DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

**NDA APPROVAL**

Portola Pharmaceuticals, Inc.
Attention: Janice Castillo
Senior Vice President, Regulatory Affairs
270 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Castillo:

Please refer to your New Drug Application (NDA) dated October 23, 2016, received October 24, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bevyxxa® (betrixaban) capsule, 40 mg and 80 mg.

This new drug application provides for the use of Bevyxxa® (betrixaban) capsule for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

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.

## EXPIRATION DATING PERIOD

Expiration dating period of 24 months for the commercial drug product when stored under controlled room temperature conditions 20°C to 25°C (68°F to 77°F) in the commercial packaging.

## 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, medication guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available 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 immediate container labels that are identical to the carton and immediate container labels submitted on June 20, 2017, 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208383**." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for betrixaban was not referred to a FDA advisory committee because this drug is not the first in its class and the evaluation of safety data when used for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

## 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 ages 0 to < 2 years because of the following:

- The necessary studies are impossible or highly impracticable. This is because the numbers of patients in this age group is low and the patients are geographically dispersed.

- There is evidence strongly suggesting that the drug product would be ineffective and unsafe in this pediatric group. The Netherlands pediatric working group, based on their extensive literature search, suggested that there is little evidence that primary prophylactic anticoagulation provided any benefit in neonates or infants and toddlers who have a central venous catheter (80% of VTE events in neonate occur as a complication of CVCs). In addition, given the variability of food intake that occurs in the subgroups (neonates, infants and toddlers), which have the potential to lead to a supra-therapeutic betrixaban level in fast state and consequently potential increase of major bleeding events in this subgroup.

We are deferring submission of your pediatric studies for ages 2 to < 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act 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)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

PMR 3229-1 Conduct a single-dose, open label pediatric pharmacokinetic/ pharmacodynamic study in the fed state. The study population will be children two years of age or older who have just completed a course of anticoagulation for venous thrombosis.

The timetable you submitted on June 19, 2017, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 09/30/2016 |
| Study Completion: | 12/31/2019 |
| Final Report Submission: | 06/30/2020 |

PMR 3229-2 Conduct a venous thromboembolism prophylaxis study in immobilized adolescents hospitalized for acute medical or surgical disease. The study will be a single-arm, open-label study of betrixaban with point estimates of events to be compared to historical controls. The objective of this study is to identify the safety and efficacy of betrixaban in the pediatric population.

The timetable you submitted on June 19, 2017, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 03/31/2018 |
| Study Completion: | 05/31/2020 |
| Final Report Submission: | 12/31/2020 |

PMR 3229-3 Conduct a randomized multi-center, active-controlled clinical trial comparing betrixaban to standard of care (in patients two years of age or older with central venous catheter) or either enoxaparin or warfarin (in patients two years of age or older with secondary prevention indication) in prevention of venous thromboembolism. The objective of this study is to identify the safety and efficacy of betrixaban in the pediatric population.

The timetable you submitted on June 19, 2017, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 03/31/2018 |
| Study Completion: | 12/31/2022 |
| Final Report Submission: | 06/30/2023 |

Submit the protocols to your IND 72679, with a cross-reference letter to this NDA.

Reports of this/these required pediatric postmarketing studyies 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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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 ).

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. 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).

## 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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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 Thomas Iype, Regulatory Project Manager, at (240) 402 6861.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of 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
06/23/2017