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APPLICATION NUMBER:

022406Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
ADDENUM TO April 6, 2009 REVIEW

NDA: **22-406**	Submission Date(s): **12/30/10**
Brand Name	**XARELTO® immediate release tablets**
Generic Name	**rivaroxaban**
Primary Reviewer	**Joseph A. Grillo, Pharm.D.**
DCP5 Team Leader	**Julie M. Bullock, Pharm.D.**
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**
SIMCYP & Drug Metabolism	**Ping Zhao, Ph.D.**
OCP Division	**5**
ORM division	**OND/OODP/DHP**
Applicant	**Johnson & Johnson Pharmaceutical Research and Development, L.L.C (J&J)**
Relevant IND(s)	**64,892**
Submission Type; Code	**Resubmission NME NDA (SDN 70), Priority Review [original OCP NME NDA review 4/6/2009]**
OCP Briefing Date	**None [original submission: March 25, 2009]**
Formulation; Strength(s)	**10 mg immediate release tablets**
Indication	**The prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.**

Table of Contents

1 Executive Summary

The original NDA application was submitted on July 22, 2008, for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. A clinical pharmacology review dated April 6, 2009, found the original application acceptable provided post-marketing related issues were addressed. A complete response letter was issued on May 27, 2009, due to Clinical and Quality related issues. Although there were no clinical pharmacology related deficiencies, the agency did proactively communicate potential a post-marketing related issue regarding the need to develop a lower strength tablet for patients with Child Pugh class B hepatic impairment without coagulopathy, concurrently taking rivaroxaban with a P-gp and strong CYP3A4 inhibitor, and concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment.

In its formal response the applicant states that it does not consider using a lower rivaroxaban dose for the treatment of Child Pugh class B patients without coagulopathy appropriate because its analysis suggests higher baseline prothrombin time (PT) and greater sensitivity between rivaroxaban plasma concentrations and PT in this population. However, the clinical relevance of the increased baseline PT and higher sensitivity in this population is not clear. There was no relationship observed between PT levels and proportion of patients with major bleeding in the 11527 and RECORD studies. Furthermore, FDA found that using the expected concentrations from a phase 2 study (11527), at the proposed clinical dose, the expected difference in PT ratio (PTR) following exposure matching in Child Pugh class B patients appears to be within the range seen in the combined analysis of the Phase 3 RECORD studies. In addition, both PT and PTR were considered to have poor predictive value for bleeding risk in the applicant's safety analysis of the RECORD studies. Therefore, FDA is not persuaded by the applicant's argument against exposure matching in this population.

In addition, the applicant does not consider using a lower rivaroxaban dose (5 mg QD) for patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitor appropriate. This is because applicant's simulations suggest that steady state, trough concentration (C_{trough}) are estimated to be approximately 6-times higher in patients taking 5 mg QD dose with strong CYP3A4 and P-gp inhibitor compared to patients taking 10 mg QD alone. The applicant's simulation analysis was limited by holding the apparent volume of distribution (Vd/F) constant in its model and decreasing only apparent clearance (CL/F) to drive change in exposure causing prolonged elimination half-life and higher trough levels. However, both Vd/F and CL/F were reduced with minimal change in half-life in drug interaction studies with these combined inhibitors.

FDA simulations of this scenario were also conducted using the same method except reducing both CL/F and Vd/F to that observed in the applicant's drug interaction studies. The resulting simulations did not support the 6-fold change in steady-state C_{trough} concentrations following exposure matching. Therefore, FDA is not persuaded by the applicant's argument against exposure matching in this population.

FDA continues to recommend that the availability of lower dose strengths of rivaroxaban is the best option to allow a larger patient population to receive this treatment and this issue should still be considered as a post marketing commitment. Until a lower dose formulation is developed FDA supports avoidance language in the labeling for these populations.

1.1 Recommendation

From a clinical pharmacology perspective, this resubmission of the original application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing commitments addressing clinical pharmacology related safety concerns with rivaroxaban treatment.

1.2 Post Marketing Requirements

None

1.3 Post Marketing Commitments

1.3.1 Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement.

Protocol submission Date: 45 days from date of action.

Submission Date: 6 months after FDA agreement to submitted protocol.

1.3.2 The applicant should evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation.

Protocol submission Date: We note the applicant has submitted a draft protocol with this NDA application and request that it be resubmitted for FDA review under the IND within 10 business days of this action.

Submission Date: 6 months after FDA agreement to submitted protocol.

1.4 Comments to the Applicant

1.4.1 The FDA suggests that the applicant evaluate the effect of a P-gp inhibitor with limited CYP3A4 inhibitory activity (e.g., quinidine) on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in healthy subjects. This study will explore the involvement of P-gp in rivaroxaban elimination so that appropriate dosing recommendations can be created following the development of the 5 mg tablet formulation.

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The original NDA application was submitted on July 22, 2008, for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. A clinical pharmacology review dated April 6, 2009, found the original application acceptable provided post-marketing related issues were addressed. A complete response letter was issued on May 27, 2009, due to Clinical and Quality related issues. Although there were no clinical pharmacology related deficiencies, the agency did proactively communicate a potential post-marketing related issue regarding the need for the development of a lower strength tablet for the following patients:

- Child Pugh class B hepatic impairment without coagulopathy

- Concurrently taking rivaroxaban with a P-gp and strong CYP3A4 inhibitor
- Concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment

This resubmission includes a response to the clinical pharmacology issue regarding the need for a lower dose formulation for Xarelto in the above populations. These responses were evaluated in this review.

In its formal response the applicant states that it does not consider using a lower rivaroxaban dose for the treatment of Child Pugh class B patients without coagulopathy appropriate because its analysis of pharmacodynamic response from the dedicated hepatic impairment study suggests greater sensitivity between rivaroxaban plasma concentrations and prothrombin time (PT) in this population. Sensitivity was derived from the slope of the exposure response plot of PT versus rivaroxaban concentration.

FDA evaluated the applicant's proposal and PT analysis and added an analysis of the ratio of PT to baseline (PTR) to rivaroxaban concentration to focus on sensitivity rather than baseline differences. The baseline PT was greater in Child Pugh class B patients (16.2 seconds) compared to healthy subjects (13.0 seconds). In addition, relationship between PT and major bleeding was explored using the data from the 11527 and RECORD studies. The FDA analysis found the following:

- Using the expected concentrations from a phase 2 study (11527), at the proposed clinical dose and assuming exposure matching between Child Pugh class B patients and healthy subjects, where the Child Pugh class B patients where given half the dose of the healthy subjects, FDA estimated the expected PTR for each group from the linear equation describing this relationship. The expected median PTR was ~1.61 in the C-P class B patients compared to ~1.34 in the health subjects. This PTR range for exposure matched C-P class B patients is within the range reported by the applicant for the PTR seen in the combined analysis of the RECORD studies.
- There was no relationship observed between steady state PT levels and proportion of patients with major bleeding in 11527 and RECORD studies.
- The applicant's integrated safety summary reports that it found no relationship between PT or PTR and relevant bleeding risk.

Based on this analysis, FDA is not persuaded by the applicant's argument against exposure matching in this population.

The applicant also states that it does not consider using a lower rivaroxaban dose for patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitor appropriate. This is because its simulations suggest that steady state, C_{trough} concentrations for 5 mg rivaroxaban co-administered with a P-gp and strong CYP3A4 inhibitor are estimated to be approximately 6-times higher as compared to steady-state C_{trough} concentrations for 10 mg rivaroxaban administered alone. Simulations were performed by the applicant using PK data of patients receiving rivaroxaban 10 mg once daily as obtained from the Phase 2 dose ranging study 11527 and inhibiting CL/F by a factor of 0.39 (observed in the Phase 1 drug interaction studies with ritonavir and ketoconazole) and leaving Vd/F constant.

The applicant's decision to decrease CL/F but hold the Vd/F constant in its model results in prolonged half-life with clearance driving the change in exposure. This is in contrast to data from five drug interaction studies with combined P-gp and CYP3A4 inhibitors of various potencies showing both Vd/F and CL/F as prominent factors causing increase in exposures such that half-life was minimally changed. FDA repeated the applicant's simulations using the same method except reducing CL/F by a factor of 0.39 and Vd/F by a factor of 0.48 as observed in the Phase 1 drug interaction studies with ritonavir and ketoconazole. These simulations did not support the significant change in steady-state C_{trough} concentrations

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