



NDA 022406/S-024

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Huy Truong, MS
Associate Director, Global Regulatory Affairs
920 U.S. Highway 202, PO Box 300
Raritan, NJ 08869-0602

Dear Mr. Truong:

Please refer to your Supplemental New Drug Application (sNDA) dated April 28, 2017, received April 28, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XARELTO® (rivaroxaban) tablets, 10 mg, 15 mg, and 20 mg.

We also refer to our approval letter dated October 27, 2017 which contained the following error: incorrect signature block.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain October 27, 2017, the date of the original approval letter.

This Prior Approval supplemental new drug application provides for the new dosing regimen of 10 mg once daily for the reduction in the risk of recurrence of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients at continued risk for DVT and/or PE after completion of initial treatment lasting at least 6 months.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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, except with the revisions indicated, the enclosed labeling (text for the package insert, 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 via 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 with the revisions indicated above approved in this supplemental application, 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).

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 remind you of the following PREA PMRs listed in the November 2, 2012 supplement approval letter as follows:

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.

| | |
|--------------------------|---------|
| 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.

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.

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

The above PMRs are also applicable to Supplement S-024.

Submit the protocol(s) 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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. 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, contact Katie Chon, Regulatory Project Manager at katie.chon@fda.hhs.gov or (240) 402-6578.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ALBERT B DEISSEROTH
10/27/2017