CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208383Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 22, 2017
Requesting Office or Division:	Division of Hematology Products
Application Type and Number:	NDA 208383
Product Name and Strength:	Bevyxxa (betrixaban) capsules, 40 mg and 80 mg
Applicant/Sponsor Name:	Portola Pharmaceuticals, Inc.
Submission Date:	June 20, 2017
OSE RCM #:	2016-2480-3
DMEPA Primary Reviewer:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Bevyxxa (betrixaban) capsules, 40 mg and 80 mg (Appendix A), to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a]

2 CONCLUSION

The revised container labels and carton labeling is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rimmel, S. Label and Labeling Review for BevyxXa (NDA 208383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 16. RCM No.: 2016-2480.
Rimmel, S. Label and Labeling Review for BevyxXa (NDA 208383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. RCM No.: 2016-2480-1.
Rimmel, S. Label and Labeling Review for Bevyxxa (NDA 208383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 15. RCM No.: 2016-2480-2.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SUSAN RIMMEL
06/22/2017

HINA S MEHTA
06/22/2017

PMR/PMC Development Template

NDA #	208383
Product:	Bevyxxa (betrixaban)

PMR 3229-1 Description:	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.
Schedule Milestones:	Final Protocol Submitted: 09/30/2016 Study Completion: 12/31/2019 Final Report Submission: 06/30/2020
PMR 3229-2 Description:	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.
Schedule Milestones:	Final Protocol Submission: 03/31/2018 Study Completion: 05/31/2020 Final Report Submission: 12/31/2020
PMR 3229-3 Description:	Conduct a randomized multi-center, active-controlled clinical trial comparing betrixaban to standard of care (in patient 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.
Schedule Milestones:	Final Protocol Submission: 03/31/2018 Trial Completion: 12/31/2022 Final Report Submission: 06/30/2023

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Pediatric sub-population

2. Describe the particular review issue and the goal of the study/clinical trial. If the study or clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Efficacy and safety in various pediatric age groups: 2 to < 6 years, 6 to < 12 years and 12 to < 18 years.

3. If the study or clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pediatric PK/PD, efficacy, and safety studies.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation):
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation):

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify):
☐ Other:

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study or clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized, controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

BARRY W MILLER
06/21/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 15, 2017
Requesting Office or Division:	Division of Hematology Products
Application Type and Number:	NDA 208383
Product Name and Strength:	BevyxXa (betrixaban) capsules, 40 mg and 80 mg
Applicant/Sponsor Name:	Portola Pharmaceuticals, Inc.
Submission Date:	June 13, 2017
OSE RCM #:	2016-2480-2
DMEPA Primary Reviewer:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for BevyxXa (betrixaban) capsules, 40 mg and 80 mg (Appendix A), to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a] Of note, the Applicant has revised the color scheme and graphics in the proposed updated labeling submission.

2 CONCLUSION

The revised container labels and carton labeling is unacceptable from a medication error perspective. The revised container labels and carton labeling can still be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion.

[a] Rimmel, S. Label and Labeling Review for BevyxXa (NDA 208383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 16. RCM No.: 2016-2480.
Rimmel, S. Label and Labeling Review for BevyxXa (NDA 208383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. RCM No.: 2016-2480-1.

3 RECOMMENDATIONS FOR PORTOLA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton and Container Labels

1. To minimize confusion and wrong strength selection errors, consider moving the strengths below the "Tradename (betrixaban) Capsules" statement. For example:

Tradename (betrixaban) Capsules 80 mg	or	Tradename (betrixaban) Capsules 80 mg

2. The color contrast of white text for the 40 mg strength against the proposed reddish-orange background may affect readability of the strength. To lessen the visual strain on the eyes, consider darkening the reddish-orange hue to increase readability. Alternatively, consider changing the font color of "40 mg" to your proposed reddish-orange background color, with a white background and outlining the strength with your proposed background color and shape. The latter approach will ensure the strength is not difficult to read.
3. Revise the (b) (4) font color of the "Tradename (betrixaban) Capsules" statement or revise the (b) (4) background of the 80 mg strength so that either the strength, or proprietary name and established name appears in its own unique color and does not overlap with any other colors utilized in highlighting the strengths. The use of the (b) (4) font color for the proprietary name, established name, and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.[b]

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[b] Draft Guidance: Container and Carton, April 2013 (lines 374-376).

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/s/

SUSAN RIMMEL
06/15/2017

HINA S MEHTA
06/15/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 12, 2017
Requesting Office or Division:	Division of Hematology Products
Application Type and Number:	NDA 208383
Product Name and Strength:	BevyxXa (betrixaban) capsules, 40 mg and 80 mg
Applicant/Sponsor Name:	Portola Pharmaceuticals, Inc.
Submission Date:	May 5, 2017
OSE RCM #:	2016-2480-1
DMEPA Primary Reviewer:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for BevyxXa (betrixaban) capsules, 40 mg and 80 mg (Appendix A), to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Of note, the Applicant has decided not to manufacture the (b) (4) Thus, only revised cartons and containers for the 100 count product was submitted.

2 CONCLUSION

The revised container labels and carton labeling is unacceptable from a medication error perspective. The revised container labels and carton labeling can still be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion.

[a] Rimmel, S. Label and Labeling Review for BevyxXa (NDA 208383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 16. RCM No.: 2016-2480.

3 RECOMMENDATIONS FOR PORTOLA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton and Container Labels

1. [redacted] (b) (4) is difficult to read due to differences in font size and may cause confusion. [redacted] (b) (4) In addition, increase the font size of the strength statement to minimize wrong strength selection errors.

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/s/

SUSAN RIMMEL
05/12/2017

HINA S MEHTA
05/15/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 04/13/17

To: Thomas Iype, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

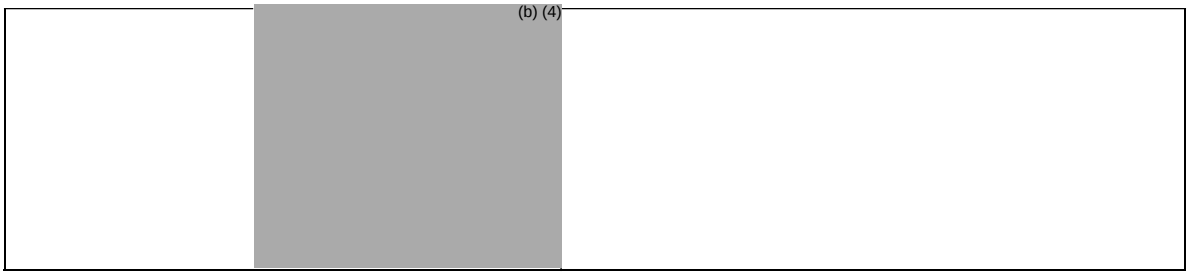
Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for [TRADENAME] (betrixaban) capsules, for oral use
NDA 208383

In response to your labeling consult request dated December 21, 2017, we have reviewed the draft Package Insert and draft Carton/Container labeling for [TRADENAME] (betrixaban) capsules, for oral use (betrixaban). The SCPI was originally emailed to OPDP on April 3, 2017; however we received an updated version of the labeling on April 11, 2017. This review is based upon the version of the draft PI emailed to OPDP on April 11, 2017 and the versions of the Carton/Container labeling accessed from GSR on April 14, 2017.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

Section	**Statement from Draft (if applicable)**	**OPDP Comment**
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	(b) (4) [redacted]	The criteria used to determine inclusion (e.g., frequency cutoff rate) should be included here in order to be consistent with the recommendation in the Guidance for Industry, *Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements*, dated February 2013.
(b) (4) [redacted]		OPDP recommends revising to change (b) (4) [redacted]



Carton/Container Labeling

OPDP acknowledges and concurs with the February 16, 2017, review of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

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/s/

RACHAEL E CONKLIN
04/13/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 13, 2017
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRADENAME (betrixaban)
Dosage Form and Route:	Capsules, for oral use
Application Type/Number:	NDA 208383
Applicant:	Portola Pharmaceuticals, Inc.

1 INTRODUCTION

On October 24, 2016, Portola Pharmaceuticals, Inc., submitted for the Agency's review a 505(b) New Drug Application (NDA) 208383 for TRADENAME (betrixaban) capsules. TRADENAME (betrixaban) is a Factor Xa (FXa) inhibitor with the proposed indication for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE. The Applicant seeks approval for 40mg and 80mg capsules.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on December 27, 2016 and December 21, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (betrixaban) capsules.

2 MATERIAL REVIEWED

- Draft TRADENAME (betrixaban) MG received on October 24,2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 3, 2017.
- Draft TRADENAME (betrixaban) Prescribing Information (PI) received on October 24, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 3, 2017.
- Approved ELIQUIS (apixaban) tablets comparator labeling dated July 20, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
04/13/2017

RACHAEL E CONKLIN
04/13/2017

LASHAWN M GRIFFITHS
04/13/2017

CLINICAL INSPECTION SUMMARY

Date	March 22, 2017
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Saleh Ayache, M.D., Medical Officer Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader Thomas Iype, Regulatory Project Manager Division of Hematology Products (DHP)
NDA	NDA 208383
Applicant	Portola Pharmaceuticals, Inc.
Drug	betrixaban capsules 40 mg and 80 mg
NME	Yes
Therapeutic Classification	Factor Xa Inhibitor
Proposed Indication	Extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE
Consultation Request Date	December 20, 2016 (signed)
Summary Goal Date	March 1, 2017 (Original); April 1, 2017 (Extension)
Action Goal Date	June 24, 2017
PDUFA Date	June 24, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical sites (Drs. Krievins, De Pellegrin, Valavicius, and Welker) were selected for inspection for Protocol 11-019 (APEX Study), a multicenter, randomized, double-blinded, double-dummy, parallel group, controlled clinical trial of 35 days of betrixaban vs. standard of care, short term (10 ± 4 days) of parenteral enoxaparin for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.

The final classification for the inspection for Dr. Welker's site is No Action Indicated (NAI). Inspections for two clinical sites (Drs. De Pellegrin and Valavicius) are preliminarily classified as (b) (5). The preliminary classification of Dr. Krievin's site is (b) (5)) with minor protocol deviations. Preliminary classifications are based on communications with the ORA investigator and Form FDA 483 (if issued). Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a

letter is issued to the inspected entity. A clinical inspection summary addendum will be provided if review of the inspection report(s) indicates significant change in the classification for the inspection.

The study data derived from these four clinical sites are considered reliable in support of the requested indication.

2. BACKGROUND

Betrixaban is an oral factor Xa (FXa) inhibitor. Activation of factor X to FXa via the intrinsic and extrinsic pathways plays an essential role in the cascade of blood coagulation. The sponsor proposed indication of betrixaban is for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.

Venous thromboembolism (VTE) in hospitalized acutely ill medical patients is a leading cause of in-hospital mortality. Currently, there is no approved or guideline-recommended anticoagulant for extended VTE prophylaxis post-hospital discharge following standard short-duration (up to 14 days) therapy due to excessive bleeding risk with extended prophylaxis found in several clinical trials with other products. The sponsor conducted a single large Phase 3 study (Protocol 11-01907/APEX Study) to evaluate the efficacy and safety of betrixaban orally administered for 35 days (+7 day window) as compared to standard of care short term (10 ± 4 days) parenteral enoxaparin for venous thromboembolic events prophylaxis in patients who are at high risk due to acute medical illness.

Protocol 11-019/APEX Study

Protocol Title: Multicenter, Randomized, Active-Controlled Efficacy and Safety Study Comparing Extended Duration Betrixaban with Standard of Care Enoxaparin for the Prevention of Venous Thromboembolism in Acute Medically Ill Patients

This was a multicenter, randomized, double-blinded, double-dummy, parallel group, controlled clinical trial of 35 days (+7 day window, i.e. 35-42 days allowed) of betrixaban vs. standard of care short term (10 ± 4 days) parenteral enoxaparin for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.

The primary objective was to demonstrate, in defined study cohorts, the superiority of extended duration anticoagulation with betrixaban as compared to the standard of care (10 ± 4 days) with enoxaparin for prophylaxis of VTE in patients who are at prolonged risk due to acute medical illness and additional risk factors.

The primary efficacy endpoint was a composite endpoint including the occurrence of any of the following events through Visit 3: asymptomatic proximal deep venous thrombosis (DVT, as detected by ultrasound), symptomatic DVT (proximal or distal), non-fatal pulmonary embolism (PE), or VTE-related death. Events that were components of the primary efficacy composite endpoint were adjudicated by a blinded independent Clinical Events Committee (CEC) or determined by a blinded ultrasound core laboratory (asymptomatic proximal DVT).

The study was to enroll patients who were identified to be at high risk of VTE following hospital admission, and for whom standard duration thromboprophylaxis was indicated based on baseline clinical and laboratory parameters. Eligibility criteria included patients who were admitted to the hospital with one of five diagnoses documented to be associated with excess risk of VTE: acutely decompensated heart failure, acute respiratory failure, acute infection, acute rheumatic disease, and acute ischemic stroke. They also were required to meet criteria in addition to their admitting medical diagnosis that placed them at high prolonged risk of VTE. These criteria included the expectation to be severely immobilized for 24 hours and either moderately or severely immobilized for at least 4 days prior or during their hospitalization, age ≥ 75, D-dimer ≥ 2 x ULN at baseline, prior history of VTE or cancer and other additional VTE risk factors. The exclusion criteria included a history of clinically significant bleeding (including intracranial hemorrhage (ICH), gastrointestinal, pulmonary, or genitourinary bleeding), anticipated major surgery, current intake of dual antiplatelet therapy, and screening hemoglobin below 9.5 g/dL.

Patients meeting the inclusion and none of the exclusion criteria at screening were randomized 1:1 to either the betrixaban or enoxaparin treatment group. To maintain the blind, patients who were randomly assigned to the betrixaban group received betrixaban capsules for 35 to 42 days and daily subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days, and patients who were randomly assigned to the enoxaparin group received daily SQ injections of enoxaparin for 10 ± 4 days and betrixaban placebo capsules for 35 to 42 days. Patients were followed on the day of discharge or Day 14, Day 35 (+ 7 day window), and 30 days after Day 35 visit.

The study screened 477 sites and randomized 7,513 patients (3,759 betrixaban; 3,754 enoxaparin) from 460 sites in the following regions: North America (U.S. and Canada), Europe (Eastern Europe and Western Europe, including Australia, Israel, South Africa), Latin America, and Asia Pacific. The study enrolled the first patient on March 29, 2012, and the last patient completed on January 15, 2016.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Krievins, Dainis Pauls Stradins Clinical University Hospital, Pilsonu Street 13, Riga, LV-1002, Latvia	Site #44 Protocol 11-019 Subjects=229	(b) (5)	Pending: Interim classification (b) (5)
De Pellegrin, Annamaria Presidio Ospedaliero di Vittorio Veneto Via Forlanini, 71 31029 Vittorio, Veneto (TV), Italy	Site #93 Protocol 11-019 Subjects=103	(b) (5)	Pending: Interim classification (b) (5)
Valavicius, Arvydas Klaipeda University Hospital Department of Internal Diseases	Site #104 Protocol 11-019 Subjects=65	(b) (5)	Pending: Interim classification

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Liepojos str. 41 LT-92288 Klaipeda, Lithuania			(b) (5)
Welker, Jim Anne Arundel Health System 2001 Medical Parkway, Suite 203 Annapolis, MD 21401	Site #260 Protocol 11-019 Subjects=44	November 28 to December 6, 2016	NAI

Key to Compliance Classifications
NAI (No Action Indicated) = No deviation from regulations.
VAI (Voluntary Action Indicated) = Deviation(s) from regulations.
OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. Dainis Krievins, M.D. (Site #44, Latvia)

The site screened 247 subjects and enrolled 229 subjects for Study Protocol 11-019. An audit of 59 enrolled subjects' records was conducted. Among the 229 enrolled subjects, 214 subjects completed the study, and 15 subjects discontinued from the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, electronic files, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted.

However, the following observations were noted with a Form FDA 483 issued by the field investigator:

(b) (5)

The above observations were shared with DHP. These protocol deviations are considered to be minor and unlikely to have significant impact on the overall study results.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Annamaria De Pellegrin, M.D. (Site #93, Italy)

The site screened 106 subjects and enrolled 103 subjects for Study Protocol 11-019. An audit of 36 of 103 enrolled subjects' records was conducted. Among the 103 enrolled subjects, 101 subjects completed the study and 2 subjects discontinued from the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events were noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Arvydas Valavicius, M.D. (Site #104, Lithuania)

The site screened 71 subjects and enrolled 65 subjects for Study Protocol 11-019. An audit of 20 of 65 enrolled subjects' records was conducted. All enrolled 65 subjects completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified

against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No underreporting of serious adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Jim Welker, M.D. (Site #260, Annapolis, MD)

The site screened 48 subjects and enrolled 44 subjects for Study Protocol 11-019. An audit of 44 enrolled subjects' records was conducted. Among the 44 subjects, 37 subjects completed the study, and 7 subjects discontinued from the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No underreporting of non-serious or serious adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., Team Leader for
Kassa Ayalew, M.D.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
Review Division /Division Director/Anne Farrell
Review Division /Medical Team Leader/Kathy Robie-Suh
Review Division/Medical Officer/ Saleh Ayache
Review Division /Project Manager/ Thomas Iype
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan Thompson
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP Reviewer/Min Lu
OSI/ GCP Program Analyst/Yolanda Patague

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/s/

MIN LU
03/23/2017

JANICE K POHLMAN
03/23/2017

SUSAN D THOMPSON
03/23/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 16, 2017
Requesting Office or Division:	Division of Hematology Products
Application Type and Number:	NDA 208383
Product Name and Strength:	BevyxXa (betrixaban) Capsules 40 mg 80 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Portola Pharmaceuticals, Inc.
Submission Date:	October 24, 2016 and January 9, 2017
OSE RCM #:	2016-2480
DMEPA Primary Reviewer:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) consulted DMEPA to evaluate the proposed labels and labeling submitted for the new molecular entity (NME), BevyxXa, under NDA 208383. As part of the approval process for BevyxXa, we reviewed the proposed label and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Portola Pharmaceuticals submitted a 505(b)(1) NDA to obtain marketing approval of BevyxXa (betrixaban) capsules. We performed a risk assessment of the container labels, carton labeling, Medication Guide, and Prescribing Information to identify deficiencies that may lead to medication errors and other areas of improvement. We identified several areas of the proposed labeling that could be improved to promote the safe use of the product.

For the Division, we identified the abbreviation "P-gp" (P-glycoprotein) throughout the PRESCRIBING INFORMATION (PI) that was not clearly defined, which makes it vulnerable to confusion and misinterpretation. In addition, we noted the following changes to the PI and Medication Guide that will clarify information with regard to use of the product: strengthening attention to the P-gp inhibitor drug interactions (b) (4) modifying the (b) (4) statement, adding the route of administration, and including the duration of treatment statement. Further, we identified that the National Drug Code (NDC) number is designated with a placeholder, thereby limiting our ability to evaluate

this important safety feature, and that the [redacted] statement is not specified in the HOW SUPPLIED/STORAGE AND HANDLING.

For the Applicant, we identified areas of the proposed container and carton labeling that were vulnerable to medication errors. We noted the difficulty in reading the 80 mg strength due to the color contrast of [redacted]. In addition, we recommended the Applicant submit the proposed NDC numbers for each strength so that we can provide an adequate safety assessment of the assigned numbers. Finally, we suggested the following enhancements or changes to mitigate any confusion: including the net quantity where applicable, repositioning the net quantity statements [redacted], specifying a space for lot number and expiration date on the carton labeling, clarifying the meaning of "XXXXXX" on the labeling, and repositioning the [redacted] placeholder.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information (HPI)

1. The abbreviation "P-gp" appears throughout the HPI. Mistakes can result from the use of abbreviations, symbols, and dose designations whose meaning is non-standardized and/or unfamiliar to the healthcare professional or other target reader.[a] We recommend defining P-gp (e.g., P-glycoprotein [P-gp]) the first time it is presented in the HPI. Thereafter, we agree the abbreviation can be used throughout the HPI.
2. DOSAGE AND ADMINISTRATION Section
    a. The second bullet lacks the attention needed to draw the reader to the P-gp inhibitor drug interactions, which have important implications for the dosing regimen. In addition, the duration of treatment and route of administration is not included, and the placement of [redacted] statement could be misinterpreted. For clarity, we recommend the Division consider revising this section as follows:
    - The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily. (2.1)
    - [redacted] P-glycoprotein (P-gp) inhibitors, [redacted]
    - [redacted]. The recommended duration of treatment is 35 to 42 days. (2.1)
3. WARNINGS AND PRECAUTIONS Section

[a] Draft Guidance: Container and Carton, April 2013 (lines 240-242).

a. We recommend [redacted] We believe this important information is relevant to practitioners at the prescribing, dosing, and dispensing phases, and should be included in that section.

B. Full Prescribing Information (FPI)
   1. The abbreviation "P-gp" appears throughout the FPI. Mistakes can result from the use of abbreviations, symbols, and dose designations whose meaning is non-standardized and/or unfamiliar to the healthcare professional or other target reader.[b] We recommend defining P-gp (e.g., P-glycoprotein [P-gp]) the first time it is presented in the FPI. Thereafter, we agree the abbreviation can be used throughout the FPI.

C. Full Prescribing Information: Section 2 DOSAGE AND ADMINISTRATION, 2.1 Recommended Dose
   1. The route of administration is not clearly stated. We recommend adding the route of administration to this section[c] and rephrasing the sentence "Daily doses should be given at the same time of day with food." as follows:
      - All doses should be taken by mouth, at the same time each day with food.

D. Full Prescribing Information: Section 5 WARNINGS AND PRECAUTIONS, [redacted]
   1. [redacted] We believe this information is relevant to practitioners at the prescribing, dosing, and dispensing phases, and should be included in that section.

E. Full Prescribing Information: Section 16 HOW SUPPLIED/STORAGE AND HANDLING, How Supplied
   1. As currently presented, the NDC number is designated with a placeholder (i.e., 69853-XXXX-X). Please confirm this information is updated when supplied by the Applicant.
   2. The listings for both strengths of the 100 count bottle [redacted] do not specify [redacted] We recommend the Applicant add [redacted] to this section for added clarity and consistency in product presentation.

F. Full Prescribing Information: Section 17 PATIENT COUNSELING INFORMATION
   1. This section does not specify to take the medication with food or describe the warning regarding co-administration with P-gp inhibitors. We recommend the Applicant include that information in this section.

[b] Draft Guidance: Container and Carton, April 2013 (lines 240-242).

[c] Guidance: Dosage and Administration Section, March 2010 (page 2).

G. Medication Guide

1. There is no statement regarding co-administration with P-gp inhibitors. We recommend adding this information to the Medication Guide or instruct the reader that certain medications may require a dose adjustment and to inform their doctor or pharmacist of all concurrent medications to determine if a different dosing regimen is needed.

4.2 RECOMMENDATIONS FOR PORTOLA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The color contrast—(b) (4)—for the 80 mg strength strains the eyes and is difficult to read. Consider enlarging the font size of "80 mg" or change the color of the background to increase its prominence, provide ease ability of reading, and adequate differentiation between the strengths in accordance with 21 CFR 201.15(a)(6).
2. As currently presented, the NDC number is designated with a placeholder (i.e., 69853-XXXX-X). Since the NDC number is often used as an additional verification tool in product selection and drug dispensing, it is an important safety feature. The use of a placeholder limits our ability to evaluate the NDC number for vulnerability that could lead to medication errors. When selecting the product code for NDC numbers of drug products with multiple strengths, FDA recommends avoiding assigning product codes that are numerically similar or identical. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug.[d] Please ensure the NDC number is in accordance with 21 CFR 207.35(b)(3)(i) and is differentiated among the strengths and container sizes to minimize the potential risk for medication errors. We also recommend the Applicant submit the proposed NDC numbers for each strength so that we can provide an adequate safety assessment of the assigned numbers.
3. (b) (4). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in (b) (4). Relocate (b) (4) such as to the bottom of the principal display panel.
4. Please clarify the intended meaning of "XXXXXX" that appears on all labeling and ensure it does not compete with the NDC number, lot number, or expiration date.

B. Carton Labeling

1. See 4.2, A.1.
2. See 4.2, A.2.

[d] Draft Guidance: Container and Carton, April 2013 (lines 521-525).

3. See 4.2, A.3.
4. See 4.2, A.4.
5. As currently presented, the carton labeling does not specify a space for lot number and expiration date. These elements are required on the carton labeling when there is sufficient space. Please display the lot number and expiration date in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively.

C.

(b) (4)

D.

[redacted]

[e] Draft Guidance: Container and Carton, April 2013 (lines 784-786).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for BevyxXa that Portola Pharmaceuticals, Inc. submitted on October 24, 2016.

Table 2. Relevant Product Information for BevyxXa	
Initial Approval Date	N/A
Active Ingredient	Betrixaban
Indication	Extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE
Route of Administration	Oral
Dosage Form	Capsule
Strength	40 mg and 80 mg
Dose and Frequency	An initial single dose of 160 mg, followed by 80 mg once daily at the same time of day with food. The recommended duration of treatment is 35 to 42 days. (b) (4)
How Supplied	For each strength: • (b) (4) • 100 count bottle (b) (4) • (b) (4)
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F)
Container Closure	For bottles: (b) (4) 100 capsules are packaged in a white, high density polyethylene (HDPE) round bottle. (b) (4)

	• (b) (4) bottle for 100-capsule count of 40 mg strength • (b) (4) bottle for 100-capsule count of 80 mg strength Each bottle is closed with a suitably- sized white, (b) (4) screw cap with an (b) (4) aluminum-faced liner. One bottle and one package insert are placed in a paperboard carton. (b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUSAN RIMMEL
02/16/2017

HINA S MEHTA
02/16/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208383

Application Type: New NDA

Drug Name(s)/Dosage Form(s): BevyxXa® (betrixaban) capsule

Applicant: Portola Pharmaceuticals, Inc.

Receipt Date: October 24, 2016

Goal Date: June 24, 2017

1. Regulatory History and Applicant's Main Proposals

NDA 208383 BevyxXa (betrixaban) capsule, 40 mg and 80 mg, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA). BevyxXa is a new molecular entity being reviewed under the Prescription Drug User Fee Act V "the Program."

On October 2, 2015, betrixaban was granted fast track for extended venous thromboembolism prophylaxis in the acutely ill medical patient population. This application will be reviewed under priority review. BevyxXa is a factor Xa inhibitor proposed for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the filing review issues identified letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 11, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *Recent Major Changes heading should be deleted.*

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *The white space between the HL Heading and HL Limitation Statement and between product title and Initial U.S. Approval should be deleted.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *Recent Major Changes heading should be deleted.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.
Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.
Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.
Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.
Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

NO 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment: The verbatim statement "***See full prescribing information for complete boxed warning.***" should be added immediately beneath the BW title.

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]."*

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Replace* [redacted] (b) (4) with "Advise the patient to read the FDA-approved patient labeling (Medication Guide)."

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

THOMAS N IYPE
12/23/2016

PATRICIA N GARVEY
01/06/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 208383
BLA#</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: BevyxXa
Established/Proper Name: betrixaban
Dosage Form: Capsule
Strengths: 40 mg, 80 mg</td></tr>
<tr><td colspan="3">Applicant: Portola Pharmaceuticals, Inc.
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: 10/23/2016
Date of Receipt: 10/24/2016
Date clock started after Unacceptable for Filing (UN): N/A</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: 6/24/2017</td><td>Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: 12/23/2016</td><td>Date of Filing Meeting: 11/30/2016</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☒ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch
☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): BEVYXXA is a factor Xa (FXa) inhibitor indicated for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 072679	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐	

If yes, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.*
Forms *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the***	☒	☐		

supporting document category, "Form 3674." ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	A consult form is not completed because for an NME - OSE is engaged in the review process
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	A consult form is not completed because for an NME - OSE/ONDP is engaged in the review process.
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL)			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

	☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	OSI; DMPP
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 10/25/2011	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 5/11/2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/30/2016

BACKGROUND: NDA 208383 BevyxXa (betrixaban) capsule, 40 mg and 80 mg, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA). BevyxXa is a new molecular entity being reviewed under the Prescription Drug User Fee Act V "the Program."

On October 2, 2015, betrixaban was granted fast track for extended venous thromboembolism prophylaxis in the acutely ill medical patient population. This application will be reviewed under priority review. BevyxXa is a factor Xa inhibitor proposed for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Thomas Iype	Y
	CPMS/TL:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	Kathy M. Robie Suh		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Saleh Ayache	Y
	TL:	Kathy M. Robie Suh	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Lars Johannesen	Y
	TL:	Sudharhsan Hariharan	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Jeffry Florian	Y

Biostatistics	Reviewer:	Xin Gao	Y
	TL:	Yuan Li Shen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shwu-Luan Lee	
	TL:	Christopher Sheth	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Anamitro Banerjee	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Sithamali Chandramouli	
• Drug Product	Reviewer:	Olen Stephens	
• Process	Reviewer:	Diane Goll	
• Microbiology	Reviewer:		
• Facility	Reviewer:	Laura Fontan	
• Biopharmaceutics	Reviewer:	Gerlie Gieser	
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: TBD ☐ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	All items included in the initial submission.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 1/19/2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

THOMAS N IYPE
12/21/2016

PATRICIA N GARVEY
12/22/2016