Our STN: BL 125586/0

ACCELERATED APPROVAL
May 3, 2018

Portola Pharmaceuticals, Inc.
Attention: Janice Castillo
270 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Castillo:

Please refer to your Biologics License Application (BLA) for coagulation factor Xa (recombinant), inactivated-zhzo, dated November 6, 2015, received December 18, 2015, submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2017 to Portola Pharmaceuticals, Inc, South San Francisco, CA, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products and according to the regulations for accelerated approval, 21 CFR 601.41. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product coagulation factor Xa (recombinant), inactivated-zhzo. Coagulation factor Xa (recombinant), inactivated-zhzo is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 02329327, 02220725, 02207725, and 01758432.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval regulations we may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the biological product further, to verify and describe its clinical benefit, where there is

uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these regulations requires, among other things, that you conduct an adequate and well-controlled clinical trial to verify and describe the clinical benefit attributable to this product. Clinical benefit is evidenced by improvement in hemostatic outcomes rated as excellent or good.

Accelerated Approval Required Study

We remind you of your postmarketing requirement specified in your submission of April 27, 2018.

Study-18-513: "A Phase 4 randomized trial of ANDEXXA in acute intracranial hemorrhage in patients receiving oral factor Xa inhibitors"

This open-label, randomized trial will include at least 440 adult patients who developed acute intracranial hemorrhage following the treatment with rivaroxaban, apixaban, or edoxaban 15 hours or less prior to randomization. The enrolled patients will be administered ANDEXXA (high or low dose) or standard of care other than ANDEXXA according to 1:1 randomization scheme. To describe and verify the hemostatic effect of ANDEXXA, patients will be assessed with the National Institute of Health Stroke Scale and computed tomography or magnetic resonance imaging at 12-hours post-randomization. The trial assessments will also include evaluation of occurrence of the safety events of special interest, including but not limited to: stroke, transient ischemic event, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, arterial systemic embolism, sudden death, and events suspicious for thrombosis, embolism, and ischemia—all to be observed at least 3 days for immediate occurrence and at least 30 days with weekly intervals for delayed occurrence. The assessments of the hemostatic effect will be made by an adjudication committee blinded to the treatment allocation.

Your trial will be conducted according to the following timetable:

Final Protocol Submission: April 17, 2018;
Study Completion Date: October 31, 2022;
Final Study Report Submission: April 30, 2023.

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of April 27, 2018.

You must conduct this study with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by coagulation factor Xa (recombinant), inactivated-zhzo, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43 (b), withdraw or modify approval if:

- A postmarketing clinical study fails to verify clinical benefit
- You fail to perform the required postmarketing study with due diligence

- Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product
- You fail to adhere to the postmarketing restrictions agreed upon
- The promotional materials for your product are false or misleading
- Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

Please submit the protocol(s) to your IND 15089, with a cross-reference letter to this BLA, STN BL 125586/0 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Your accelerated approval postmarketing required study is subject to the reporting requirements of 21 CFR 601.70. You must describe the study's status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the Federal Food, Drug, and Cosmetic Act (FDCA) are fulfilled or released.

Please submit final study report(s) as a supplement to this BLA, STN BL 125586/0. For administrative purposes, all submissions related to these postmarketing study requirements must be clearly designated as "Subpart E Postmarketing Study Requirements."

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture coagulation factor Xa (recombinant), inactivated-zhzo drug substance at (b) (4) . The final formulated product will be manufactured and filled at (b) (4) and labeled and packaged at (b) (4) .

You may label your product with the proprietary name ANDEXXA and market it in a 100-mg vial size.

We did not refer the application to the Blood Products Advisory Committee because senior leadership in the product office and center determined that a decision regarding the information submitted in the BLA, including the clinical study design and trial results, would not likely have benefited from additional discussion at an advisory committee.

DATING PERIOD

The dating period for coagulation factor Xa (recombinant), inactivated-zhzo shall be 24 months from the date of manufacture when stored at +2°C to +8°C. The date of

manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at ::; (b) (4) . We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of coagulation factor Xa (recombinant), inactivated-zhzo to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on FORM FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of coagulation factor Xa (recombinant), inactivated-zhzo, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 136, dated May 2, 2018, and the draft carton and container labeling submitted under amendment 126, dated April 27, 2018.

Please provide your final content of labeling including the carton and container labels in Structured Product Labeling (SPL) format. All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125586 at the time of use (prior to marketing) and include implementation information on FORM FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

PROMOTIONAL MATERIALS

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for dissemination after the first 120 days following approval must be submitted to the FDA at least 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval, and an accompanying FORM FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by FORM FDA 2253 (21 CFR 601.12(f)(4)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry, *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event reporting System website http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

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 biological products 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 biological products 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, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey -S

Digitally signed by Mary A. Malarkey -S
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Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Wilson Bryan -S

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Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research