DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022406/S-001
NDA 022406/S-002
NDA 022406/S-003

SUPPLEMENT APPROVAL

Janssen Research & Development, LLC
Attention: Huy Q. Truong
Associate Director, Global Regulatory Affairs
920 Highway 202, South
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Truong:

Please refer to your Supplemental New Drug Applications (sNDAs) dated May 1 and 28, 2012, received May 2 and 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XARELTO® (rivaroxaban) 15 and 20 mg immediate release tablets.

We acknowledge receipt of your amendments dated May 7, 28, July 26, 30, 31, August 2, 3, 6, 27, 29, September 4, 27, October 4, 19, 23 and November 2, 2012.

These "Prior Approval" supplemental new drug applications provide for the treatment of deep vein thrombosis, the treatment of pulmonary embolism, the reduction in risk for deep vein thrombosis and the reduction in risk for pulmonary embolism.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

- In the highlights section, 2nd bullet: remove the underline for "15 mg orally...21". (Treatment of DVT, PE, and Reduction in the Risk of Recurrence of DVT and of PE: 15 mg orally twice daily with food for the first 21)

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on May 2, 2012, as soon as they are available, but no more than 30 days after they are printed.

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 deferring submission of your pediatric studies until October 2013, April 2014, July 2015 and October 2017, respectively, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

PMR 1966-1 Submit the results of a single-dose pharmacokinetic (PK)/pharmacodynamic (PD) and tolerability trial in pediatric patients aged ≥ 6 months to < 17 years with

venous thromboembolic event(s) (VTE) in appropriate age cohorts to determine dosing of rivaroxaban (tablets and oral suspension) that will provide similar exposure and/or PD effect compared to recommended doses in adults. Enroll into sequential age cohorts (e.g., beginning with 12 to < 17 years) and use the information from the older age cohorts to inform dosing in the younger age cohorts.

Final Protocol Submission: 6/2013
Trial Completion: 12/2014
Final Report Submission: 6/2015

PMR 1966-2 Conduct a randomized, dose-exploration, multicenter clinical trial evaluating the multiple dose PK/PD profile and safety of oral rivaroxaban (tablets or oral suspension) in pediatric patients aged 6 years to <17 years with VTE. Enroll into sequential age cohorts (e.g., beginning with ages 12 to < 17 years) and use the information from the older age cohorts to inform dosing in the younger age cohorts.

Final Protocol Submission: 6/2013
Trial Completion: 6/2016
Final Report Submission: 6/2017

PMR 1966-3 Conduct a randomized, dose-exploration, multicenter clinical trial evaluating the multiple dose PK/PD profile and safety of oral rivaroxaban (tablets or oral suspension) in pediatric patients aged 6 months to < 6 years with VTE.

Final Protocol Submission: 12/2016
Trial Completion: 12/2019
Final Report Submission: 6/2020

PMR 1966-4 Conduct a single-dose PK/PD and tolerability trial in pediatric patients age birth to < 6 months with VTE to determine doses of rivaroxaban (oral suspension) that provide similar exposure and/or PD effect to those seen in older pediatric cohorts.

Final Protocol Submission: 12/2015
Trial Completion: 12/2019
Final Report Submission: 6/2020

PMR 1966-5 Conduct a dose-exploration, multicenter clinical trial evaluating the multiple dose PK/PD profile and safety of oral rivaroxaban (oral suspension) in pediatric patients aged birth to <6 months with VTE.

Final Protocol Submission: 12/2015
Trial Completion: 12/2019
Final Report Submission: 12/2020

PMR 1966-6 Conduct a randomized, active-controlled, multicenter clinical trial evaluating the safety, efficacy and PK/PD (sparse sampling) of at least 3 months of treatment with oral rivaroxaban (tablets or oral suspension) in pediatric patients aged birth to < 17 years of age who have acute VTE. Patients who require treatment for longer than 3 months will be offered continuation of treatment in an open label extension of this study with treatment duration of up to 12 months. Patients from birth to <6 months of age may be enrolled only after data from a planned interim analysis have shown efficacy and safety of rivaroxaban in the older pediatric age groups. Age distribution of patients in the study should reflect the occurrence of VTE in the pediatric population.

Final Protocol Submission:	6/2017
Trial Completion:	12/2022
Final Report Submission:	6/2023

Submit the protocols to your IND 064892, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on 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).

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

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.