



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202439

NDA APPROVAL

Janssen Pharmaceuticals, Inc.
c/o: Alla Rhoge Pharm.D., Associate Director
Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Rhoge:

Please refer to your New Drug Application (NDA) dated January 4, 2011, received January 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for XARELTO[®] (rivaroxaban) Tablets.

We also refer to your submissions received January 18 (two), 21, 28, and 31, February 2, 4 (two), 8, 9, 11, 15 (two), 16, 18 (four), 25, 28, and March 1, 4, 8, 16, 18 (two), 28, 29, 30, 31, April 1, 6, 8, 15 (two), 18, 22, 25, 26, 28, 29 (two), May 2, 4 (two), 5 (two), 6, 10, 13 (two), 16, 17 (two), 23 (three), 27 (two), June 3 (three), 9, 10 (five), 13, 16, 20, 22, 27, 29 (two), 30 (two), July 5, 11 (two), 14, 15, 19 (two), 20, 21 (two), 22, 26, 28, 29 (two), August 3, 4 (two), 9, 11 (two), 17, 19, 23, September 13, 23, 29, 30 (two), October 7, 11, 20, 21, 28, November 2 (four), 3 (four), and 4 (three), 2011.

This new drug application provides for the use of XARELTO for the following 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.

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 and Medication Guide). 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your November 1, 2011, submission containing final printed carton and container labels.

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 because the disease is rare in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of the following postmarketing requirements detailed in the approval letter of NDA 22406:

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

The timetable you submitted on June 30, 2011, to NDA 22406, 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

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, to NDA 22406, 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 NDA 22406. Submit all final reports to NDA 22406. 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 report periodically 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, to NDA 22406, 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 also remind you of your postmarketing commitment detailed in the approval letter of NDA 22406:

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, to NDA 22406, states that you will conduct this study according to the following schedule:

Final CMC Supplement Submission: April 2012

As a reminder, submit chemistry, manufacturing, and controls protocols and all final reports to NDA 22406. 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 for NDA 22406. 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**.”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for XARELTO to ensure the benefits of the drug outweigh the risks of increased risk of thrombotic events, including stroke, if XARELTO is discontinued or not taken daily with the evening meal to maximize absorption.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that XARELTO poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of XARELTO. The Medication Guide stresses patient adherence to directions for use, which is crucial to the drug’s effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed XARELTO.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on November 2nd and 3rd, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you market XARELTO for this new indication into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of XARELTO.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
4. A report on the distribution of DHCP letters.
5. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with XARELTO.
6. With respect to the REMS goals, an assessment of the extent to which the REMS is meeting its goals or whether the goals or other elements should be modified.
7. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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
Office of Prescription Drug Promotion
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 Office of Prescription Drug Promotion (OPDP), 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>.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

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

/s/

NORMAN L STOCKBRIDGE
11/04/2011