroxaban or that satisfactory safety margins had been demonstrated relative to human therapeutic exposures.

**Office of New Drug Quality Assessment (ONDOA), Branch I, Review** (31 January 2011, 27 June 2011, 27 September 2011)

The chemistry, manufacturing, and controls (CMC) section of NDA 202439 was reviewed by Dr. Chu. Upon a preliminary review of the CMC section, an information request letter was sent to the sponsor on 12 June 2011. The sponsor provided responses to the IR questions on 30 June 2011, which Dr. Chu found acceptable. Meanwhile, the Office of Compliance determined the drug substance, drug product and packaging facilities were adequate. Pre-approval inspections for the drug substance, drug product and packaging sites were not needed based on profile. This NDA was recommended for **approval** from the perspective of CMC.

❖ **CONSULTS REVIEWS**

**Office of Surveillance and Epidemiology Review - Liver** (16 June 2011)

The liver related data from ROCKET was reviewed as part of NDA 22406 and the review by Dr. Senior can be found under the action package for that NDA.

**Office of Surveillance and Epidemiology Review – REMS and Medication Guide** (19 October and 4 November 2011)

Latonia Ford was the OSE reviewer of the Medication Guide. Her review and recommendations were received on 19 October 2011. Dr. Danielle Smith conducted a review of the REMS/Communication plan and finalized her review on 4 November 2011.

**Division of Scientific Investigations (DSI) Summary Review** (31 August 2011)

Seven clinical investigator sites and the sponsor were inspected in support of this application. The inspection documented regulatory violations at Dr. Rubin's, Dr. Militaru's, and Dr. Jandik's sites regarding protocol violations. In addition, there were recordkeeping and informed consent violations at Dr. Tirador's site. The minor and infrequent regulatory violations documented at these sites should have no significant impact on data integrity or subject safety.

In general, inspection at the sites of Drs. Zelenka, Alvarez, and Raev as well as the sponsor Johnson & Johnson Research & Development LLC revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

*Follow-Up Actions:* The observations for Johnson & Johnson Research & Development are based on preliminary communications with the FDA Field investigator and for Dr. Militaru on preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

**Division of Drug Marketing, Advertising and Communications (DDMAC)** (19 October and 21 October 2011)

The review of the patient labeling section of the Medication Guide, by Zarna Patel, can be found as part of Latonia Ford's review. The Full Prescribing Information was reviewed by Emily Baker and was finalized on 21 October 2011.

**CONCLUSION**

XARELTO® (rivaroxaban) Tablets for non-valvular atrial fibrillation was approved on 4 November 2011. An approval letter detailing the terms of the approval was drafted and signed by Norman Stockbridge, M.D., Ph.D. The final agreed upon Carton & Container Labeling, Package Insert, Medication Guide, Communication Plan and REMS were appended to the approval letter.



## SEALD LABELING: PI SIGN-OFF REVIEW

|   |  |
|---|--|
| APPLICATION NUMBER                                      | NDA 202439   |
| APPLICANT   | Janssen Pharmaceuticals, Inc.  |
| PRODUCT NAME  | XARELTO (rivaroxaban)  |
| SUBMISSION TYPE   | Efficacy supplement reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation |
| SUBMISSION DATE   | 5 January 2011   |
| PDUFA DATE  | 5 November 2011  |
| SEALD SIGN-OFF DATE                                     | 4 November 2011  |
| OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING | Laurie Burke   |

This memo confirms that all Selected Requirements for Prescribing Information (SRPI) criteria are met in the final agreed-upon PI as noted in the SEALD Labeling Review filed today, 4 November 2011. SEALD has no objection to PI approval at this time.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LAURIE B BURKE  
11/04/2011

## SEALD LABELING REVIEW for XARELTO (rivaroxaban)

This SEALD Labeling Review evaluates whether there are major aspects of the prescription labeling (U.S. prescribing information) that do not meet the requirements of 21 CFR 201.56 and 201.57 or related CDER labeling guidances and policies.

|                          |  |
|--------------------------|--|
| APPLICATION NUMBER       | NDA 202439   |
| APPLICANT                | Janssen Pharmaceuticals, Inc.  |
| PRODUCT NAME             | XARELTO (rivaroxaban)  |
| TYPE OF APPLICATION      | Efficacy Supplement  |
| INDICATION               | Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation |
| TYPE OF PRODUCT          | Anticoagulant  |
| OFFICE/DIVISION          | ODEI/DCRP  |
| DIVISION PROJECT MANAGER | Alison Blaus   |
| SUBMISSION DATE          | January 5, 2011  |
| PDUFA DATE               | November 5, 2011   |
| SEALD REVIEW DATE        | November 4, 2011   |
| SEALD LABELING REVIEWERS | Perry Mackrill and Eric Brodsky, M.D.  |

The following checked Selected Requirements for Prescribing Information (SRPI) items have been reviewed for this efficacy supplement. These 46 specific SRPI items assess mostly labeling format according to regulations and labeling guidances. These reviewers actively engaged with the Division of Cardio Renal Products (primary review division) and the Division of Hematology Products on the content and the format of the XARELTO prescribing information. Based on this SRPI review, there are **NO** outstanding labeling issues that must be corrected before the final Xarelto prescribing information is approved.

## SEALD LABELING REVIEW

### Review of Selected Requirements for Prescribing Information (SRPI) for Xarelto

#### **Conclusion: No SRPI deficiencies based on review of 11/4/11 USPI**

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. Only identified deficiencies are checked (no checks means no deficiencies).

#### **Highlights (HL)**

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

|  |
|--|
| • <b>Highlights Limitation Statement</b> (required statement)  |
| • <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information) |
| • <b>Initial U.S. Approval</b> (required information)  |
| • <b>Boxed Warning</b> (if applicable)   |
| • <b>Recent Major Changes</b> (for a supplement)   |
| • <b>Indications and Usage</b> (required information)  |
| • <b>Dosage and Administration</b> (required information)  |
| • <b>Dosage Forms and Strengths</b> (required information)   |
| • <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)                          |
| • <b>Warnings and Precautions</b> (required information)   |
| • <b>Adverse Reactions</b> (required AR contact reporting statement)   |
| • <b>Drug Interactions</b> (optional heading)  |
| • <b>Use in Specific Populations</b> (optional heading)  |
| • <b>Patient Counseling Information Statement</b> (required statement)   |
| • <b>Revision Date</b> (required information)  |

## SEALD LABELING REVIEW

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

## SEALD LABELING REVIEW

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

### • General Format

- A horizontal line must separate the TOC and FPI.
- The heading **FULL PRESCRIBING INFORMATION** must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

### • Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

### • Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

## SEALD LABELING REVIEW

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

**SEALD Reviewer Comment: In the Adverse Reactions section of the Xarelto full prescribing information, the term “bleeding events” is used. However, according to the DCRP division this term is recognized in the field and the terms “bleeding reactions” is not recognized. Therefore, this is not a SRPI deficiency.**

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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ERIC R BRODSKY  
11/04/2011

FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Center of Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Promotion/Division of Direct-to-Consumer  
Promotion

## Memorandum

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** October 21, 2011

**To:** Alison Blaus  
Regulatory Project Manager  
Division of Cardio-Renal Products (DCRP)

**From:** Emily Baker, PharmD  
Regulatory Review Officer  
Division of Professional Promotion (DPP)  
Office of Prescription Drug Promotion (OPDP)

Zarna Patel, PharmD  
Regulatory Review Officer  
Division of Direct-to-Consumer Promotion (DDTCP)  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **Drug: Xarelto® (rivaroxaban) tablets**  
**NDA: 202439**

OPDP has viewed the proposed Package Insert (PI) and Medication Guide submitted for consult on October 11, 2011, for Xarelto® (rivaroxaban) tablets. OPDP's comments are provided directly in the attached marked-up copy of the proposed labeling.

Our comments are based on the proposed labeling at the following EDR location:  
<\\CDSESUB1\EVSPROD\NDA202439\202439.ENX>.

DDTCP also reviewed the comments on the proposed Medication Guide from the Division of Risk Management (DRISK) dated October 19, 2011.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PI, please contact Emily Baker at 301.796.7524 or [emily.baker@fda.hhs.gov](mailto:emily.baker@fda.hhs.gov)

If you have any questions on the comments for the Medication Guide, please contact Zarna Patel at 301.796.3822 or [zarna.patel@fda.hhs.gov](mailto:zarna.patel@fda.hhs.gov).

34 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
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/s/  
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EMILY K BAKER  
10/21/2011

**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**

**Label and Labeling Review**

|                         |   |
|-------------------------|---|
| Date                    | October 21, 2011  |
| Reviewer                | Denise V. Baugh, PharmD, BCPS<br>Division of Medication Error Prevention and Analysis |
| Team Leader             | Todd Bridges, R.Ph.<br>Division of Medication Error Prevention and Analysis           |
| Deputy Director         | Kellie Taylor, PharmD, MPH<br>Division of Medication Error Prevention and Analysis    |
| Division Director       | Carol Holquist, R.Ph.<br>Division of Medication Error Prevention and Analysis         |
| Drug Name and Strength  | Xarelto (Rivaroxaban) Tablets<br>15 mg and 20 mg                                      |
| Application Type/Number | NDA 202439  |
| Applicant               | Johnson & Johnson Pharmaceutical Research &<br>Development                            |
| OSE RCM                 | 2011-438  |

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

## 1 INTRODUCTION

This review evaluates the container labels, carton and insert labeling for Xarelto (Rivaroxaban) Tablets for the strengths of 15 mg and 20 mg under NDA 202439. The 10 mg strength for this drug product was approved July 1, 2011 for NDA 022406. We provide recommendations in Section 4 for improvements to the labels and labeling.

### 1.1 BACKGROUND AND REGULATORY HISTORY

Xarelto (Rivaroxaban) Tablets, 10 mg was approved July 1, 2011 (NDA 022406). It is indicated for the prophylaxis of DVT in patients undergoing knee or hip replacement surgery. The proposed indication for NDA 202439 is to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and the proposed strengths will be 15 mg and 20 mg.

On October 3, 2011, the Division of Cardiovascular and Renal Products (DCRP) for NDA 202439 noted that the food requirements for drug administration, the dosage adjustments for renal impairment, drug-drug interactions, and warnings and precautions sections of the insert labeling differed from NDA 022406 which is the same active ingredient, Rivaroxaban (See Table 1 for comparisons in treatment regimens). The Division was concerned about the complexity of the insert labeling and the risk for erroneous prescribing and monitoring if these two indications were addressed in one insert labeling and whether a dual trade name with two separate inserts was a safer path. Based upon post marketing experience, DMEPA's concern was for the potential for accidental duplicate therapy if dual trade names were allowed to exist in the marketplace. The Applicant's preference is for one insert labeling with one proprietary name. After discussions between the Division of Hematology Products, the Applicant and DMEPA, it was decided that one proprietary name and insert labeling would be a safer option.

### 1.2 PRODUCT INFORMATION

The following table summarizes the product characteristics for NDA 022406 (approved July 1, 2011) and NDA 202439.

**Table 1.** Differences in Treatment Regimens between Xarelto (Rivaroxaban) Prescribed for DVT and atrial fibrillation

|                   | <b>Xarelto<br/>(Rivaroxaban)<br/>NDA 022406</b>  | <b>Xarelto<br/>(Rivaroxaban)<br/>NDA 202439</b>   |
|-------------------|--|---|
| <b>Indication</b> | Indication for prophylaxis of DVT which may lead to PE in pts undergoing knee or hip replacement surgery | Indication to reduce risk of stroke and systemic embolism in pts with non-valvular a. fib |
| <b>Strength</b>   | 10 mg, 15 mg, 20 mg  | 10 mg, 15 mg, 20 mg   |
| <b>Dose</b>       | 10 mg  | 15 mg or 20 mg  |

|   |  |   |
|---|--|---|
| <b>Dosage form and route of administration</b>        | Tablet; oral   | Tablet; oral  |
| <b>Frequency of administration</b>                    | Daily  | Daily   |
| <b>How supplied</b>                                   | Bottle of 30 tablets; blister package containing 100 tablets (10 blister cards containing 10 tablets each)                                   | Bottle of 30 tablets of 15 mg; blister package containing 100 tablets of 15 mg (10 blister cards containing 10 tablets each)<br><br>Bottle of 30 tablets and 90 tablets of 20 mg; blister package containing 100 tablets of 20 mg (10 blister cards containing 10 tablets each)           |
| <b>Tablet Description</b>                             | Round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side. | Round, red, biconvex film-coated tablets marked with a triangle pointing down above a "15" on one side, and an "Xa" on the other side.<br><br>Triangle-shaped, dark red film-coated tablets marked with a triangle pointing down above a "20" on one side, and an "Xa" on the other side. |
| <b>Use in Specific Populations (Renal Impairment)</b> | Avoid use in patients with CrCl less than 30 mL/min; use with caution in patients with CrCl 30 mL/min to less than 50 mL/min.                | Decrease dose to 15 mg orally once daily with food for CrCL 30 to less than 50 mL/min;<br><br>Avoid use with CrCL less than 15 mL/min.  |
| <b>Drug Interactions</b>                              | Combined Cytochrome P450 3A4 Enzyme inhibitors and Drug Transport Systems: No precautions are necessary during co-administration             | Combined CYP3A4 inhibitors and Drug Transport Systems: Avoid concomitant use due to increased bleeding risk<br><br>Combined Cytochrome  |

|  |  |   |
|--|--|---|
|  | <p>with Xarelto.</p> <p>Combined CYP3A4 inducers and Drug Transport System: Consider an increased dose of Xarelto if these drugs are co-administered</p> <p>Clonidogrel: was previously different depending upon the diagnosis; Applicant proposes new language that could be used with either diagnosis (see Section X)</p> | <p>P450 3A4 Inducer and Drug Transport System: Avoid concomitant use with Xarelto</p>   |
| <p><b>Warnings &amp; Precautions</b></p> |  | <p>Discontinuation: discontinuing Xarelto places patients at an increased risk of thrombotic events. If anticoagulation with Xarelto must be interrupted or discontinued for a reason other than pathological bleeding, initiate another anticoagulant.</p> <p>Patients requiring cardioversion: There is little experience with Xarelto in patients undergoing cardioversion for atrial fibrillation</p> |

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 29, 2011 (Appendix B)
- Carton Labeling submitted September 29, 2011 (Appendix D)
-  (b) (4)
- Blister Label submitted September 29, 2011 (Appendix E)
- Insert Labeling provided by the Division October 11, 2011 (no image)
- Container Label and Carton Labeling for NDA 22406 which was submitted July 15, 2011 (Appendix F)
- Image of each tablet strength submitted October 13, 2011 via e-mail from the Division (Appendix G)

We compared the proposed Xarelto labels and labeling to the currently marketed Xarelto labels to identify any potential safety concerns.

Additionally, since Xarelto is a currently marketed product, we conducted an Adverse Event Reporting System (AERS) database search to identify medication errors involving Xarelto. The October 12, 2011, AERS search used the following search terms: active ingredient “Rivaroxaban”, trade name “Xarelto”, and verbatim terms “Rivar%” and “Xarel%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitation was set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series included those that did not describe a medication error.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 3 RESULTS AND DISCUSSION

The following sections describe the relevant medication error cases identified in AERS and discuss DMEPA's evaluation of the proposed labels and labeling for Xarelto.

#### 3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) SELECTION OF CASES

After individual review, 5 reports were not included in the final analysis because they were adverse events not related to medication errors (see Appendix A).

The remaining three cases were medication errors which occurred in July, August and September of 2011.

The three cases are as follows: prescriber error (n = 1), wrong dose (n = 1), and inappropriate schedule of drug administration (n = 1). In the first case (ISR 7680590-6), the patient received Rivaroxaban and Lovenox (enoxaparin) simultaneously for two days. It was reported that the patient was not aware that Rivaroxaban was an anti-coagulant and the prescriber "may have thought that Rivaroxaban was an anti-anxiety medication". The patient was subsequently re-hospitalized for monitoring and discharged four days later. No further details were provided. The second case (ISR 7730558-6) describes a patient who received Rivaroxaban 40 mg in error which required transferring the patient to the emergency department for evaluation. In the remaining case (ISR 7804718-X), the patient received Rivaroxaban the morning following knee surgery and subsequently sustained a deep vein thrombosis. The reporter stated that the patient may have been started on therapy after the recommended window to initiate therapy. No further details were provided for the second or third case.

#### 3.2 CONTAINER AND BLISTER LABELS AND CARTON LABELING – 15 MG AND 20 MG

Our evaluation of the proposed container and blister labels, carton and insert labeling, identified vulnerability to medication errors. Specifically, we made recommendations to improve the readability of the statement of strength and to improve the differentiation between the labels and labeling for the product strengths. Additionally, we recommend revising the color scheme for the 15 mg strength container label because the prominence of the strength is minimized as currently proposed.

#### 3.3

(b) (4)

(b) (4)

### 3.4 INSERT LABELING

As acknowledged by the Division, the following sections may be a source of confusion to the healthcare providers: Dosage and Administration, Drug Interactions, and Warnings and Precautions. We offer recommendations in Section 4.1 which help to organize and clarify important information in these areas of the insert labeling.

### 3.5 TABLET DIFFERENTIATION

In view of the differing treatment plans associated with the two diagnoses, we evaluated the differences in the tablets to determine if the patient is likely to be able to tell the difference between the three strengths. (See Appendix G for images). This may be important should a dispensing error or miscommunication occur with the treatment plan. We determined that the tablets appear to be adequately differentiated and it is likely that the patient will be able to identify the differences between them. As an additional safety measure, it would be helpful to include the actual image of the tablet on the container label.

## 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container and blister labels, carton and insert labeling, introduce vulnerability that can lead to medication errors. Section 4.1, *Comments to the Division of Cardiovascular and Renal Products (DCRP)*, contains our recommendation for the proposed insert labeling for Xarelto. In Section 4.2, *Comments to the Applicant*, we have provided recommendations for the container and blister labels, professional sample container labels, and carton labeling. Please forward these recommendations to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If the Division has further questions or need clarifications, please contact Nina Ton, OSE Project Manager, at 301-796-1648.

### 4.1 COMMENTS TO THE DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Recommendations # 1 through # 3 pertain to the Full Prescribing Information Section of the insert labeling, Dosage and Administration Subsection (2):

1. Delete the statement beginning with “ (b) (4) . This statement is not complete and can be addressed solely in the Drug Interactions subsection of the insert labeling (Section 7.3).
2. Delete the statement beginning with (b) (4) See Recommendation #3 for location of this important information.
3. Subsection 2.1 (Atrial Fibrillation): Revise the sequence of information as follows: (b) (4)

[Redacted] (b) (4)

Recommendations # 1 through # 3 pertain to the Full Prescribing Information Section of the insert labeling, Warnings and Precautions (5):

1. [Redacted] (b) (4)
2. [Redacted]
3. [Redacted]

Recommendations # 1 through # 5 pertain to the Full Prescribing Information Section of the Insert Labeling, Drug Interactions (7):

1. Following the Drug Interactions Heading (7), revise the statement beginning with [Redacted] (b) (4) to read “Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may . . .” to clarify the meaning of a drug transport system in the remaining text.
2. Where the statement [Redacted] (b) (4) appears, revise it to state the specific diagnosis to which the information applies. For example, if it applies to both diagnoses, [Redacted] (b) (4),” should be revised to state [Redacted] (b) (4).
3. Relocate Subsection 7.2 (statement beginning with “Drug-Disease Interactions . . .”) to follow Subsection 7.6 (Clopidogrel) to complete the list of drug-drug interactions prior to addressing concerns with drug-disease interactions.
4. In Subsection 7.3, revise the statement [Redacted] (b) (4) to [Redacted] (b) (4).
5. In Subsection 7.6 (Clopidogrel), we recommend language which would be applicable to either diagnosis. In correspondence from the Applicant October 11, 2011, they propose adding the following statement: [Redacted] (b) (4).  
[Redacted] We recommend that this statement be follow the Clopidogrel Heading if the Division agrees.

## 4.2 COMMENTS TO THE APPLICANT

### 4.2.1 Container Labels and Carton Labeling – 15 mg and 20 mg

1. Add a space between the number and mg unit of measure to improve the readability of the statement of strength. For example, “15mg” should be revised to read “15 mg”.
2. We remind the Applicant of their requirement to comply with 21 CFR 208.24:

A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or if it is enclosed in the carton (for example, for unit of use packaging configurations):

“Dispense the enclosed Medication Guide to each patient.” or  
“Dispense the accompanying Medication Guide to each patient.”

Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:

A minimum of four Medication Guides would be provided with a bottle of 100 or a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

A minimum of one Medication Guide would be provided with a unit of use container where it is expected that all tablets/capsules would be supplied to the patient.

3. Increase the prominence of the three middle numbers in the NDC number as this information is how the pharmacist identifies the correct strength for drug products. For example, NDC 50458-578-30 becomes 50458-**578**-30 for the 15 mg strength of Xarelto.
4. Add an image of the tablet to the container label.

#### 4.2.2 Container Label and Carton Labeling – 15 mg only

Revise the color block for the 15 mg strength such that it is not the same color as the proprietary name (purple) and it does not overlap in color with the other strengths. The use of the same colors for both areas of the label diminishes the prominence of the strength.

#### 4.2.3 Container Labels

Decrease the prominence of the graphic that appears just after the manufacturer's name, 'Janssen' at the bottom of the label.

#### 4.2.4

(b) (4)



#### 4.2.5 Blister Labels – 15 mg and 20 mg

Revise the proposed blister labels such that the strengths for this drug product are well differentiated. As proposed, the same information is presented in the same sized, black font on a white background and looks similar to the approved 10 mg strength.

**APPENDICES**

**Appendix A** : Adverse Event Reports (AERS) Reports Excluded from Further Analysis

|           |           |           |
|-----------|-----------|-----------|
| 5494578-7 | 5494592-1 | 6036403-1 |
| 7778879-5 | 5618905-2 |           |

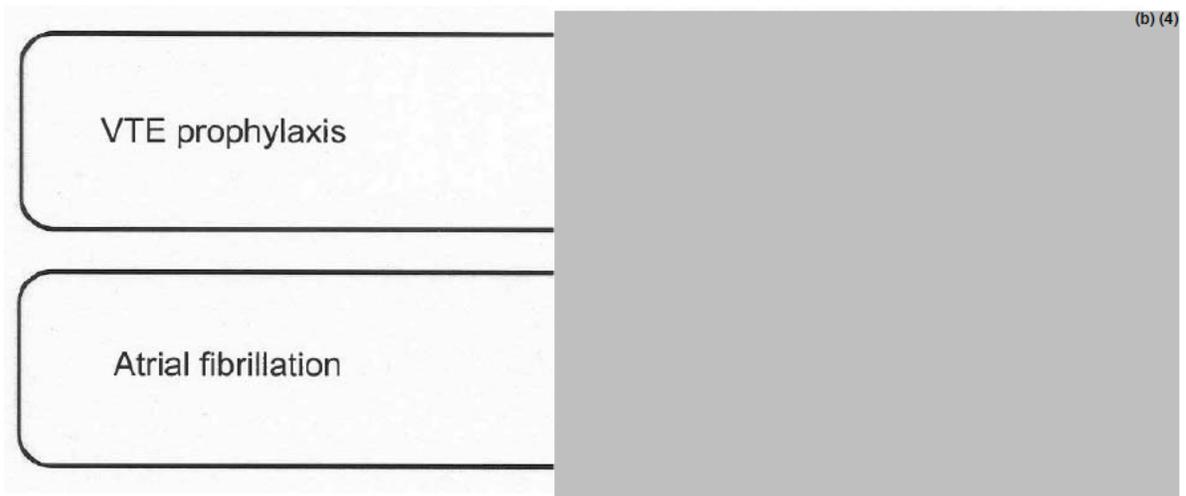
**Appendix B:**

Proposed Container label for 30 count bottle 15 mg and 20 mg



9 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

**Appendix G.** Drug Product Image (submitted via correspondence October 13, 2011)



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/s/  
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DENISE V BAUGH  
10/21/2011

CAROL A HOLQUIST  
10/21/2011

**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**

**PATIENT LABELING REVIEW**

Date: October 19, 2011

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Barbara Fuller, RN, MSN, CWOCN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): XARELTO (rivaroxaban)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 202439

Applicant: Johnson & Johnson Pharmaceutical Research & Development, LLC

OSE RCM #: 2011-271

## **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 Medication Guide (MG) for Xarelto (rivaroxaban) tablets, for oral use.

On January 5, 2011, Johnson & Johnson Pharmaceutical Research & Development, LLC submitted original New Drug Application (NDA) 202439 for Xarelto (rivaroxaban) tablets, for oral use. Xarelto (rivaroxaban) is a factor Xa inhibitor with the proposed indications to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. The Applicant seeks approval for the 10 mg, 15 mg, and 20 mg strength tablets for oral use.

Xarelto (rivaroxaban) 10 mg film-coated oral tablets NDA 22406, was approved July 1, 2011, for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

The proposed REMS is being reviewed by DRISK and will be provided to DCRP under separate cover.

## **2 MATERIAL REVIEWED**

- Draft Xarelto (rivaroxaban) tablets for oral use Medication Guide (MG) received on January 5, 2011 and revised by the review division throughout the current review cycle and received by DRISK on October 12, 2011.
- Draft Xarelto (rivaroxaban) tablets for oral use Prescribing Information (PI) received January 5, 2011, revised by the review division throughout the current review cycle and received by DRISK on October 12, 2011.
- Approved Pradaxa (dabigatran etexilate mesylate) capsule comparator labeling dated March 4, 2011.

## **3 REVIEW METHODS**

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is consistent with the approved comparator labeling where applicable.
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

14 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/  
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LATONIA M FORD  
10/19/2011

LASHAWN M GRIFFITHS  
10/19/2011

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 08/30/2011

From: Ashkan Emadi, M.D., Ph.D.  
Division of Hematology Products (DHP)  
Office of Oncology Drug Products, CDER

Through: Qin Ryan, M.D., Ph.D. (Acting Clinical Team Leader)  
Edvardas Kaminskas, M.D. (Deputy Division Director)  
Division of Hematology Products (DHP)  
Office of Oncology Drug Products, CDER

Subject: Consult Request questions regarding the statistically significant increase in the rate of stroke in patients in the rivaroxaban arm during the period from 3 to 30 days after the last dose of study drug in the phase 3, randomized trial comparing warfarin with rivaroxaban in >14,000 patients with non-valvular atrial fibrillation with the primary endpoint of time to the composite of stroke (ischemic, hemorrhagic or unknown type) or systemic embolism.

To: Martin Rose, M.D., J.D.  
Alison Blaus  
Division of Cardiovascular and Renal Products (DCRP)

# Response to Request for Consultation

|                         |   |
|-------------------------|---|
| Application Type        | NDA 202439<br>IND 75238   |
| Submission Number       | 1   |
| Date of Consult Request | August 9, 2011  |
| Desired Completion Date | September 13, 2011  |
| Reviewer Name           | Ashkan Emadi, MD, PhD   |
| Review Team Leader      | Qin Ryan, MD, PhD   |
| Review Completion Date  | September 2, 2011   |
| Type of Document        | Clinical Safety Question  |
| Name of Drug            | Xarelto (Rivaroxaban)   |
| Therapeutic Class       | Oral Direct Factor Xa Inhibitor   |
| Applicant               | Johnson & Johnson PRD   |
| Hematologic Disorder    | Thromboembolisms  |
| Consult Questions       | <ol style="list-style-type: none"><li>1) In general, how would you approach the question of whether there is a hypercoagulable state in patients who take rivaroxaban for an extended period and then stop suddenly and start warfarin treatment?</li><li>2) If a clinical study is done, what sort of subjects should be recruited?</li><li>3) How long should subjects be on rivaroxaban?</li><li>4) What testing should be done to determine hypercoagulability in human subjects?</li><li>5) Many of the strokes occurred in patients switched to warfarin, and many of the ischemic strokes occurred early. Does this suggest to you that protein S or protein C derangements may have played a role in the strokes?</li><li>6) Are there any preclinical studies that might be helpful?</li></ol> |

## Summary and Recommendation

On February 18, 2011, Division of Hematologic Products (DHP) received a consult request from Division of Cardiovascular and Renal Products (DCRP) regarding the Phase 3, warfarin controlled ROCKET study of rivaroxaban in > 14,000 patients with non-valvular atrial fibrillation at risk for stroke, in which there was a remarkable and statistically significant increase in the rate of primary endpoint events in completing patients during the period from 3 to 30 days after the last dose of study drug. This period comprised 28 days after the end of the on-treatment period. The primary endpoint analysis was the composite of stroke (ischemic, hemorrhagic or unknown type) or systemic embolism. All events in this period were strokes (18 ischemic + 4 hemorrhagic in the rivaroxaban arm; 6 ischemic in the warfarin arm). During this period, >90% of completers received vitamin K antagonist (VKA) therapy. However, unlike other recent studies of new anticoagulants for stroke prevention in atrial fibrillation patients, transition to warfarin or other VKA from study drug was abrupt. There was no period when both agents were taken concurrently, as in the other studies. A similar phenomenon was observed in the much smaller (1200 patient) J ROCKET trial conducted in Japan.

DCRP had six questions for DHP. Here we first answer the questions and provide our final comment. In this consult document, we summarized the key results from ROCKET AF study, reviewed the data about occurrence of thromboembolic events in two different patient populations in ROCKET AF, the patient who discontinued the study drug early and the patients who completed the study and were switched from rivaroxaban to VKA.

Question 1: In general, how would you approach the question of whether there is a hypercoagulable state in patients who take rivaroxaban for an extended period and then stop suddenly and start warfarin treatment?

*DHP Response: The data presented by DCRP related to ROCKET AF study suggest a transient hypercoagulable state in less than 0.2% of patients who discontinued abruptly rivaroxaban after being on rivaroxaban for an extended period of time and started warfarin without any overlapping period with close laboratory (INR) monitoring. This potential period of transient hypercoagulability appears most noticeable within the first week after discontinuation of rivaroxaban. It should be noted that the numbers are very small and the mechanism for such correlation is speculative at present time.*

Question 2: If a clinical study is done, what sort of subjects should be recruited?

*DHP Response: The patient population in ROCKET AF or J ROCKET studies appears to be appropriate. Based on this result, we think recruitment of healthy subjects might not be ethical. Recruitment of non-high risk patients or patients without atrial fibrillation probably will not result in production of useful and conclusive information.*

Question 3: How long should subjects be on rivaroxaban?

*DHP Response: The median duration of treatment exposure in ROCKET AF was approximately 600 days. For establishing or excluding the existence of such hypercoagulable state, a much shorter study duration should suffice. Requesting a trial with similar primary endpoints as ROCKET AF will require a very large sample*

size, which is costly, unrealistic and probably not feasible. However, we suggest that the sponsor design a small short duration clinical study with appropriate correlative endpoints and propose it to DCRP. DHP will provide comments about such study if deemed necessary by DCRP review team.

Question 4: What testing should be done to determine hypercoagulability in human subjects?

*DHP Response: We are unclear as to your question. If you wish to investigate whether the patients who had a stroke during the period when warfarin was being initiating have an underlying hypercoagulable state, there are a number of investigations that can be performed depending on what the patient is on in terms of medications. The sponsor can send in a proposal to study these patients and we will be happy to review it.*

Question 5: Many of the strokes occurred in patients switched to warfarin, and many of the ischemic strokes occurred early. Does this suggest to you that protein S or protein C derangements may have played a role in the strokes?

*DHP Response: This is difficult to answer. Congenital or acquired protein C or protein S deficiencies usually increase the risk for venous thromboembolisms not arterial clot including stroke. Based on current knowledge on mechanism of action of rivaroxaban, it does not interfere with protein C level or activated protein C function. However, it seems plausible that the transient decrease in protein C level immediately after initiation of warfarin (known short hypercoagulable time) potentiates any unknown and probable underlying rebound hypercoagulable state after discontinuation of rivaroxaban. This combination and not necessarily either one alone may result in an increase in thromboembolic event rates during the period of 3 to 7 days after the last dose of rivaroxaban. Please also see Question 4, and the final comment.*

Question 6: Are there any preclinical studies that might be helpful?

*DHP Response: No.*

DHP Final Comment: *Based on the current data and until further studies are performed, and in case that rivaroxaban is approved for this indication, we recommend administration of a period of overlapping (bridging) rivaroxaban and warfarin with a close and frequent INR evaluations, should rivaroxaban be discontinued for any reason. Warfarin should be started while patient still takes rivaroxaban and rivaroxaban should be continued until INR is at least 2 times greater than baseline. Because rivaroxaban does prolong INR by itself, we recommend the decision for the time of rivaroxaban discontinuation be based on each patient baseline INR before warfarin and not simply based on INR between 2 to 3.*

## Overview of Clinical Trial ROCKET AF

ROCKET AF (Rivaroxaban once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) was a randomized, double-blind, event-driven trial, which aimed to establish the noninferiority of rivaroxaban compared with warfarin in patients with non-valvular AF who have a history of stroke or at least 2 additional independent risk factors for future stroke. Patients were randomly assigned to receive rivaroxaban, 20 mg once daily, or dose-adjusted warfarin titrated to a target international normalized ratio (INR) of range 2.0 - 3.0 using point-of-care INR devices to receive true or sham INR values, depending on the study drug allocation. The primary efficacy end point was a composite of all-cause stroke and non-central nervous system systemic embolism. The primary safety end point was the composite of major and clinically relevant non-major bleeding events. From December 2006 through June 2009, over 14,000 patients were randomized at 1,100 sites across 45 countries. The study was terminated on May 28, 2010. Thirty-two patients were lost to follow-up.

The median duration of treatment exposure was 590 days; the median follow-up period was 707 days. In the primary analysis, the primary end point occurred in 189 patients in the rivaroxaban group (1.7% per year) and in 243 in the warfarin group (2.15% per year) (hazard ratio (HR) in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.65 to 0.95;  $P < 0.001$  for noninferiority;  $p = 0.015$  for superiority, unadjusted). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (HR 0.88; 95% CI, 0.74 to 1.03;  $P < 0.001$  for noninferiority;  $P = 0.12$  for superiority). Major and non-major clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (HR 1.03; 95% CI, 0.96 to 1.11;  $P = 0.44$ ), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%,  $P = 0.02$ ) and fatal bleeding (0.2% vs. 0.5%,  $P = 0.003$ ) in the rivaroxaban group.

### Events (Composite of Stroke or Systemic Embolism) Occurred After Discontinuation (Completing Patients and Early Discontinuation Patients) in ROCKET AF

In ROCKET, for primary and secondary endpoint efficacy analyses, only events that occurred in the "on treatment" period counted. On treatment period was from randomization to the last dose of study drug plus 2 days (1<sup>st</sup> row, Table 1). After discontinuation of the study, however, the number of additional events increased and this increase was greater in the rivaroxaban arm to the extent that the statistical significance of the superiority finding that was present in "on treatment" analysis was no longer present in the last dose plus 7 day analysis (2<sup>nd</sup> row, Table 2). In the 5 days between day 3 and day 7, there were an additional 31 primary endpoint events in the rivaroxaban arm, compared to 12 in the warfarin arm. There was also an excess of events in the rivaroxaban arm over the remainder of the period depicted in the table, only not as marked as in the first 5 days.

**Table 1. Primary Endpoint Events On Treatment and One Month after Discontinuation of the Rivaroxaban**

| Event Window                    | Rivaroxaban  |                       | Warfarin     |                       | Rivaroxaban vs. Warfarin HR (95% CI) | p value |
|---------------------------------|--------------|-----------------------|--------------|-----------------------|--------------------------------------|---------|
|                                 | n / N (7061) | Event Rate (% per yr) | n / N (7082) | Event Rate (% per yr) |                                      |         |
| Last dose+2 days (On treatment) | 189          | 1.70                  | 243          | 2.15                  | 0.79 (0.65, 0.95)                    | 0.015   |
| Last dose+7 days                | 220 (189+31) | 1.96                  | 255 (243+12) | 2.24                  | 0.88 (0.73, 1.05)                    | 0.149   |
| Last dose+14 days               | 235 (220+15) | 2.07                  | 271 (255+16) | 2.35                  | 0.88 (0.74, 1.05)                    | 0.150   |
| Last dose+30 days               | 251 (235+16) | 2.16                  | 281 (271+10) | 2.38                  | 0.91 (0.76, 1.07)                    | 0.252   |

These post-discontinuation events occurred in two different populations; in patients who discontinued the study early for different reasons, and in patients who continued the treatment to the end of study.

Approximately one third (2256 out of 7061 in rivaroxaban arm and 2155 out of 7082 in warfarin arm) of study patients discontinued study drug early. These patients, similarly in both arms, had a very high rate of events from Day 3 to Day 30 after the last dose of study drug. Discontinuations may have been because of health related reasons that might have been associated with an increased risk of efficacy events. In this “early discontinuation group”, there were 42 versus 36 primary endpoint events in the rivaroxaban and warfarin arms, respectively, yielding respective event rates of approximately 25% and 22% events per year, which is about one log increase over the event rates on treatment period. The difference between treatment arms was not statistically significant. Approximately half of patients who discontinued the study early, in both arms, were started on vitamin K antagonist (VKA, e.g. warfarin) therapy in different days in the first 30 days after the last dose of blinded study medication. INR information was not routinely collected in patients who discontinued study drug early.

Approximately two thirds of patients continued treatment to the end of the study for whom the last dose of study drug was on or after the notification date to the sites that the event target had been reached and the end of study procedures should be implemented. These “completer group” of patients had a total lower rate of events, but the difference between the rivaroxaban and warfarin arms was more marked for primary endpoint events (22 [6.42%/yr] in rivaroxaban arm vs. 6 [1.73%/yr] in warfarin arm, HR 3.72; 95% CI, 1.51 to 9.16; P=0.004). The warfarin arm event rate during this period was roughly comparable with the warfarin arm event rate during treatment, while the rivaroxaban arm event rate during this period was approximately 4 fold higher than during treatment. All primary efficacy endpoint events during this period were strokes in the patients who completed therapy. In the rivaroxaban arm, 18 patients had an ischemic stroke and 4 had a hemorrhagic stroke. In the warfarin arm, 4 patients had an ischemic stroke and 2 had a stroke of unknown type. These 28 patients were a high risk group of patients with more than 80% of them having a history of prior stroke, or transient ischemic attacks, compared to 55% for the whole study.

During the period from Day 3 to day 30 after the last dose of study drug, approximately 92% of completers received VKA therapy. Transition to warfarin or other VKA from rivaroxaban was abrupt with no period when both agents were taken

concurrently. More than 80% of these patients started open label VKA therapy in the same day as their last dose of study drug or one day later. The end of study visit usually occurred on the day after the last dose of study drug, which occurred in the evening; this day was by far the most common day to start VKA in this cohort of patients. This was unlike other recent studies of new anticoagulants for stroke prevention in atrial fibrillation patients. A similar phenomenon was observed in the much smaller (1200 patient) J ROCKET trial conducted in Japan. Table 2 suggests a relationship between the event rates and the start of VKA relative to the last dose of rivaroxaban in the period from Day 3 to Day 30 after the last dose of rivaroxaban. *Interestingly, there were no reported events in the 47 patients who started VKA before the last dose of rivaroxaban.* In the patients who did not start VKA by day 30 of the last dose of rivaroxaban, there were only 2 patients in rivaroxaban arm who had events. This data suggests that the initiation of VKA immediately after discontinuation of rivaroxaban, in the absence of overlap with rivaroxaban or heparin, may create a transient period of clinically significant hypercoagulable states during which patients are at increased risk for thromboembolic events including stroke.

**Table 2. Primary Endpoint Events in the Period from 3 to 30 Days after the Last Dose of Rivaroxaban**

|   | <b>Rivaroxaban</b> | <b>Warfarin</b> |
|---|--------------------|-----------------|
| <b>Days between last dose of rivaroxaban and VKA initiation</b> | <b>n / N</b>       | <b>n / N</b>    |
| VKA before the last dose  | 0 / 47             | 0 / 61          |
| 0-2 days after the last dose                                    | 17 / 3992          | 6 / 4022        |
| 3-7 days after the last dose                                    | 2 / 144            | 0 / 156         |
| 7-30 days after the last dose                                   | 1 / 49             | 0 / 52          |
| Did not start VKA by day 30                                     | 2 / 356            | 0 / 363         |

It is noteworthy to mention that spotty INR information was collected from these patients. There was no dedicated page in the case record for these data, but the sites were instructed to capture it on the local laboratory results page. The sites were also instructed not to use of the point of care device during the post-treatment period and not to get an unblinded INR until the 3<sup>rd</sup> day after the last dose of study medication.

Among 22 completer patients in rivaroxaban arm who had events between day 3-30 after the last dose of rivaroxaban while on VKA, 7 (37%) had INR <1.5, 5 (26%) had INR between 1.5-1.8, 4 (21%) had INR between 2-3, 2 (10%) had INR > 3, one had no INR record, and 3 are unknown. Among the 6 completer patients in warfarin arm with events, 2 were in therapeutic range, 3 were below the range and 1 had no INR record. These data are quite interesting and somehow difficult to explain in a way that at least 6 patients in rivaroxaban arm with events had INR in therapeutic range.

## Sponsor's Response to DCRP Questions

On 17 March 2011, DCRP requested the following information from the sponsor: "In both ROCKET and J ROCKET, the rate of stroke and non-CNS systemic emboli increased markedly in rivaroxaban-treated subjects in the period immediately following discontinuation of rivaroxaban. We are concerned that this finding suggests that cessation of rivaroxaban results in a hypercoagulable state. If so, patients who miss doses of rivaroxaban may be at increased risk for thrombotic events, reducing or eliminating its effectiveness. Additionally, it does not appear that you have adequate data to instruct health care providers in a method for safely transitioning patients from rivaroxaban to other anticoagulant therapies (e.g., warfarin and dabigatran)."

### Sponsor Response:

Cessation of any antithrombotic agent including heparins, fondaparinux, warfarin, direct thrombin inhibitors and anti-platelet agents can be associated with the occurrence of post-treatment thrombotic events. It is difficult, however, to establish if these post-therapy events are due simply to the removal of the protective effect of the agent or to a rebound hypercoagulable state. The underlying mechanism is thought to be related to a transient change of coagulation homeostasis from hypocoagulation during treatment to an untreated baseline wherein the patient no longer receives an anticoagulant. The available evidence from preclinical investigations and clinical trials does not support a hypothesis of rebound hypercoagulability after cessation of rivaroxaban treatment.

Sponsor performed an experiment in an *in vivo* rat model and *in vitro* human plasma assays, and showed that the administration of rivaroxaban did not result in hypercoagulability and did not suppress the thrombin-mediated anticoagulant action of Activated Protein C. However, these two experiments and their design do not answer the concern about hypercoagulability after discontinuation of rivaroxaban and more importantly in the presence of VKA. Sponsor acknowledges that these experiments were not conducted specifically to ascertain the existence of rebound hypercoagulability.

The sponsor analyzed different large clinical trials for occurrence of thrombotic events during the active treatment phase and after stop of active treatment. This analysis was performed based on data from the completed studies of the RECORD program, the EINSTEIN program, J-ROCKET and the ATLAS ACS Phase 2 study. Sponsor concluded that the cessation of rivaroxaban does not lead to a post-treatment thrombotic risk, as evidenced by the absence of an excess in thrombotic events in the 30 days after study completion. The result of this analysis is not conclusive or relevant to ROCKET AF study. Patient population, design and post-rivaroxaban anticoagulation treatment were significantly different from ROCKET AF.

Sponsor acknowledged that "A close examination of the end-of-study period in both ROCKET AF and J-ROCKET revealed that patients transitioning from blinded rivaroxaban therapy to open-label VKA experienced a relative disadvantage compared to patients transitioning from blinded warfarin therapy to open-label VKA. In order to maintain the study blind during this period, INR measurements were discouraged for at least 3 days after the last dose of blinded study medication. The data reveal an overall lower proportion of and slower time course to attainment of a

therapeutic INR in patients who had received rivaroxaban compared to those who had received warfarin. Patients who transitioned from warfarin to open-label VKA received uninterrupted antithrombotic protection. Conversely, however, due to the shorter  $t_{1/2}$  patients who transitioned from rivaroxaban had no early antithrombotic coverage until their INR was therapeutic. Therefore, patients previously receiving rivaroxaban experienced a period of under-anticoagulation during the initiation of VKA, in contrast to the more effective anticoagulation transition experienced by their previously warfarin-treated counterparts. Although rebound hypercoagulability cannot be definitively excluded, the sponsor's opinion is that, in J-ROCKET and ROCKET AF, a period of under-anticoagulation for rivaroxaban-treated patients is the most likely explanation for the increase in Day 3-30 post-treatment ischemic events."

## **Conclusion**

1. These data suggest a transient hypercoagulable state in patients whose rivaroxaban discontinued abruptly after being on rivaroxaban for an extended period of time and warfarin started without any overlapping period with close INR monitoring. However, these data should be interpreted with caution, since the event numbers are small and the mechanism for such correlation is speculative at the present time.
2. We suggest that the sponsor design a small study with shorter study duration and appropriate correlative endpoints with respect to rivaroxaban and warfarin half lives, the time of discontinuation of rivaroxaban and initiation of warfarin. It is important to consider that there are no validated assays to definitively detect rebound hypercoagulability (see answer to question 5).
3. Based on the current data and until further studies are performed in this patient population, we recommend a period of overlapping (bridging) rivaroxaban and warfarin with a close laboratory (such as INR) evaluations, should rivaroxaban be discontinued for any reason. Warfarin should be started while patient still takes rivaroxaban and rivaroxaban should be continued until INR is at least 2 times greater than baseline. Because rivaroxaban does prolong INR by itself, we recommend the decision for the time of rivaroxaban discontinuation be based on each patient baseline INR before warfarin and not simply based on INR between 2 to 3.

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/s/  
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ASHKAN EMADI  
09/12/2011

EDVARDAS KAMINSKAS  
09/15/2011

QIN C RYAN  
09/15/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL INSPECTION SUMMARY

DATE: August 29, 2011

TO: Alison Blaus, Regulatory Health Project Manager  
Martin Rose, M.D., J.D., Medical Officer  
Preston Dunmon, M.D., Medical Officer  
Division of Cardiovascular & Renal Products

FROM: Susan Thompson, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Acting Division Director  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202439

APPLICANT: Johnson & Johnson Research & Development LLC

DRUG: Xarelto (Rivaroxaban)  
NME: No  
THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

CONSULTATION REQUEST DATE: February 25, 2011  
INSPECTION SUMMARY GOAL DATE: September 5, 2011  
DIVISION ACTION GOAL DATE: November 5, 2011  
PDUFA DATE: November 5, 2011

**I. BACKGROUND:**

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, and it is an independent risk factor for cardiogenic thromboembolic events. AF predisposes patients to the development of atrial thrombi, most commonly in the left atrial appendage and a greater risk of stroke and non-CNS embolism. In the absence of treatment, patients with non-valvular AF have a 2- to 7- fold higher incidence of ischemic stroke than age-matched controls without AF, whereas patients with valvular AF have a 17-fold higher incidence. Vitamin K antagonists such as warfarin have been established as the most effective therapy for the prevention of thromboembolic events in patients with AF. However, their use is limited to patients with AF at highest risk of thromboembolic events due to concern for bleeding events.

Rivaroxaban is a highly selective direct Factor Xa (FXa) inhibitor. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and this reaction leads to fibrin clot formation and activation of platelets by thrombin. Selective inhibition of FXa by rivaroxaban prevents the burst of thrombin generation. Rivaroxaban offers the potential advantages of fixed oral dosing, predictable pharmacokinetics with little potential for food interactions, interactions with a relatively limited number of commonly used drugs, and more predictable anticoagulant effect. In contrast, Vitamin K antagonist medications require International Normalized Ratio (INR) monitoring and frequent dose adjustment. Bayer Schering Pharma (BSP) and Johnson and Johnson Pharmaceutical Research and Development (J&JPD) are co-developing rivaroxaban. According to the ROCKET Study Report, J&JPD had primary responsibility for the pivotal study submitted in this NDA, while BSP was responsible for the bioanalysis and drug supply release, held the compound safety database, and was responsible for global pharmacovigilance for the study. The contract research organization, (b) (4) and the academic research organizations Duke Clinical Research Institute (DCRI) and the Canadian Heart Research Center (CHRC) were involved in site management for the study. (b) (4) was also involved in site monitoring as well as processing of serious adverse event reports, and DCRI was also involved in data management. A rivaroxaban NDA was recently approved by the Division of Hematology Products for the indication of prevention of deep venous thrombosis after total hip or total knee replacement surgery.

A brief synopsis of the protocol for which the review division has requested clinical investigator inspections is given below.

**Protocol 39039039AFL3001:** A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation

This prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter, event-driven study was conducted at more than 1170 centers in 45 countries including the U.S. between December, 2006 and September 2010. The primary objective of the study was to demonstrate that the efficacy of rivaroxaban is noninferior to that of dose-

adjusted warfarin for the prevention of thromboembolic events in subjects with non-valvular AF as measured by the composite of stroke and non-central nervous system (CNS) systemic embolism. The major secondary efficacy objectives were to compare the effects of rivaroxaban and warfarin with respect to the composite of stroke, non-CNS systemic embolism, and vascular death, and the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose-adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

Included in the study were men and women aged  $\geq 18$  years with non-valvular atrial fibrillation and a history of prior stroke, transient ischemic attack or non-CNS systemic embolism cardioembolic in origin or with 2 or more of the following risk factors: heart failure and/or left ventricular ejection fraction  $\leq 35\%$ , hypertension, age  $\geq 75$  years, or diabetes mellitus. Key exclusion criteria were: hemodynamically significant mitral valve stenosis, prosthetic heart valve, planned cardioversion, transient AF caused by a reversible disorder, active internal bleeding, history of or condition associated with increased bleeding risk, anemia (hemoglobin  $< 10$  g/dL), platelet count  $< 90,000/\mu\text{L}$  at screening, sustained uncontrolled hypertension, severe, disabling stroke within 3 months or any stroke within 14 days before randomization, calculated CrCl  $< 30$  mL/min at screening, known significant liver disease or alanine aminotransferase (ALT)  $> 3$  times the upper limit of normal (ULN). The study was divided into a double-blind treatment period closing with an end-of-study visit (EOS), and a posttreatment observation. Warfarin and matching rivaroxaban placebo, or rivaroxaban and matching warfarin placebo, were dose-adjusted based on either real or sham INR values, respectively. During the study, INR monitoring was to occur as clinically indicated but at least every 4 weeks. Unblinded INR measurements were not performed while subjects were on study drug, except in case of a medical emergency. The following medications were not permitted concomitantly with study drug during the study: fibrinolytic therapy, aspirin, chronic nonsteroidal anti-inflammatory drug (NSAID) treatment, or systemic treatment with a strong inhibitor/inducer of cytochrome P450 3A4. An independent blinded Clinical Endpoint Committee applied the protocol-specified definitions and adjudicated and classified the study endpoints. The primary efficacy outcome was the composite of stroke and non-CNS systemic embolism. The principal safety endpoint was the composite of major and non-major clinically relevant bleeding events. The duration of the treatment period for a given subject depended on the time required to accrue 405 adjudicated primary efficacy endpoint events.

### Brief Summary of Results

In total, 17,232 screenings for study eligibility occurred and 14,264 unique subjects were randomly assigned to treatment with either rivaroxaban or warfarin. A total of 12,064 (84.7%) subjects completed the study. The total number of subjects who permanently discontinued study drug was similar between the two treatment groups: 2,250 rivaroxaban subjects (35.4%) and 2,468 warfarin subjects (34.6%). The treatment groups were balanced with respect to demographic and baseline characteristics. The majority of the subjects were male (60.3%), white (83.3%), and the mean age was 71 years (range 25 to 97 years). A total of 210 (1.5%) subjects were excluded from the per protocol population; the most common protocol deviation was "Received excluded concomitant treatment". In addition, 2.8% of subjects who entered the study did not meet entry criteria. As a measure of treatment compliance in the warfarin

arm, the mean and median Time in Therapeutic Range (TTR; INR range of 1.8 to 3.2) was used as an indirect measure of treatment compliance; the mean TTR was 70.2%.

According to the Applicant, the event rate for the rivaroxaban group was significantly lower (1.71/100 patients years) compared with the warfarin group (2.16/100 patient years) demonstrating noninferiority of rivaroxaban to warfarin. The incidence of CEC-adjudicated bleeding events was comparable for the principal safety endpoint (20.7% for rivaroxaban and 20.3% for warfarin), and there was no statistically significant difference between the treatment groups. The incidence and types of adverse events were similar between the treatment groups, although more subjects in the rivaroxaban group had epistaxis compared with warfarin (10.1% versus 8.6%, respectively). The incidence of adverse events resulting in discontinuation of study drug was 15.7% in the rivaroxaban group and 15.1% in the warfarin group. Treatment-emergent serious adverse events based on the rivaroxaban group were reported in 35.0% of rivaroxaban subjects and 36.5% of warfarin subjects. According to the applicant, the overall liver safety profile of rivaroxaban was comparable to warfarin, with no evidence of imbalance in laboratory parameters or hepatic adverse events.

Seven clinical investigator site inspections and 1 sponsor inspection were conducted in support of the application. The clinical sites were selected for inspection mainly based on high enrollment.

## II. RESULTS (by Site):

| Name of CI   | Protocol # and # of Subjects                              | Inspection Date        | Final Classification |
|--|---|------------------------|----------------------|
| Jason T. Zelenka, M.D.<br>Clearwater Cardiovascular and<br>Interventional Consultants –<br>Countryside Office<br>1840 Mease Dr., Ste. 202<br>Safety Harbor, FL 34695 | Protocol 39039039-AFL-3001<br>Site 001362<br>42 Subjects  | April 18 – 22, 2011    | NAI                  |
| Michael R. Rubin, M.D.<br>Florida Heart Associates<br>1550 Barkley Circle<br>Fort Myers, FL 33907  | Protocol 39039039-AFL-3001<br>Site 001342<br>43 Subjects  | April 29 – May 6, 2011 | VAI                  |
| Pere Alvarez, M.D.<br>Hospital de Viladecans<br>Avda. Gava 38<br>Servicio de Cardiologia<br>Viladecans, Barcelona, 08840<br>Spain                                    | Protocol 39039039-AFL-3001<br>Site 034039<br>47 Subjects  | May 16 – 20, 2011      | NAI                  |
| Louie S. Tirador, M.D.<br>Saint Paul's Hospital<br>Rm. 206 Gen. Luna St.<br>Iloilo City, Western Visayas, 5000<br>Phillippines                                       | Protocol 39039039-AFL-3001<br>Site 063004<br>129 Subjects | May 30 – June 9, 2011  | VAI                  |

|  |  |                    |                 |
|--|--|--------------------|-----------------|
| Constantin Militaru, M.D.<br>Cardiomed<br>SRL, str N Titulescu bloc E ap 1<br>Craiova, Dolj, 200147<br>Romania             | Protocol 39039039-AFL-3001<br>Site 040012<br>66 Subjects | May 23 – 27, 2011  | Preliminary VAI |
| Josef Jandik, Ph.D.<br>Oblastni Nemocnice Nachod<br>Purkynova 446<br>Nachod, Nachod, 547 01<br>Czech Republic              | Protocol 39039039-AFL-3001<br>Site 042022<br>39 Subjects | May 23 – 27, 2011  | VAI             |
| Dimitar Raev, M.D.<br>MI-Central Clinical Hospital<br>Ministry of Interior<br>79 Skobelev Blvd.<br>Sofia, 1606<br>Bulgaria | Protocol 39039039-AFL-3001<br>Site 359002<br>90 Subjects | May 16 – 20, 2011  | NAI             |
| Johnson & Johnson Research &<br>Development LLC<br>920 U.S. Highway 202<br>Raritan, NJ 08869-0602                          | Protocol 39039039-AFL-3001                               | June 27 – 30, 2011 | NAI             |

Key to Classifications

NAI No deviation from regulations.

VAI Deviation(s) from regulations.

OAI Significant deviations from regulations. Data unreliable.

Pending Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Jason T. Zelenka, M.D.**  
**Clearwater Cardiovascular and Interventional Consultants – Countryside Office**  
**1840 Mease Dr., Ste. 202**  
**Safety Harbor, FL 34695**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. There were 56 subjects screened and 43 subjects enrolled in Study 39039039AFL3001 ROCKET at this site. Four subjects withdrew consent and discontinued from the study early. The medical records for 17 subjects were reviewed in depth, including informed consents, medical history, inclusion ECG, laboratory values including INR, randomization, protocols, source documents, CRFs, financial disclosures, adverse events, SAEs, drug accountability, drug inventory, and drug storage. There were no limitations to the inspection. The observations noted were based on the EIR.
- b. General observations/commentary: No issues were noted with the record review including study drug accountability, adverse event reporting, IRB approval, or general conduct of the study. No issues with informed consent document were noted. No Form FDA 483 was issued to the investigator. The EIR noted several issues, however, that were discussed with site staff at the conclusion of the inspection:

- Subject 110594 received more than the protocol-specified limit of 14 days of a NSAID (Advil) while taking study drug.
  - Subject 107748 had a coronary angiogram on (b) (6) with hospitalization for elective cardiac stent placement on (b) (6). Although the subject was hospitalized for more than 12 hours, the event was reported as an adverse event, not a serious adverse event.
- c. Assessment of data integrity: The inspectional findings appear isolated in nature and are unlikely to significantly impact data reliability. The data from Dr. Zelenka's site appear acceptable for use in support of the NDA.

2. **Michael R. Rubin, M.D.**  
**Florida Heart Associates**  
**1550 Barkley Circle**  
**Fort Myers, FL 33907**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. At this site, 87 subjects were screened, 45 subjects were randomized, and 27 subjects completed the study. There were 4 deaths reported. One subject was listed as lost to follow-up, 11 subjects were discontinued from the study, and two subjects completed the study at another site. An audit of 20 subjects' records was conducted. Subject records reviewed included office and hospital visit records, data collection sheets, drug dispensing/tracking forms, and adverse event and concomitant medication tracking sheets. All informed consent documents were reviewed. There were no limitations to the inspection. The observations noted were based on the FDA Form 483 and EIR.
- b. General observations/commentary: Site source documents were compared with sponsor submitted data, and no discrepancies, underreporting of adverse events, or endpoints were noted. During the inspection it was documented that the investigator did not adhere to the investigational plan. Specifically, two subjects received primidone prior to and after study enrollment in violation of the protocol amendment excluding subjects taking cytochrome P450 3A4 inducers. This protocol amendment took effect on 6/8/07. Subject 101260 was enrolled on 8/14/07 and received 142 days of study drug before being discontinued from the study due to receipt of prohibited concomitant medications. Subject 103104 was enrolled on 10/30/07 and received 57 days of study drug before being discontinued from the study due to receipt of prohibited concomitant medications.

*Medical Officer Comment: Rivaroxaban combined with a strong inducer of cytochrome 3A4 results in a 50% decrease in rivaroxaban AUC, C<sub>max</sub>, and t<sub>1/2</sub>. Neither subject had adverse events or SAEs likely to result from undercoagulation.*

In a letter dated May 20, 2011, in response to the Form FDA 483 observations, Dr. Rubin's Director of Research noted that an additional full-time certified research coordinator was hired to prevent future oversights of this nature.

- c. Assessment of data integrity: The enrollment of Subjects 101260 and 103104, in violation of the protocol exclusion of subjects receiving inducers of cytochrome 3A4, appears to have been isolated events, which are unlikely to affect overall study outcome. With the exception of this regulatory violation, the study appears to have been conducted adequately, and the efficacy and safety data generated by this site may be used in support of the respective indication.

3. **Pere Alvarez, M.D.**  
**Hospital de Viladecans**  
**Avda. Gava 38**  
**Servicio de Cardiologia**  
**Viladecans, Barcelona, 08840 Spain**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. At this site, 51 subjects were screened, and 4 subjects were screen failures. Forty-seven (47) subjects were enrolled, and 36 subjects completed the study. There were five deaths and 37 SAEs reported. Review of 100% of informed consent documents was performed. The following records and source data were reviewed for 24 subjects: adequacy of documentation, inclusion and exclusion criteria, randomization, concomitant medications, review and reporting of adverse events, laboratory testing, test article accountability, study monitoring, and protocol deviations. Source documents were compared with electronic CRFs and the data listings. There were no limitations to the inspection. The observations noted were based on the EIR.
- b. General observations/commentary: The study appears to have been conducted appropriately at this site. No regulatory violations or discrepancies between source data and NDA data listings were noted. A Form FDA 483 was not issued.
- c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. **Louie S. Tirador, M.D.**  
**Saint Paul's Hospital**  
**Rm. 206 Gen. Luna St.**  
**Iloilo City, Western Visayas, 5000**  
**Phillippines**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. At this site, 159 subjects were screened, 130 subjects were randomized, and 112 subjects completed the study. An audit of 42 subject records was conducted. These subject records were reviewed for subject initials, date of birth, enrollment date, date of first medication, date of last medication/termination date, adverse events, protocol deviations, stroke or MI, and death. All informed consent documents were reviewed. There were no limitations to the inspection. The observations noted were based on the EIR.
- b. General observations/commentary: During the inspection it was determined that the investigator did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and did not obtain appropriate informed consent prior to study drug administration. Specifically, the following violations were cited:

Recordkeeping Violations [21 CFR 312.62(b)]

- Subject 103413 missed the study drug dose for May 27, 2008 according to the medical history. The dose was recorded as 2.5 mg study drug taken on May 27, 2008.  
*Medical Officer's Comment: Subject 103413 was in the warfarin treatment arm, so this omission of a study drug (rivaroxaban placebo) dose did not have an effect on study outcome.*
- The INR Calculation Worksheet for Subject 102823 shows 3 missing warfarin doses for January 1, 2, and 3, 2010. The cardiologist's note stated that the subject only missed the January 3, 2010 dose.  
*Medical Officer's Comment: The omission of 3 warfarin doses for Subject 102823 (randomized to warfarin arm) could potentially result in an increased risk of the primary endpoints of stroke and non-CNS embolism. However, this subject did not have either of those events, so there was no significant effect of this error on study outcome.*
- Subject 102929 had conflicting data as to whether 1.0 mg or 2.5 mg tablets were dispensed. The INR Calculation Worksheet dated November 14, 2007 states that a 2.5 mg dose was taken for 3 days. The Source Document Worksheet for November 7, 2007 states that the warfarin dose was reduced from 2.5 mg to 1 mg daily. Source documents indicate that a kit of 1 mg tablets was dispensed. The INR call in sheets dated September 13, 2007 list the previous 3 days of warfarin dose of 2.5 mg.  
*Medical Officer's Comment: This regulatory violation resulted in Subject 102929 receiving either too much or too little warfarin (randomized to the warfarin arm) for 3 days. Subject 102929 did not have any bleeding adverse events or stroke/non-CNS embolism, so there was no significant effect on study outcome.*
- Subject 103613 was prescribed 2.5 mg warfarin daily on May 7, 2009. However, at the following visit the INR Calculation Call Worksheet listed the previous three doses as 1.0 mg.  
*Medical Officer's Comment: This regulatory violation resulted in Subject 103613 receiving either too much or too little warfarin (randomized to the warfarin arm) for 3 days. Subject 103613 did not have any bleeding adverse events or stroke/non-CNS embolism, so there was no effect on study outcome.*

- A letter to the IRB dated March 15, 2010 provides information regarding Subject (b) (6) whose number is 110565. However Subject (b) (6) is Subject 110722 and Subject 110565 is (b) (6)
- The following errors were noted in the data contained in the Source Document Worksheets which are completed at the time of subject visit:
  - Subject 108972 had an INR result of 3.8 in IVRS, while the ClinPhone INR Calculation gives the INR as 2.8 on May 20, 2009.  
*Medical Officer's Comment: Subject 108972 was randomized to the rivaroxaban arm, so that sham calculation of the placebo warfarin dose would have no effect on subject or study outcome.*
  - Subject 101648 had an INR result of 1.2, while the ClinPhone INR Calculation gives the INR as 1.4 on May 23, 2009.  
*Medical Officer's Comment: If the incorrect INR of 1.4 was used for warfarin dose calculation for Subject 101648, the dose of warfarin would have been lower than if the correct INR was used. The subject had no stroke or non-CNS embolism. Although the adverse event of hematuria was recorded, it cannot be attributed to the recordkeeping error.*
  - Subject 108972 has "none" checked for adverse events on January 2, 2009 on the Source Document Worksheet; however, the physician notes from that day reflect that the subject had a right forearm fracture after a fall. The data listings contain the right forearm fracture as an adverse event.

#### Informed Consent [21 CFR 50]

Four subjects did not sign the most recent informed consent document in a timely manner, although they did sign the original informed consent prior to study enrollment. Version 2 of the informed consent document was released on July 17, 2008. Subjects 101453 and 101648 were seen twice after approval of Version 2, and eventually signed Version 5 on October 31, 2008. Subject 101784 and 101785 were seen once after approval of Version 2 before signing Version 2 on August 19 and 18, 2008, respectively.

- c. Assessment of data integrity: Despite deficiencies in recordkeeping and obtaining appropriate informed consent in a timely manner as outlined above, it is unlikely that these errors significantly impacted the outcome of the study or human subject safety. The data generated by this site may be used in support of the respective indication.

5. **Constantin Militaru, M.D.**  
**Cardiomed**  
**SRL, str N Titulescu bloc E ap 1**  
**Craiova, Dolj, 200147**  
**Romania**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. At this site, 66 subjects were enrolled and 42 subjects completed the study. A review of informed consent documents was conducted for all 66 subjects. An in depth audit of 26 subject records was conducted. These subject records were reviewed for medical history, inclusion

ECG, laboratory values including INR, randomization, protocols, source documents, CRFs, financial disclosures, adverse events, SAEs, drug accountability, drug inventory, and drug storage. The observations noted were based on preliminary review of the EIR.

- b. General observations/commentary: In general, the records reviewed were found to be in order and the data verifiable. No issues with informed consent document were noted. No Form FDA 483 was issued to the investigator. The EIR noted an issue, however, that was discussed with Dr. Militaru at the conclusion of the inspection. One reason for choosing his site chosen for inspection was that his was the highest enrolling site with a time in treatment range of <40%, reflecting a relatively low time where subjects in the warfarin arm were appropriately anticoagulated. The protocol specified that the INR should be maintained between 2.0 and 3.0; Dr. Militaru stated that his site intentionally maintained the INR between 1.5 and 2.0 because of concern about possible bleeding complications. Dr. Militaru stated that he had not informed the sponsor of this fact. This failure to follow the protocol had the potential to bias the study, in that the undercoagulated subjects would be more prone to occurrence of the primary study endpoint. However, none of the subjects in the warfarin arm at Dr. Militaru's site had stroke or non-CNS embolic event, the primary study endpoint.
- c. Assessment of data integrity: Although Dr. Militaru did not follow the protocol by maintaining subject INR between 1.5 and 2.0 rather than the protocol specified 2.0 to 3.0, this violation did not result in an alteration in study outcome, as assessed by the absence of occurrence of primary study endpoints in the warfarin arm. The review division is aware that the time in treatment range at Dr. Militaru's site was low. With the exception of this regulatory violation, the study appears to have been otherwise conducted adequately, and the efficacy and safety data generated by this site may be used in support of the respective indication.

6. **Josef Jandik, Ph.D.**  
**Oblastni Nemocnice Nachod**  
**Purkynova 446**  
**Nachod, Nachod, 547 01**  
**Czech Republic**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. At this site, 50 subjects were screened, 39 subjects were randomized, and 20 subjects completed the study. There were 13 deaths and 41 SAEs reported. An audit of 20 subjects' records was conducted. Subject records reviewed included informed consent documents, study eligibility (inclusion/exclusion criteria), diagnosis, randomization, study visit and schedules, laboratory testing, concomitant medication, adverse events, and test article accountability. Source documents were compared against electronic

Case Report Forms (eCRFs). Primary endpoints were verified against the data listings. There were no limitations to the inspection. The observations noted were based on the FDA Form 483 and the EIR.

- b. General observations/commentary: During the inspections it was observed that the investigator did not adhere to the investigational plan and a Form FDA 483 was issued to Dr. Jandik containing the following observation: four subjects received prohibited concomitant medications or concomitant medications for a longer duration than the protocol specified.
- Subject #103897 received the prohibited concomitant medication Klacid SR (clarithromycin) from 3/10/09 to 3/19/09 while receiving study medication. Concomitant use of rivaroxaban with a CYP3A4 inhibitor is prohibited due to potential increased blood levels of rivaroxaban and possible bleeding complications.
  - Subject #101290 received the prohibited concomitant medication Klacid SR (clarithromycin) from 3/4/09 to 3/17/09 while receiving study medication. Concomitant use of rivaroxaban with a CYP3A4 inhibitor is prohibited due to potential increased blood levels of rivaroxaban and possible bleeding complications. In addition, Subject #101290 received Coxtral, a NSAID from 4/2/08 to 4/28/08 together with study drug. The protocol prohibits more than two weeks of daily dosing with a NSAID.
  - Subject #102619 received the NSAID diclofenac from 6/4/08 to 7/2/08 together with the study drug. The protocol prohibits more than two weeks of daily dosing with a NSAID.
  - Subject #103255 received the NSAID Coxtral, a NSAID from 12/11/07 to 3/27/08. The protocol prohibits more than two weeks of daily dosing with a non-steroidal anti-inflammatory drug.

Dr. Jandik responded to the Form FDA 483 observations in a letter dated June 9, 2011. In his written response, Dr. Jandik acknowledged the above protocol violations. He notes that Subjects #102619 and #103255 were prescribed NSAIDs in boxes of 30 tablets, and subjects were instructed to take the NSAIDs only if needed, not continuously. However, he acknowledges that there is no record of how the subjects actually took the NSAIDs. Subjects #103897, #101290, #102619, and #103255 had no bleeding adverse events.

- c. Assessment of data integrity: Although Dr. Jandik prescribed medications to four subjects which were prohibited (Klacid SR, a CYP3A4 inhibitor) or prescribed NSAIDs in a duration prohibited by the protocol, there were no apparent adverse events in these subjects as a result. The study appears to have been otherwise conducted adequately, and the data generated by this site may be used in support of the respective indication.

**7. Dimitar Raev, M.D.  
MI-Central Clinical Hospital**

**Ministry of Interior  
79 Skobelev Blvd.  
Sofia, 1606  
Bulgaria**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 738.811. At this site, 90 study subjects were screened and were enrolled into the study. The medical records for 36 subjects were reviewed in depth, including: medical history, inclusion ECG, laboratory values including INR, randomization, protocol, source documents, CRFs, financial disclosures, monitoring, adverse events, SAEs, drug accountability, drug inventory, and drug storage. All informed consent documents were reviewed. There were no limitations to the inspection. The observations noted were based on the EIR.
- b. General observations/commentary: In general, the records reviewed were found to be in order and the data verifiable. No discrepancies were noted. A Form FDA 483 was not issued.
- c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

**8. Johnson & Johnson Research & Development LLC  
920 U.S. Highway 202  
Raritan, NJ 08869-0602**

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. During this inspection, the following were reviewed: sponsor oversight of clinical trials, adverse events reporting, and records for the seven clinical investigator sites inspected. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. General observations/commentary: This inspection has been completed, and no Form FDA 483 was issued. No significant findings were reported. The sponsor maintained adequate oversight of the clinical trial. Appropriate steps were taken by the sponsor to bring noncompliant sites into compliance. There was no evidence of underreporting of adverse events, and the primary efficacy endpoint data were verifiable. As a Form FDA 483 was not issued at this site, it is unlikely that significant violations affecting data integrity occurred at this site.
- c. Assessment of data integrity: At this time, the data from this site appear acceptable for use in the NDA. If conclusions change when the EIR is reviewed, a CIS addendum will be generated and the review division notified.

## IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Seven clinical investigator sites and the sponsor were inspected in support of this application. The inspection documented regulatory violations at Dr. Rubin's, Dr. Militaru's, and Dr. Jandik's sites regarding protocol violations. In addition, there were recordkeeping and informed consent violations at Dr. Tirador's site. The minor and infrequent regulatory violations documented at these sites should have no significant impact on data integrity or subject safety. In general, inspection at the sites of Drs. Zelenka, Alvarez, and Raev as well as the sponsor Johnson & Johnson Research & Development LLC revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

Follow-Up Actions: The observations for Johnson & Johnson Research & Development are based on preliminary communications with the FDA Field investigator and for Dr. Militaru on preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Susan D. Thompson, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.  
Acting Division Director  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Bldg. 51, Rm. 5358  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

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/s/  
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SUSAN D THOMPSON  
08/31/2011

TEJASHRI S PUROHIT-SHETH  
08/31/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Hematology Products, Attn George Shashaty**

FROM (Name, Office/Division, and Phone Number of Requestor): **Alison Blaus, DCRP, (301) 796-1138**

DATE  
9 August 2011

IND NO.  
75238

NDA NO.  
202439

TYPE OF DOCUMENT  
NDA

DATE OF DOCUMENT  
5 January 2011

NAME OF DRUG  
**XARELTO (rivaroxaban)**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
~ 13 September 2011

NAME OF FIRM: **Johnson & Johnson PRD**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END OF PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END OF PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN VIVO WAIVER REQUEST     |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** In the Phase 3, warfarin controlled ROCKET study of rivaroxaban in > 14,000 patients with non-valvular AF at risk for stroke, there was a dramatic and statistically significant increase in the rate of primary endpoint point events in completing patients during the period from 3 to 30 days after the last dose of study drug. This period comprised 28 days after the end of the on-treatment period. The primary endpoint analysis was time to the composite of stroke (ischemic, hemorrhagic or unknown type) or systemic embolism, but all events in the relevant period were strokes (18 ischemic + 4 hemorrhagic in the riva arm; 6 ischemic in the warfarin arm). During this period, >90% of completers received VKA therapy. However, unlike other recent studies of novel anticoagulants for stroke prevention in AF patients, transition to warfarin or other VKA from study drug was abrupt. There was no period when both agents were taken concurrently, as in the other studies.

A similar phenomenon was observed in the much smaller (1200 patient) J ROCKET trial conducted in Japan.

There is ample evidence that warfarin management in the post-study drug period in ROCKET was sub-optimal. Also the study patients were at a quite high risk of stroke in general, and > 80% of patients in each arm who had a stroke in the relevant period had a baseline history of stroke/TIA/or systemic embolism. While this could explain what

happened, the sponsor has done nothing in our view to rule out the existence of a hypercoagulable state in patients who take rivaroxaban for an extended period and then stop suddenly. Please help us design a study or studies to rule out this possibility.

Our questions are:

1. In general, how would you approach the question of whether there is a hypercoagulable state in patients who take rivaroxaban for an extended period and then stop suddenly and start warfarin treatment?
2. If a clinical study is done, what sort of subjects should be recruited?
3. How long should subjects be on rivaroxaban?
4. What testing should be done to determine hypercoagulability in human subjects?
5. Many of the strokes occurred in patients switched to warfarin, and many of the ischemic strokes occurred early. Does this suggest to you that protein S/protein C derangements may have played a role in the strokes?
6. Are there any preclinical studies that might be helpful?

The attached document is an excerpt from the draft medical review of NDA 202439 regarding the issue of strokes occurring after the discontinuation of study drug. The second attachment is the sponsor's response to our IR regarding possible hypercoagulability.

|  |  |
|--|--|
| SIGNATURE OF REQUESTOR<br>Alison Blaus | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |
| PRINTED NAME AND SIGNATURE OF RECEIVER | PRINTED NAME AND SIGNATURE OF DELIVERER  |

Excerpt from Draft Review of NDA 202439 –

Rivaroxaban for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation

Section on Events Following Discontinuation of Study Drug.

23 Pages have been Withheld in Full immediately following this page.  
Please refer to the Medical Review dated August 10, 2011 at Pages  
165 - 186 for the information that has been withheld from this Review.

An additional 33 Pages been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

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

/s/  
-----

ALISON L BLAUS  
08/10/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

| Application Information   |   |                                  |
|---|---|----------------------------------|
| NDA # 202439<br>BLA# n/a  | NDA Supplement #:S- n/a<br>BLA STN # n/a  | Efficacy Supplement Type SE- n/a |
| Proprietary Name: XARELTO<br>Established/Proper Name: rivaroxaban<br>Dosage Form: Tablets<br>Strengths: 20 mg & 15 mg (CrCl 30 to <50 mL/min)   |   |                                  |
| Applicant: Ortho-McNeil-Janssen Pharmaceuticals<br>Agent for Applicant (if applicable): Johnson & Johnson / Bayer Pharmaceuticals   |   |                                  |
| Date of Application: 5 January 2011<br>Date of Receipt: 5 January 2011<br>Date clock started after UN: n/a  |   |                                  |
| PDUFA Goal Date: 5 November 2011  | Action Goal Date (if different): n/a  |                                  |
| Filing Date: 6 March 2011   | Date of Filing Meeting: 3 February 2011   |                                  |
| Chemical Classification: (1,2,3 etc.) (original NDAs only): 1   |   |                                  |
| Proposed indication(s)/Proposed change(s): XARELTO <sup>®</sup> (rivaroxaban) tablets are indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation  |   |                                  |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:   | <input checked="" type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)   |                                  |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:<br/> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a><br/>           and refer to Appendix A for further information.</i> |   |                                  |
| Review Classification:  | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority<br><br><input type="checkbox"/> Tropical Disease Priority Review Voucher submitted  |                                  |
| <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i><br><br><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>  |   |                                  |
| Resubmission after withdrawal? <input type="checkbox"/>   | Resubmission after refuse to file? <input type="checkbox"/>   |                                  |
| Part 3 Combination Product? <input type="checkbox"/>  | <input type="checkbox"/> Convenience kit/Co-package<br><input type="checkbox"/> Pre-filled drug delivery device/system<br><input type="checkbox"/> Pre-filled biologic delivery device/system<br><input type="checkbox"/> Device coated/impregnated/combined with drug<br><input type="checkbox"/> Device coated/impregnated/combined with biologic<br><input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Separate products requiring cross-labeling<br><input type="checkbox"/> Possible combination based on cross-labeling of separate products<br><input type="checkbox"/> Other (drug/device/biological product) |                                  |
| <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>  |   |                                  |

| <input type="checkbox"/> Fast Track<br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other:  | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |    |    |  |
|---|--|----|----|--|
| Collaborative Review Division ( <i>if OTC product</i> ): n/a  |  |    |    |  |
| List referenced IND Number(s): 75,238   |  |    |    |  |
| Goal Dates/Product Names/Classification Properties  | YES  | NO | NA | Comment  |
| PDUFA and Action Goal dates correct in tracking system?<br><br><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>  | X  |    |    | Priority review was not granted, therefore, priority goal dates were amended to standard dates in DARRTS |
| Are the proprietary, established/proper, and applicant names correct in tracking system?<br><br><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>   | X  |    |    |  |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i><br><br><i>If no, ask the document room staff to make the appropriate entries.</i> | X  |    |    | Priority review was not granted, therefore, priority goal dates were amended to standard dates in DARRTS |
| Application Integrity Policy  | YES  | NO | NA | Comment  |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>  |  | X  |    |  |
| If yes, explain in comment column.  |  |    |    |  |
| If affected by AIP, has OC/DMPQ been notified of the submission? <b>If yes</b> , date notified:   |  |    |    |  |
| User Fees   | YES  | NO | NA | Comment  |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature?   | X  |    |    |  |

| <p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>   | <p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid<br/> <input type="checkbox"/> Exempt (orphan, government)<br/> <input type="checkbox"/> Waived (e.g., small business, public health)<br/> <input type="checkbox"/> Not required</p> |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
|--|--|------------------|------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|-----------------|--|
| <p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>   | <p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears<br/> <input type="checkbox"/> In arrears</p>  |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p><b>505(b)(2)</b><br/> <b>(NDAs/NDA Efficacy Supplements only)</b></p>   | <p><b>YES</b></p>  | <p><b>NO</b></p> | <p><b>NA</b></p>       | <p><b>Comment</b></p>  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>  |  |                  | <p><b>X</b></p>        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>   |  |                  | <p><b>X</b></p>        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>   |  |                  | <p><b>X</b></p>        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i><br/> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="201 1465 1349 1598"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> | Application No.  | Drug Name        | Exclusivity Code       | Exclusivity Expiration |  |  |  |  |  |  |  |  |  |  |  |  |  |  | <p><b>X</b></p> |  |
| Application No.  | Drug Name  | Exclusivity Code | Exclusivity Expiration |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
|  |  |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
|  |  |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
|  |  |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>  |  |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p><b>Exclusivity</b></p>  | <p><b>YES</b></p>  | <p><b>NO</b></p> | <p><b>NA</b></p>       | <p><b>Comment</b></p>  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |
| <p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i><br/> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p>  |  | <p><b>X</b></p>  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                 |  |

|  |   |   |   |  |
|--|---|---|---|--|
| <b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?<br><br><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>   |   |   | X |  |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )<br><br>If yes, # years requested: FIVE<br><br><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>   | X |   |   |  |
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?  |   | X |   |  |
| <b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?<br><br><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i> |   |   | X |  |

| Format and Content  |   |    |    |         |
|---|---|----|----|---------|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>   | <input type="checkbox"/> All paper (except for COL)<br><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br><input checked="" type="checkbox"/> CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD) |    |    |         |
| If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?  | n/a   |    |    |         |
| Overall Format/Content  | YES   | NO | NA | Comment |
| If electronic submission, does it follow the eCTD guidance? <sup>1</sup><br>If not, explain (e.g., waiver granted).   | X   |    |    |         |
| <b>Index:</b> Does the submission contain an accurate comprehensive index?  | X   |    |    |         |
| Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including: | X   |    |    |         |

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

|   |            |           |           |                |
|---|------------|-----------|-----------|----------------|
| <input checked="" type="checkbox"/> legible<br><input checked="" type="checkbox"/> English (or translated into English)<br><input checked="" type="checkbox"/> pagination<br><input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)   |            |           |           |                |
| <b>If no, explain.</b>  |            |           |           |                |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  |            |           | X         |                |
| <b>If yes, BLA #</b>  |            |           |           |                |
| <b>Forms and Certifications</b>   |            |           |           |                |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> |            |           |           |                |
| <b>Application Form</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?   | X          |           |           |                |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>   |            |           |           |                |
| Are all establishments and their registration numbers listed on the form/attached to the form?  | X          |           |           |                |
| <b>Patent Information (NDAs/NDA efficacy supplements only)</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?   | X          |           |           |                |
| <b>Financial Disclosure</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?   | X          |           |           |                |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  |            |           |           |                |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>   |            |           |           |                |
| <b>Clinical Trials Database</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is form FDA 3674 included with authorized signature?  | X          |           |           |                |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  |            |           |           |                |
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>  |            |           |           |                |
| <b>Debarment Certification</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is a correctly worded Debarment Certification included with authorized signature?   | X          |           |           |                |

|  |            |           |           |                |
|--|------------|-----------|-----------|----------------|
| <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> |            |           |           |                |
| <b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| <p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>  | X          |           |           |                |

| <b>Controlled Substance/Product with Abuse Potential</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
|--|------------|-----------|-----------|----------------|
| <p><u>For NMEs:</u><br/>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u><br/><i>Date of consult sent to Controlled Substance Staff:</i></p> |            | X         |           |                |

| <b>Pediatrics</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>   |
|---|------------|-----------|-----------|--|
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | X          |           |           | PERC (George Greeley) contacted. George scheduled Riva for 28Sep11 on PERC Calendar w/out consult. |
| <p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>   | X          |           |           |  |

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

|  |   |           |           |  |
|--|---|-----------|-----------|--|
| <b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?<br><br><i>If no, request in 74-day letter</i>                            |   |           | X         |  |
| <b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?<br><br><i>If no, request in 74-day letter</i>                                     | X   |           |           | Adequate waiver was not initially submitted – Sponsor submitted evidence in support of a full waiver on 4 Feb 2011 |
| <b>BPCA (NDAs/NDA efficacy supplements only):</b><br><br>Is this submission a complete response to a pediatric Written Request?<br><br><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i> |   | X         |           |  |
| <b>Proprietary Name</b>  | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b>   |
| Is a proposed proprietary name submitted?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</i>  |   | X         |           | Separate trade name request not submitted – Sponsor to submit in Feb 2011  |
| <b>REMS</b>  | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b>   |
| Is a REMS submitted?<br><br><i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>   | X   |           |           |  |
| <b>Prescription Labeling</b>   | <input type="checkbox"/> <b>Not applicable</b>  |           |           |  |
| Check all types of labeling submitted.   | <input checked="" type="checkbox"/> Package Insert (PI)<br><input type="checkbox"/> Patient Package Insert (PPI)<br><input type="checkbox"/> Instructions for Use (IFU)<br><input checked="" type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labels<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent<br><input type="checkbox"/> Other (specify) |           |           |  |
|  | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b>   |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br><i>If no, request in 74-day letter.</i>  | X   |           |           |  |
| Is the PI submitted in PLR format? <sup>4</sup>  | X   |           |           |  |

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

|  |  |           |           |                         |
|--|--|-----------|-----------|-------------------------|
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request PLR format in 74-day letter.</i> |  |           | X         |                         |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?   | X  |           |           | Sent on 4Feb2011        |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )   | X  |           |           | Sent on 4Feb2011        |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?   | X  |           |           | Sent on 4Feb2011        |
| <b>OTC Labeling</b>  | <input checked="" type="checkbox"/> <b>Not Applicable</b>  |           |           |                         |
| Check all types of labeling submitted.   | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify) |           |           |                         |
|  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>          |
| Is electronic content of labeling (COL) submitted?<br><br><i>If no, request in 74-day letter.</i>  |  |           |           |                         |
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><br><i>If no, request in 74-day letter.</i>  |  |           |           |                         |
| If representative labeling is submitted, are all represented SKUs defined?<br><br><i>If no, request in 74-day letter.</i>  |  |           |           |                         |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?  |  |           |           |                         |
| <b>Other Consults</b>  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>          |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)<br><br><i>If yes, specify consult(s) and date(s) sent:</i> DSI (negotiating sites for consult at time of filing), Carcinogenicity Statistics (25Jan11)  | X  |           |           |                         |
| <b>Meeting Minutes/SPAs</b>  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>          |
| End-of Phase 2 meeting(s)?<br><b>Date(s):</b> 12Sep2006<br><br><i>If yes, distribute minutes before filing meeting</i>   | X  |           |           | Minutes dated 25Sep2006 |

|   |          |          |  |  |
|---|----------|----------|--|--|
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> 27Oct2009<br><br><i>If yes, distribute minutes before filing meeting</i>                | <b>X</b> |          |  | Minutes dated<br>6Nov2009: P3 Top<br>Line Meeting on<br>8Nov2010 – Minutes<br>dated 7Dec2010 |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b> n/a<br><br><i>If yes, distribute letter and/or relevant minutes before filing meeting</i> |          | <b>X</b> |  |  |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 3 February 2011

**BLA/NDA/Supp #:** 202439

**PROPRIETARY NAME:** XARELTO

**ESTABLISHED/PROPER NAME:** rivaroxaban

**DOSAGE FORM/STRENGTH:** 15 & 20 mg Tablets

**APPLICANT:** Ortho-McNeil-Janssen Pharmaceuticals

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

**BACKGROUND:** Rivaroxaban (BAY 59-7939) is an oral Factor Xa inhibitor being co-developed for the prevention of stroke and non-central nervous system (non-CNS) systemic embolism in patients with non-valvular atrial fibrillation (AFib).

The sponsors have completed two Phase 3 trials under IND 75,238, ROCKET-AF and J-ROCKET-AF. ROCKET-AF was a randomized, double-blind, double-dummy, noninferiority study evaluating the efficacy and safety of administering rivaroxaban 20 mg once daily (15 mg for renal impaired) compared to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. J-ROCKET-AF study is specifically designed for the Japanese NDA and is not powered as a stand-alone pivotal study.

**REVIEW TEAM:**

| <b>Discipline/Organization</b>                      | <b>Names</b>   |   | <b>Present at filing meeting? (Y or N)</b> |
|---|----------------|---|--|
| Regulatory Project Management                       | RPM:           | Alison Blaus  | Y  |
|   | CPMS/TL:       | Edward Fromm  | Y  |
| Cross-Discipline Team Leader (CDTL)                 | Aliza Thompson |   | Y  |
| Clinical  | Reviewer:      | Preston Dunnmom                                       | Y  |
|   |                | Martin Rose   | Y  |
|   | TL:            | Shari Targum<br>Thomas Marciniak<br>Abraham Karkowsky | Y<br>Y<br>Y                                |
| Social Scientist Review ( <i>for OTC products</i> ) | Reviewer:      | n/a   | n/a  |
|   | TL:            | n/a   | n/a  |

|  |           |                                |        |
|--|-----------|--------------------------------|--------|
| OTC Labeling Review ( <i>for OTC products</i> )                                      | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| Clinical Microbiology ( <i>for antimicrobial products</i> )                          | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| Clinical Pharmacology  | Reviewer: | Sreedharan Sabarinath          | Y      |
|  | TL:       | Raj Madabushi                  | Y      |
| Biostatistics  | Reviewer: | Philip Dinh                    | Y      |
|  | TL:       | James Hung                     | Y      |
| Nonclinical (Pharmacology/Toxicology)  | Reviewer: | Patricia Harlow                | Y      |
|  | TL:       | Albert DeFelice                | N      |
| Statistics (carcinogenicity)   | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> ) | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| Product Quality (CMC)  | Reviewer: | Pei-I Chu (DP)<br>Tapash Ghosh | Y<br>Y |
|  | TL:       | Kasturi Srinivasachar          | Y      |
| Quality Microbiology ( <i>for sterile products</i> )                                 | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| CMC Labeling Review  | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| Facility Review/Inspection   | Reviewer: | n/a                            | n/a    |
|  | TL:       | n/a                            | n/a    |
| OSE/DMEPA (proprietary name)   | Reviewer: | None                           | n/a    |
|  | TL:       | None                           | n/a    |

|                                  |  |                        |     |
|----------------------------------|--|------------------------|-----|
| OSE/DRISK (REMS)                 | Reviewer:  | Cynthia LaCivita       | Y   |
|                                  | TL:  | n/a                    | n/a |
| OC/DCRMS (REMS)                  | Reviewer:  | n/a                    | n/a |
|                                  | TL:  | n/a                    | n/a |
| Bioresearch Monitoring (DSI)     | Reviewer:  | Susan Thompson         | Y   |
|                                  | TL:  | Tejashri Purohit-Sheth | N   |
| Controlled Substance Staff (CSS) | Reviewer:  | n/a                    | n/a |
|                                  | TL:  | n/a                    | n/a |
| Other reviewers                  | Nhi Beasley  |                        | Y   |
| Other attendees                  | Norman Stockbridge (DCRP Division Director), Stephen Grant (DCRP Deputy Division Director), Mary Ross Southworth (DCRP Safety Deputy Director), Nina Ton (OSE PM), Tu-Van Lambert (ONDQA PM), Tzu-Yun McDowell (OCP), Hobart Rogers (Pharmacogenomics), Megan Moncur |                        |     |

**FILING MEETING DISCUSSION:**

|   |   |
|---|---|
| <p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>             | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p> | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> None</p>                              | <input type="checkbox"/> Not Applicable   |
| <p><b>CLINICAL</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input checked="" type="checkbox"/> Review issues for 74-day letter |

|  |  |
|--|--|
| <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> Advisory Committee Meeting targeted for early September 2011</p> <p><b>If no, for an original NME or BLA application, include the reason. For example:</b></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> | <input checked="" type="checkbox"/> YES<br>Date if known:<br><input type="checkbox"/> NO<br><input type="checkbox"/> To be determined<br><br>Reason:   |
| <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>   | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO   |

|  |   |
|--|---|
| <p><b>BIostatISTICS</b></p> <p><b>Comments:</b> The extent of Dr. Dinh's review of J-ROCKET will be determined during the review.</p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter  |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> Dr. Harlow to consult with the Division of Hematology rivaroxaban reviewer. Dr. Harlow will write a review on items not covered in the Hematology review. Exec CAC meeting planned for early May. Carcinogenicity biostatistics consult already completed.</p> | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter  |
| <p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter  |
| <p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Drug Substance (DS) is being reviewed as part of the Hematology NDA (same formulation). Drug Product for this application will be reviewed by Dr. Chu. Tapash Ghosh will complete a biopharmaceutics review.</p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter  |
| <p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>                           | <input checked="" type="checkbox"/> Not Applicable<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO |

|  |  |
|--|--|
| <p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b> Facilities inspection already completed as part of the Hematology NDA. Same manufacturing facility inspection for both NDAs (inspection not dependant on dose).</p> | <input checked="" type="checkbox"/> Not Applicable<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO       |
| <p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b> n/a</p>   | <input type="checkbox"/> Review issues for 74-day letter   |

| <b>REGULATORY PROJECT MANAGEMENT</b>  |   |
|---|---|
| <p><b>Signatory Authority:</b> Robert Temple, M.D.</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b> If rivaroxaban is approved in Hematology (NDA 22406) prior to the PDUFA for NDA 202439, signatory authority for NDA 202439 will change to Norman Stockbridge, M.D., Ph.D.</p> |   |
| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>  |   |
| <input type="checkbox"/>  | The application is unsuitable for filing. Explain why:  |
| <input checked="" type="checkbox"/>   | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |
| <b>ACTIONS ITEMS</b>  |   |
| <input type="checkbox"/>  | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).  |
| <input type="checkbox"/>  | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).  |
| <input type="checkbox"/>  | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.   |
| <input type="checkbox"/>  | BLA/BLA supplements: If filed, send 60-day filing letter  |
| <input type="checkbox"/>  | <p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>   |
| <input checked="" type="checkbox"/>   | Send review issues/no review issues by day 74   |

|                          |  |
|--------------------------|--|
| <input type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter  |
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ] |
| <input type="checkbox"/> | Other  |

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

ALISON L BLAUS  
02/17/2011