

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**022406Orig1s000**

***Trade Name:*** Xarelto 10 mg immediate release Tablets.

***Generic Name:*** riyaroxaban

***Sponsor:*** Johnson and Johnson Pharmaceutical Research and  
Development, LLC

***Approval Date:*** July 1, 2011

***Indications:*** For the prophylaxis of deep vein thrombosis and  
pulmonary embolism in patients  
undergoing: hip replacement surgery or knee  
replacement surgery.

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## 022406Orig1s000

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*APPLICATION NUMBER:*

**022406Orig1s000**

**APPROVAL LETTER**



NDA 022406

**NDA APPROVAL**

Johnson and Johnson Pharmaceutical Research and Development, LLC  
Attention: Andrea F. Kollath, DVM  
Director, Regulatory Affairs  
920 Route 202, P.O. Box 300  
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated July 28, 2008, received July 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xarelto<sup>®</sup> (rivaroxaban) 10 mg immediate release Tablets.

We acknowledge receipt of your amendments dated January 4, February 2, 18, 25, March 25, April 18, 25, 26, 28, May 2, 4, 6, 10, 11, 25 and June 8, 20 and 30, 2011.

The December 30, 2010, submission constituted a complete response to our May 27, 2009, action letter.

This new drug application provides for the use of Xarelto<sup>®</sup> (rivaroxaban) 10 mg immediate release Tablets, for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing: hip replacement surgery or knee replacement surgery.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22406.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable and because there are too few children with disease/condition to study.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the serious risks of major bleeding events and renal impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1797-1 A postmarketing pharmacovigilance study of the risk factors, clinical management, and outcome of cases of major bleeding in association with Xarelto<sup>®</sup> (rivaroxaban) use.

You agree to conduct an “Enhanced Pharmacovigilance Plan” that will consist of the collection, analysis, and reporting of events termed “major bleeding,” to consist of active solicitation of the events and associated risk factors, subsequent therapy, and outcomes. Major bleeding is defined as in the clinical protocols and current drug labeling.

You agree to provide reports quarterly for the first three years following drug approval, then annually. The final plan will be submitted by October 30, 2011.

Submit summary information (total cases and summary of key facts in those cases, with pertinent expert analysis of clinically relevant information from the case series and any potential regulatory implications such as label changes) quarterly for 3 years, then annually.

The timetable you submitted on June 30, 2011 states that you will conduct this study according to the following schedule.

Final Protocol Submission:	November 30, 2011
Interim report submission:	Quarterly thereafter for 3 years, then annually
Study Completion:	June 30, 2016
Final Report Submission:	December 30, 2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the serious risks of renal impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1797-2 Perform a clinical trial to 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.

The timetable you submitted on June 30, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted February 4, 2011
Trial Completion:	February 29, 2012
Final Report Submission:	June 30, 2012

Submit protocols to your IND 64892, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify each submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required**

**Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENT NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

PMC 1797-3 Develop and propose a 5 mg strength 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. For a scored 10 mg tablet, show that half-tablets follow the same dissolution profile and specifications (based on percent) as the whole and show that the half-tablets are otherwise proportionately equivalent. A 5 mg strength tablet should be sufficiently distinguishable from the 10 mg tablet in physical characteristics. If feasible, we recommend that you consider a proportional formulation for a 5 mg strength tablet. Full chemistry, manufacturing and controls (CMC) information for a 5 mg tablet including the batch data and stability data, labels, updated labeling, a request for a biowaiver for the lower 5 mg strength based on [proportional] formulation and the F2 metric, and an updated environmental assessment section will be submitted in a prior approval supplement.

The timetable you submitted on June 30, 2011, states that you will conduct this study according to the following schedule:

Final CMC Supplement Submission: April 2012

Submit chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

**POST-ACTION FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Tyree Newman, Regulatory Project Manager, at (301) 796-3907.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling  
Carton and Container Labeling

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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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RICHARD PAZDUR  
07/01/2011