CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208383Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208383 SUPPL # HFD # 161

Trade Name Bevyxxa

Generic Name Betrixaban

Applicant Name Portola Pharmaceuticals

Approval Date, If Known 06/23/2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Thomas Iype, PharmD
Title: Regulatory Project Manager, Division of Hematology Products (DHP)
Date: 04/21/2017

Name of Division Director signing form: Albert Deisseroth, MD, PhD for Ann T. Farrell, MD
Title: Director, DHP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

THOMAS IYPE
06/23/2017

ALBERT B DEISSEROTH
06/23/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208383 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Bevyxxa Established/Proper Name: betrixaban Dosage Form: capsule		Applicant: Portola Pharmaceuticals Inc. Agent for Applicant (if applicable):
RPM: Thomas Iype, PharmD		Division: Division of Hematology Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 24, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics [3]

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other – Burst to ASH
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval; 06/23/2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included (enclosed with approval letter)
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included (enclosed with approval letter)
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptable letter: 06/14/2017 Unacceptable letter: 02/17/2017 Reviews: 06/13/2017; 02/16/2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 01/06/2017 DMEPA: 06/22/2017; 06/15/2017; 05/15/2017; 02/16/2017 DMPP/PLT (DRISK): 04/13/2017 OPDP: 04/13/2017 SEALD: ☒ None CSS: ☒ None Product Quality: 03/13/2017 Other: ☒ None

Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	12/22/2016 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 06/14/2017 If PeRC review not necessary, explain: _____	PeRC PREA Template: 5/09/2017
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	06/16/2017; 06/09/2017 (2); 05/15/2017; 04/14/2017; 04/13/2017; 03/31/2017; 03/03/2017; 02/28/2017 (2); 02/17/2017; 01/26/2017 (2); 12/27/2016; 12/23/2016; 12/22/2016; 12/20/2016 (3); 12/16/2016 (2); 12/02/2016 (2); 11/29/2016; 11/08/2016; 11/03/2016; 10/28/2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	CMC Telecon: 03/10/2017

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	05/11/2016
• EOP2 meeting *(indicate date of mtg)*	10/25/2011; 06/27/2007
• Mid-cycle Communication *(indicate date of mtg)*	02/07/2017
• Late-cycle Meeting *(indicate date of mtg)*	04/28/2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	Pre-NDA - WRO (CMC) - 04/29/2016
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	Co-signed 06/23/2017
Division Director Summary Review *(indicate date for each review)*	Review: 06/23/2017
Cross-Discipline Team Leader Review *(indicate date for each review)*	Review: 06/22/2017
PMR/PMC Development Templates *(indicate total number)*	Template: 06/21/2017
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 03/29/2017 review
• Clinical review(s) *(indicate date for each review)*	03/29/2017 combined review with statistical
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	pg. 19 of Clinical/Statistical Review - 03/29/2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	03/23/2017
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Letter: 05/05/2017 Review: 03/23/2017

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 03/29/2017 review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 03/29/2017 review
Statistical Review(s) *(indicate date for each review)*	03/29/2017 – Combined with the clinical review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review Addendum – 06/16/2017; Co-signed 04/03/2017 review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Addendum – 06/16/2017; Co-signed 04/03/2017 review
Clinical Pharmacology review(s) *(indicate date for each review)*	Addendum -06/16/2017; 04/03/2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	03/27/2017
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	04/07/2017; 03/23/2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	Integrated Quality Assessment 05/19/2017 Executive Summary: 05/11/2017 Drug Substance: 03/15/2017 Drug Product: 03/13/2017 Labeling: 03/13/2017 Process: 03/08/2017 Assessment of Facilities: 4/6/2017 Biopharmaceutics: 03/09/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	Method Verification: 03/20/2017
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Pg. 4 of Integrate Quality Assessment – Executive Summary
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

THOMAS IYPE
06/26/2017

From:	Iype, Thomas
To:	jdombroski@portola.com
Cc:	Janice Castillo
Subject:	NDA 208383 (betrixaban) – Labeling Response to Applicant – 06/22/2017
Date:	Thursday, June 22, 2017 10:54:00 AM
Attachments:	NDA 208383 - Medication Guide - 06-20-2017 FDA"s Response to Applicant on 06-22-2017.doc NDA 208383 - Prescribing Information - 06-20-2017 FDA"s Response to Applicant on 06-22-2017.docx

Dear Dr. Dombroski,

NDA 208383 (betrixaban) – Labeling Response to Applicant – 06/22/2017

With reference to **NDA 208383** for **betrixaban**, FDA's current edits/comments on the labeling (**USPI** and **Med Guide**) are attached.

Please review and provide revisions and comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes and a different color from that used by FDA). If necessary, edit but **do not** "reject" the FDA-proposed changes.
- When inputting comments, please use the following format "To FDA: …..".

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Kindly acknowledge receipt and please provide a response as soon as possible, but no later than 3 pm (ET) on June 22, 2017.

Regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3209
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us via email response to the sender or at the telephone number listed above.

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

/s/

THOMAS IYPE
06/22/2017

From: Iype, Thomas
To: "Jacqueline Dombroski"
Cc: Janice Castillo; Manitp sitkul, Wana
Subject: NDA 208383 (betrixaban) – PMR/Labeling Response to Applicant – 06/16/2017
Date: Friday, June 16, 2017 2:12:00 PM
Attachments: Bottle carton 40 mg 100 count 06-13-2017.pdf
Bottle carton 80 mg 100 count 06-13-2017 FDA"s Response to Applicant on 06-16-2017.pdf
Bottle label 40 mg 100 count 06-13-2017 FDA"s Response to Applicant on 06-16-2017.pdf
Bottle label 80 mg 100 count 06-13-2017 FDA"s Response to Applicant on 06-16-2017.pdf
NDA 208383 - Medication Gu de - 06-13-2017 FDA"s Response to Applicant on 06-16-2017.doc
NDA 208383 (betrixaban) - PREA PMR.doc
NDA 208383 - Prescribing Informat on - 06-13-2017 FDA"s Response to Applicant on 06-16-2017.docx

---

Dear Dr Dombroski,

NDA 208383 (betrixaban) – PMR/Labeling Response to Applicant – 06/16/2017

With reference to **NDA 208383** for **Betrixaban**, FDA s current edits/comments on the labeling (**USPI**, **Med Guide, and Carton Container labels**) are attached

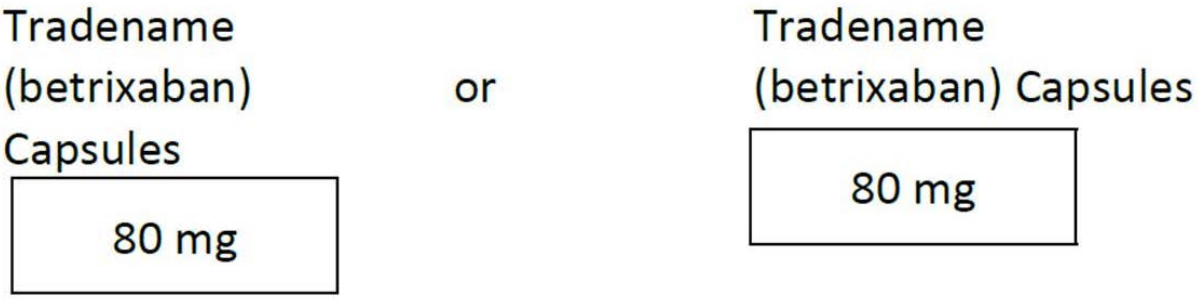
Please review and provide revisions and comments to the attached FDA proposed labeling Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes and a different color from that used by FDA) If necessary, edit but **do not** "reject" the FDA-proposed changes
- When inputting comments, please use the following format "To FDA: … "

In addition to content, we often make significant revisions to the format in our review of patient labeling Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes Please accept all formatting changes Using our attached document will ensure specifically that the formatting changes are preserved Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing)

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:



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

Lastly, we are also providing you with proposed post marketing studies Please review the attached FDA proposed PMRs and provide your response using Track Changes Upon mutual agreement, we ask you to submit both by email and officially to the NDA, a copy of the PMR studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial

Kindly acknowledge receipt Please provide a response to the labeling via email and an amendment to the NDA *by 12 pm (ET) on June 19, 2017.*

Regards,
Thomas Iype, Pharm D
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3209
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas iype@fda hhs gov

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/s/

THOMAS IYPE
06/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Portola Pharmaceuticals, Inc.
270 East Grand Avenue
South San Francisco, CA 94080

ATTENTION: Janice Castillo
Senior Vice President, Regulatory Affairs

Dear Ms. Castillo:

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

We also refer to:

- your correspondence, dated and received April 6, 2017, requesting review of your proposed proprietary name, Bevyxxa
- and your amendment, dated and received May 8, 2017, to your request for name review

We have completed our review of the proposed proprietary name, Bevyxxa and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitpisitkul, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Thomas Iype, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
06/14/2017

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	Manitpisitkul, Wana; Janice Castillo
Subject:	NDA 208383 (betrixaban) – Labeling Response to Applicant – 06/09/2017 - Acknowledgement of Receipt
Date:	Friday, June 09, 2017 4:44:00 PM
Attachments:	NDA 208383 - Prescribing Information - 05-05-2017 - FDA"s Response to Applicant on 06.09.2017.docx 300027rev05-btx-40mg-100ct-bottle-label-us.pdf 300029rev08-btx-80mg-100ct-bottle-label-us.pdf 300031rev05-btx-40mg-100ct-bottle-carton-us.pdf 300033rev07-btx-80mg-100ct-bottle-carton.pdf NDA 208383 - Medication Guide - 04-04-2017 - FDA"s Response to Applicant on 06.09.2017.doc
Sensitivity:	Confidential

Dear Dr. Dombroski,

NDA 208383 (betrixaban) – Labeling Response to Applicant – 06/09/2017

Please note that we have deleted some comments from the prescribing information.

With reference to **NDA 208383** for **Betrixaban**, FDA's current edits/comments on the labeling (**USPI**, **Med Guide, and Carton Container labels**) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

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- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes and a different color from that used by FDA). If necessary, edit but **do not** "reject" the FDA-proposed changes.
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Lastly, we recommend the following be implemented prior to approval of this NDA:

Carton and Container Labels

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

Please update your labeling and submit your revised labeling response to me via email and an amendment to the NDA by **12pm ET on Tuesday, June 13, 2017.**

Kindly acknowledge receipt.

Regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3209
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS IYPE
06/09/2017

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	Manitpisitkul, Wana; Janice Castillo
Subject:	NDA 208383 (betrixaban) – Labeling Response to Applicant – 06/09/2017
Date:	Friday, June 09, 2017 10:46:00 AM
Attachments:	300027rev05-btx-40mg-100ct-bottle-label-us.pdf 300029rev08-btx-80mg-100ct-bottle-label-us.pdf 300031rev05-btx-40mg-100ct-bottle-carton-us.pdf 300033rev07-btx-80mg-100ct-bottle-carton.pdf NDA 208383 - Prescribing Information - 05-05-2017 - FDA"s Response to Applicant on 06.09.2017.docx NDA 208383 - Medication Guide - 04-04-2017 - FDA"s Response to Applicant on 06.09.2017.doc

Dear Dr. Dombroski,

NDA 208383 (betrixaban) – Labeling Response to Applicant – 06/09/2017

With reference to **NDA 208383** for **Betrixaban**, FDA's current edits/comments on the labeling (**USPI**, **Med Guide, and Carton Container labels**) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

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- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes and a different color from that used by FDA). If necessary, edit but **do not** "reject" the FDA-proposed changes.
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- (b) (4) is difficult to read due to differences in font size and may cause confusion. (b) (4) In addition, increase the font size of the strength statement to minimize wrong strength selection errors.

Please update your labeling and submit your revised labeling response to me via email and an amendment to the NDA by **12pm ET on Tuesday, June 13, 2017.**

Kindly acknowledge receipt.

Regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3209
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS IYPE
06/09/2017

From: LucciVaughn, Ashley
To: "Jacqueline Dombroski"
Cc: Janice Castillo; Iype, Thomas; Carioti, Theresa
Subject: RE: NDA 208383 Betrixaban Capsules - Follow-up on the Telephone Call on Friday 05/12/17
Date: Monday, May 15, 2017 2:23:00 PM
Sensitivity: Confidential

Good Afternoon Dr. Dombroski,

In reference to your request for a teleconference with our Clinical Pharmacology reviewers, regarding NDA 208383 for betrixaban capsules, submit your clarification questions to me via email (cc: Dr. Iype). Upon receipt I will distribute your information request to our review team for further clarification and promptly follow-up upon their response .

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

From: Jacqueline Dombroski [mailto:jdombroski@Portola.com]
Sent: Monday, May 15, 2017 12:34 PM
To: LucciVaughn, Ashley
Cc: Janice Castillo; Iype, Thomas
Subject: FW: NDA 208383 Betrixaban Capsules - Follow-up on the Telephone Call on Friday 05/12/17
Importance: High
Sensitivity: Confidential

15 May 2017
NDA 208383 Betrixaban Capsules
Follow-up on the Telephone Call on Friday 05/12/17

Dear Ms LucciVaughn:
I am forwarding a message that I have just sent to Dr. Iype because I received an Out of Office response that gave your name as a contact. Portola is requesting a clarification telephone call as soon as possible with the Clinical Pharmacology reviewers who are reviewing NDA 208383 for betrixaban capsules. I am wondering if you can assist with this request, please?

Kind regards,
Jacqui

Jacqueline A. Dombroski, PhD
Senior Director Regulatory Affairs,
Portola Pharmaceuticals,
270 East Grand Avenue,
South San Francisco,
California 94080, USA

Direct: +1 (650) 246-7379
Mobile (b) (6)
Fax: +1 (650) 246-7768
Email: jdombroski@portola.com

From: Jacqueline Dombroski
Sent: Monday, May 15, 2017 9:29 AM
To: Iype, Thomas (Thomas.Iype@fda.hhs.gov)
Cc: Janice Castillo
Subject: NDA 208383 Betrixaban Capsules - Follow-up on the Telephone Call on Friday 05/12/17
Importance: High
Sensitivity: Confidential

15 May 2017
NDA 208383 Betrixaban Capsules
Follow-up on the Telephone Call on Friday 05/12/17

Dear Dr. Iype:
I am following up on the voice message that I left for you this morning.

I have had a discussion with the Portola team members this morning regarding the brief feedback from the Clinical Pharmacology reviewers about concomitant use of betrixaban and P-gp inhibitors that you provided on Friday during our telephone conversation. Portola wishes to request a telephone conversation as soon as possible with the Clinical Pharmacology reviewers to obtain further clarification about the data that the reviewers are looking for to support the USPI. Portola is wondering whether we misunderstood the feedback and request for information provided during the discussion at the Late Cycle Communication Meeting. Therefore, we would appreciate the opportunity to clarify the data of interest so that we can provided it in the responses due on Thursday, 18 May 2017, by close of business Pacific time.

Thank you for your assistance.
Kind regards,
Jacqui

Jacqueline A. Dombroski, PhD
Senior Director Regulatory Affairs,
Portola Pharmaceuticals,
270 East Grand Avenue,
South San Francisco,
California 94080, USA

Direct: +1 (650) 246-7379
Mobile: (b) (6)
Fax: +1 (650) 246-7768
Email: jdombroski@portola.com

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/s/

ASHLEY S LUCCI VAUGHN
05/15/2017

For CDER NDA/BLA reviews only: We are requesting that Division RPMs upload the PeRC PREA Template as a Memo To File into DARRTS in advance of your scheduled PeRC meeting.

Note: The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. The final PeRC meeting minutes are linked to the NDA/BLA application in DARRTS.

Complete the section(s) of this template that are relevant to your current review. Sections that are not applicable can be deleted.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Definitions:

Deferral *– A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.*

Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.*

Pediatric Plan *– A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient- *21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page *– The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ **Full Waiver** ☒ **Partial Waiver** ☐ **Pediatric Assessment** ☒ **Deferral/Pediatric Plan**

BLA/NDA#: 208383

PRODUCT PROPRIETARY NAME: (Pending) **ESTABLISHED/GENERIC NAME: Betrixaban**

APPLICANT/SPONSOR: Portola Inc.

PREVIOUSLY APPROVED INDICATION/S:
(1) None _____
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
(1) for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.
(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: 10/24/2016

PDUFA GOAL DATE: 6/24/2017

SUPPLEMENT TYPE: NA

SUPPLEMENT NUMBER: NA

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐

Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan? Yes ☐ No ☒

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived. Birth to < 2 years

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

   ☒ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. Provide justification for Waiver: There is evidence suggesting that betrixaban may be ineffective or unsafe in preterm and term neonates, infants, and toddlers. Also, any necessary studies are impossible or highly impracticable because the numbers of patients in these age groups are small and the patients are geographically dispersed.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- acute bacterial exacerbations of chronic bronchitis (a complication of chronic obstructive pulmonary disease)
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- ankylosing spondylitis
- atherosclerotic cardiovascular disease
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - cholangiocarcinoma
  - endometrial
  - esophageal
  - fallopian tube
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - liposarcoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - peritoneal
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
  - chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- degenerative intervertebral disc disease
- diabetic peripheral neuropathy/macular edema
- diabetic foot infections
- diabetic retinopathy
- digestive disorders (gallstones)
- dry eye syndrome (keratoconjunctivitis sicca)
- dupuytren's disease and manifestations
- erectile dysfunction essential thrombocytosis
- giant cell arteritis
- gout
- heavy menstrual bleeding associated with uterine fibroids
- Huntington's chorea
- idiopathic pulmonary fibrosis
- infertility & reproductive technology
- juvenile psoriatic arthritis
- memory loss
- menopause and perimenopausal disorders
- mesothelioma
- microscopic polyangiitis
- myelodysplasia
- myelofibrosis & myeloproliferative disorders
- opioid induced constipation in chronic, non-cancer pain
- osteoarthritis
- overactive bladder
- Parkinson's disease
- paroxysmal nocturnal hemoglobinuria
- persistent facial erythema assoc. with rosacea in adult
- plasma cells and antibody production disorders
- polycythemia vera
- polymyalgia rheumatica (PMR)
- postmenopausal osteoporosis
- prevention of stroke and systemic embolic events in atrial fibrillation
- psoriatic arthritis
- reduction of thrombotic cardiovascular events in patients with coronary artery disease
- retinal vein occlusions stress
- urinary incontinence
- Sjogren's Syndrome
- temporary improvement in the appearance of caudal lines
- treatment of heavy uterine bleeding associated with uterine leiomyomata
- treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women
- treatment of incompetent great saphenous veins and varicosities
- type 2 diabetic mellitus with cardiovascular disease
- type 2 diabetic nephropathy
- vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

☒ ***Pediatric Record***

1. **Age groups included in the deferral request: 2 to < 6 years, 6- <12 years and 12 to < 18 years.**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:** the incidence of VTE in patients age < 2 years is rare and there is evidence suggesting that betrixaban may be ineffective or unsafe in preterm and term neonates, infants, and toddlers.

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval

4. **Provide projected date for the submission of the pediatric assessment (deferral date): June 2023**

5. **Did applicant provide certification of grounds for deferring assessments?** ☒ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☒ **Yes** ☐ **No**
   Proposed timeline appears reasonable.

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** ☒ **Yes** ☐ **No**

The sponsor submitted an initial Pediatric Study Plan (PSP) to DHP on 5/2/2016 (IND 072679). The Division provided comments and recommendations from DHP to the sponsor on 7/8/2016, 8/31/2016 and 9/16/2016. The sponsor submitted a revised PSP (Agreed-Upon Initial PSP) to DHP on 9/27/2016. On 10/20/2016 DHP issued a letter to the sponsor confirming DHP agreement to the submitted Agreed-Upon Initial PSP.

2. Does the division agree with the sponsor's plan? ☒ **Yes** ☐ **No**

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** ☒ **Yes** ☐ **No**
    a. **Protocol Submission: March 2018**
    b. **Study Completion: December 2022**
    c. **Study Submission: June 2023**

4. **Has a Written Request been issued?** ☐ **Yes** ☒ **No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted?** ☐ **Yes** ☒ **No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:
Clinical Study 1: Single Dose, Open Label Pediatric PK/PD Study in the Fed State. The study population will be children 2 years or older who have just completed a course of anticoagulation for venous thrombosis.

Clinical Study 2: VTE Prophylaxis in Immobilized Adolescents Hospitalized for Acute Medical or Surgical Disease. The designed as a single arm, open-label study of betrixaban with point estimates of events to be compared to historical controls. The objective of this study

to identify the safety and efficacy of betrixaban in pediatric population.

Clinical Study 3: (b) (4) **. A randomized multi-center, active-controlled clinical trial comparing betrixaban to standard of care (in patients with central venous catheter) or either enoxaparin or warfarin (in patients with secondary prevention indication) in prevention of VTE. Pediatric patients ≥ 2 years of age** (b) (4) **.**

Age group and population (indication) in which study will be performed:

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☒ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☒ **No**

Will a DSMB be required? ☒ **Yes** ☐ **No**

Other comments:

Division comments on product efficacy:

Based on reviews to date, the product appears efficacious in adults.

Division comments on sponsor proposal to satisfy PREA:

The Agreed PSP continues to appear acceptable.

PeRC ASSESSMENT TEMPLATE

N/A

Please attach:

☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***

☐ ***Pediatric Record***

Date of PREA PMR:

Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols.*

Number of Centers _____ **Number and Names of Countries _____**
Drug information: *Examples in italics* • **Route of administration**: *Oral* • ***Formulation:** • **Dosage:** • **Regimen:** **If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*
Types of Studies/ Study Design:
Age group and population in which study/ies was/were performed:
Number of patients studied or power of study achieved:
Entry criteria: This section should list pertinent inclusion/exclusion criteria. .
Clinical endpoints:

Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted.
Timing of assessments:
Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

THOMAS IYPE
05/09/2017

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	Janice Castillo
Subject:	208383 NDA (505B1) – Betrixaban – Information Request – 04/14/2017
Date:	Friday, April 14, 2017 12:27:00 PM

Dear Dr. Dombroski,

208383 NDA (505B1) – Betrixaban – Information Request – 04/14/2017

Please provide a summary table of the numbers of patients who experienced any event with a bleeding-related preferred term (e.g., epistaxis, hematoma, hematuria, etc) that were not considered major or CRNM in the APEX trial.

Kindly acknowledge receipt and provide a response via email and an amendment to the NDA by 12 noon (ET) on 04/17/2017.

Kind regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3209
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS IYPE
04/14/2017

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	Janice Castillo
Subject:	208383 NDA (505B1) – Betrixaban – Labeling Comments to Applicant – 03/31/2017
Date:	Friday, March 31, 2017 10:43:00 AM
Attachments:	MG-Received 10-24-2016 -- FDA"s Comment to Applicant 03-31-2017.docx PI - Received 01-09-2017 -- FDA"s Comments to the Applicant - 03-31-2017.docx

Dear Dr. Dombroski,

208383 NDA (505B1) – Betrixaban – Labeling Comments to Applicant – 03/31/2017

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes and a different color from that used by FDA). If necessary, edit but do not "reject" the FDA-proposed changes.
- When inputting comments, please use the following format "To FDA: …..".

Please update your labeling and submit your revised labeling response to me via email as soon as possible, but no later than 12 pm (ET) on April 3, 2017 followed by an official submission to the NDA.

We also 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. [redacted] (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 [redacted] (b) (4) [redacted] Relocate [redacted] (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 A.1.

2. See A.2.

3. See A.3.

4. See 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. [redacted] (b) (4)

D. [redacted]

Product Quality's Carton/Container Label Comments:

1. Provide salt equivalency statements on all HDPE bottle (b) (4). The statement should indicate that each capsule "contains XX mg betrixaban equivalent to YY mg betrixaban maleate.

Kind regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products

Center for Drug Evaluation and Research | Food and Drug Administration

10903 New Hampshire Avenue, WO22 - Room 3209

Silver Spring, MD 20993

Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

content of this communication is not authorized. If you have received this document in error, please immediately notify us via email response to the sender or at the telephone number listed above.

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

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/s/

THOMAS IYPE
03/31/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 10, 2017

Application Number: 208383
Product Name: BevyxXa™ (Betrixaban)
Sponsor/Applicant Name: Portola Pharmaceuticals, Inc.

Subject: Teleconference regarding Methods Verification

FDA Participants
Olen Stephens, Ph.D.
Rabiya Laiq, Pharm.D.

Sponsor/Applicant Participants

Portola Pharmaceuticals (for all topics)

Janice Castillo, Senior Vice President, Regulatory Affairs

Jacqueline Dombroski, PhD, Senior Director, Regulatory Affairs

Anu Garg, PhD, Senior Scientist II, Analytical Development, Analytical Chemistry

Kihlon Golden, Senior Manager QA, Pharmaceutical Development

Shoba Gopalan, PhD, Director Project Management-Betrixaban, Clinical Operations

Yvonne Kim, Director, Regulatory Affairs

Dan Lee, Senior Scientist I, Quality Control Pharmaceutical Development

Anjali Pandey, PhD, Senior Vice President Medicinal Chemistry and Chemical Development

Evan Susser, Senior Director, QA, Pharmaceutical Development

(b) (4)

1.0 BACKGROUND:

FDA is in the process of verifying the methods submitted for NDA 208383. Three issues were identified that require further interrogation and we would like to have a short discussion with the personnel responsible for the drug substance and drug product analytical method development. Specifically, FDA has the following observations:

1. Drug substance method CRIC2853 (b) (4) contains a formula on page 5 for (b) (4), but on page 6 there are more defined variables for this equation than present in the equation. FDA would like clarification on the accuracy of the equation and formula and requests an amendment to this section.

2. Drug product method CTMLP-2893 contains a formula for potency. Portola asked for clarification

Clarification of Point 2:

- Drug product method CTMLP-2893 contains a formula for potency which is incorrect. (b) (4)

3. During the verification for content uniformity, FDA obtained results that fail both level 1 and level 2 criteria for USP<905>. Batch data for all registration batches meet level 1 acceptance criteria as well as for most clinical and supportive batches. However, the calculated value for supportive batches A7001A, A7002A, A7005A, and A7006A is not provided. Provide the calculated content uniformity values for these supportive batches and comment on the quality of the material submitted to the FDA laboratories used for method verification regarding potential causes for the failure in their initial verification attempt.

2.0 DISCUSSION:

FDA thanked Portola for providing written responses to our information requests received March 9, 2016, SDN 27. FDA discussed question 2 with the Protola team to change the (b) (4) term (b) (4). Dr. Frank Cui on Portola's behalf accepted FDA's recommendation. FDA recommended that both changes to the methods verification should be submitted to the NDA as amendments and advised Portola that the methods verification process may not be completed prior to taking NDA action and our communication with Portola may continue post action.

3.0 ACTION ITEMS:

Portola to submit amendments to the NDA with above information.

1.11.1 QUALITY INFORMATION AMENDMENT

Response to Request for Telephone Conference *(03 March 2017)*

FDA Comments

Request for Telephone Conference (03 March 2017)

FDA would like to schedule a quick 30 minute teleconference next week with Portola. We specifically would like to speak with the team members involved in the 2 analytical methods: for the drug substance CRIC2853 (b) (4) *and for the drug product method CTMLP-2893 and anyone involved in batch data. We understand we are coming close to the end of the review clock and would like to quickly resolve a concern.*

Clarifications Received on 07 March 2017

FDA is in the process of verifying the methods submitted for NDA 208383. Three issues were identified that require further interrogation and we would like to have a short discussion with the personnel responsible for the drug substance and drug product analytical method development. Specifically, FDA has the following observations:

1. *Drug substance method CRIC2853* (b) (4) *contains a formula on page 5 for* (b) (4)*, but on page 6 there are more defined variables for this equation than present in the equation. FDA would like clarification on the accuracy of the equation and formula and requests an amendment to this section.*

2. *Drug product method CTMLP-2893 contains a formula for potency*

   Clarification of Point 2 received 07 March 2017:

   Drug product method CTMLP-2893 contains a formula for potency which is incorrect. (b) (4)

3. *During the verification for content uniformity, FDA obtained results that fail both level 1 and level 2 criteria for USP<905>. Batch data for all registration batches meet level 1 acceptance criteria as well as for most clinical and supportive batches. However, the calculated value for supportive batches A7001A, A7002A, A7005A, and A7006A is not provided. Provide the calculated content uniformity values for these supportive batches and comment on the quality of the material submitted to the FDA laboratories used for method verification regarding potential causes for the failure in their initial verification attempt.*

PORTOLA'S RESPONSES

Office of Product Quality's (OPQ)'s Request for Telephone Conference (03 March 2017)

FDA would like to schedule a quick 30 minute teleconference next week with Portola. We specifically would like to speak with the team members involved in the 2 analytical methods: for the drug substance CRIC2853 (b) (4) *and for the drug product method CTMLP-2893 and anyone involved in batch data. We understand we are coming close to the end of the review clock and would like to quickly resolve a concern.*

Portola's Response to the OPQ Request for Telephone Conference

In an electronic message responding to OPQ's clarifications received on 07 March 2017, Portola suggested that the telephone conference be set up for **Friday 10 March 2017 at 9:15 am PST/ 12:15 noon EST /** (b) (4) The OPQ agreed to this suggestion.

Tentative List of Participants

Portola Pharmaceuticals (for all topics)

Janice Castillo, Senior Vice President, Regulatory Affairs

Jacqueline Dombroski, PhD, Senior Director, Regulatory Affairs

Anu Garg, PhD, Senior Scientist II, Analytical Development, Analytical Chemistry

Kihlon Golden, Senior Manager QA, Pharmaceutical Development

Shoba Gopalan, PhD, Director Project Management-Betrixaban, Clinical Operations

Yvonne Kim, Director, Regulatory Affairs

Dan Lee, Senior Scientist I, Quality Control Pharmaceutical Development

Anjali Pandey, PhD, Senior Vice President Medicinal Chemistry and Chemical Development

Evan Susser, Senior Director, QA, Pharmaceutical Development

Portola will provide details of the dial-in information for the telephone conference by electronic mail before the meeting.

OPQ's Comment 1

Drug substance method CRIC2853 (b) (4) contains a formula on page 5 for (b) (4), but on page 6 there are more defined variables for this equation than present in the equation. FDA would like clarification on the accuracy of the equation and formula and requests an amendment to this section.

Portola's Response

An inconsistency in the equation (b) (4) in the sample and the respective table of calculation components was found in Analytical Method CRIC2853 Revision 02 that was submitted in NDA 208383. All components in the table are correct, however the equation, as presented, is incorrect. The equation should be corrected as follows:

(b) (4)

Revision 02 (approved on 29 July 2016) has the inaccurate equation; however, no batch analysis results have been issued with Analytical Method CRIC2853 Revision 02 and there is no impact on any batches of betrixaban drug substance. Analytical Method CRIC2853 Revision 00 and Revision 01 that had the correct equation and formula were used for all batch analyses at (b) (4) reported in NDA 208383. The typographical error in the formula was due to an inadvertent oversight both during the preparation and internal revision of the analytical method.

(b) (4) is following up by promptly correcting the error in Analytical Method CRIC2853 Revision 02 and Portola will submit the revised method to NDA 208383 (Analytical Method CRIC2853 Revision 03) as an NDA Quality Information Amendment. Portola (b) (4) existing Standard Operating Procedures, including Change Control Procedures will be followed, in accordance with current Good Manufacturing Practice requirements.

OPQ's Comment 2

Drug product method CTMLP-2893 contains a formula for potency

Clarification of Point 2 received 07 March 2017:

Drug product method CTMLP-2893 contains a formula for potency which is incorrect. The (b) (4)

Portola's Response

(b) (4)

OPQ's Comment 3

During the verification for content uniformity, FDA obtained results that fail both level 1 and level 2 criteria for USP<905>. Batch data for all registration batches meet level 1 acceptance criteria as well as for most clinical and supportive batches. However, the calculated value for supportive batches A7001A, A7002A, A7005A, and A7006A is not provided. Provide the calculated content uniformity values for these supportive batches and comment on the quality of the material submitted to the FDA laboratories used for method verification regarding potential causes for the failure in their initial verification attempt.

Portola's Response

Portola has divided the comment and response into three segments.

"During the verification for content uniformity, FDA obtained results that fail both level 1 and level 2 criteria for USP<905>. Batch data for all registration batches meet level 1 acceptance criteria as well as for most clinical and supportive batches."

Portola proposes a discussion of this unexpected result during the telephone conference. Reference may be made to Portola's experience with the method and the data obtained during testing, as needed.

"However, the calculated value for supportive batches A7001A, A7002A, A7005A, and A7006A is not provided. Provide the calculated content uniformity values for these supportive batches."

The calculated content uniformity values and the Acceptance Values for the supportive batches A7001A, A7002A, A7005A, and A7006A are provided in Table 1.11.1-1. The Acceptance value AV was calculated using unrounded values according to USP <905> and reported to one decimal place.

Table 1.11.1-1: Content Uniformity Acceptance Value Results for DP Lots A7001A, A7002A, A7005A, and A7006A

Content Uniformity	Acceptance Criteria	Lot Number			
		A7001A	A7002A	A7005A	A7006A
Uniformity of Dosage Units	Meets USP <905> requirements (L1 = 15.0, L2 = 25.0)	Conforms	Conforms	Conforms	Conforms
Acceptance Value (AV) [1]		(b) (4)			
Sample Number (n)					
Mean (X)					
Standard Deviation (s)					
Reference Value (M)					
Range					

[1] AV = (b) (4) calculated by Portola for information only

"and comment on the quality of the material submitted to the FDA laboratories used for method verification regarding potential causes for the failure in their initial verification attempt."

Portola proposes a discussion of this topic during the telephone conference. Reference may be made to Portola's experience with the method and the data obtained during testing, as needed.

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/s/

RABIYA LAIQ
03/10/2017

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (betrixaban) – Information Request – 03/03/2017
Date: Friday, March 03, 2017 1:53:00 PM

Dear Dr. Dombroski,

NDA 208383 (betrixaban) – Information Request – 03/03/2017

Please provide the following data regarding the four metabolites of betrixaban, i.e., N-desmethyl and O-desmethyl betrixaban (PRT054156 and PRT058326) and the two amide hydrolysis products (PRT062802 (M5) and PRT063069):

- *The pharmacodynamic evaluation of these metabolites, and if available the comparisons to the parent drug in terms of FXa inhibition (Ki or IC50 values);*

- *The levels of these metabolites in human plasma, or human exposures (i.e., Cmax and/or AUC values). Also provide metabolite-to-parent drug ratio (%) if data are available;*

- *Where the source information (i.e., the Study number) is located should be included in your response.*

Kindly acknowledge receipt of this communication. Please provide a response to below information request by COB on Friday 3/10/2017.

Regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products

Center for Drug Evaluation and Research | Food and Drug Administration

10903 New Hampshire Avenue, WO22 - Room 3209

Silver Spring, MD 20993

Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us via email response to the sender or at the telephone number listed above.

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/s/

THOMAS N IYPE
03/03/2017

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (betrixaban) – Information Request – 02/28/2017
Date: Tuesday, February 28, 2017 5:22:00 PM

Dear Dr. Dombroski,

NDA 208383 (betrixaban) – Information Request – 02/28/2017

The 120 day Safety Update and the most recent DSUR indicate that (b) (4) [redacted] Please verify the IND number. Provide the protocol for this study. Also, clarify how many subjects are planned for enrollment, date first subject was dosed, whether dosing of subjects has been completed in this study, when follow up will be complete, and when a final study report will be available. Please submit all safety data that have accrued for the study including narratives for any subjects who have died or discontinued study due to adverse events.

Kind regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3209
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
02/28/2017

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (betrixaban) - Deficiency Comment - 02/28/2017
Date: Tuesday, February 28, 2017 11:48:00 AM
Importance: High

Dear Dr. Dombroski,

NDA 208383 (betrixaban) - Deficiency Comment - 02/28/2017

Please provide a response to the comment below via email and an amendment to the NDA by March 7, 2017. In addition, please update any documents affected by your response.

Based on the levels of some of the 13 Betrixaban related substances (impurities) listed in Table 3.2.S.4.5-11 that (b) (4) *the ICH Q3A qualification threshold of 0.15%, you will need to do one of the following:*

1) Control any individual impurity to a level no more than that contained in Lot A5004 (this option does not apply to impurities A and C as they were not identified in this Lot), or

2) Control any individual impurity to no more than 20 micrograms/day based on ICH M7 for less than lifetime exposures, or

3) Provide a genotoxicity assessment with levels of the impurity that support the proposed specification.

Kind regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products

Center for Drug Evaluation and Research | Food and Drug Administration

10903 New Hampshire Avenue, WO22 - Room 3209

Silver Spring, MD 20993

Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
02/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

PROPRIETARY NAME
DISCLOSURE AUTHORIZATION REQUEST

Portola Pharmaceuticals, Inc.
270 East Grand Avenue
South San Francisco, CA 94080

ATTENTION: Janice Castillo
Senior Vice President, Regulatory Affairs

Dear Ms. Castillo:

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

We also refer to:

- Your correspondence dated and received November 22, 2016, requesting review of your proposed proprietary name, BevyxXa.
- The February 17 , 2017 correspondence informing you that your proposed proprietary name, BevyxXa, is unacceptable.

You were notified in the above referenced unacceptable letter that the proprietary name, BevyxXa, you proposed could result in medication errors due to confusion with another product's proposed proprietary name that is also under review. The ultimate acceptability of your proposed proprietary name is dependent upon which underlying application is approved first. If you would like the contact information of the other affected application holder or authorized representative that has submitted the conflicting name as part of a pending application, please complete and submit contact information (non-public information) within 14 business days from the date of this correspondence. Submit this information on your letterhead to your application as General Correspondence, and provide a courtesy copy via email to Latonia Ford, Safety Regulatory Project Manager (SRPM) in the Office of Surveillance and Epidemiology (OSE) at latonia.ford@fda.hhs.gov.

Attached is a suggested format for your authorization letter permitting FDA to disclose your non-public information to the other affected application holder(s).

If OSE receives written authorization from **all** application holders or authorized representatives, OSE will provide each applicant with the name, title, and contact information of the authorized representative for the affected application holder for each affected application. OSE will not participate in any discussion between the application holders or authorized representatives. If all affected parties do not consent to disclosure of their contact information, OSE will not provide any further information to you about the product with the conflicting proposed proprietary name.

For more information, we refer you to the Manual of Policies and Procedures:
Procedures for Sharing Non-public Information on Pending Proposed Proprietary Names
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM521551.pdf

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Thomas Iype, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

ENCLOSURE: Sample Disclosure Authorization Letter

Sample Disclosure Authorization Letter

NDA/BLA/ANDA/IND #
[Insert FDA contact address]

RE: FDA sharing of non-public information concerning **[NDA/BLA/ANDA/IND #]** and regarding proposed proprietary name, **[enter proposed proprietary name]**

Dear [**FDA contact name (OSE SRPM)**]:

On behalf of **[NDA/BLA/ANDA/IND # application holder or authorized representative]**, I authorize the United States Food and Drug Administration (FDA) and its staff to disclose the information described below to the holder (or its authorized representative) of the pending application that contains a proposed proprietary name that CDER believes is in conflict with the proprietary name contained in a pending application **[NDA/BLA/ANDA/IND #]** submitted by **[NDA/BLA/ANDA/IND application holder]**. The information will be shared for the purpose of facilitating discussions between **[NDA/BLA/ANDA/IND application holder]** and the other affected application holder about the conflicting proposed proprietary names.

I understand that this information may constitute confidential commercial information that would ordinarily be protected from disclosure under FDA's regulations and relevant law. (This includes, without limitation, 21 C.F.R. §§ 20.61, 312.130, 314.430, 601.50, and 601.51; 18 U.S.C. § 1905 (the "Trade Secrets Act," and 5 U.S.C. § 552(b)(4) (the "FOIA."). I agree to hold FDA harmless for any injury caused by FDA disclosing the information to be shared.

To this end, I hereby authorize FDA to disclose the following information, understanding that doing so will also disclose the fact that **[NDA/BLA/ANDA/IND application holder]** has submitted as part of a pending application a proposed proprietary name that CDER believes is unacceptable due to potential confusion with a proprietary name proposed as part of one or more other pending applications: **Name, title, and contact information (address, telephone number, and email address) of authorized representative for NDA/BLA/ANDA/IND application holder**.

As indicated by my signature, I am authorized to provide this consent on behalf of **[NDA/BLA/ANDA/IND application holder]**, and my full name, title, address, telephone number, and email address are set out below.

Sincerely,
(Signature)
(Printed name)
(Title)
(Address, telephone number & email address)

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/s/

TODD D BRIDGES
02/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

PROPRIETARY NAME REQUEST UNACCEPTABLE

Portola Pharmaceuticals, Inc.
270 East Grand Avenue
South San Francisco, CA 94080

ATTENTION: Janice Castillo
Senior Vice President, Regulatory Affairs

Dear Ms. Castillo:

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

We also refer to your correspondence, dated and received November 22, 2016, requesting review of your proposed proprietary name, BevyxXa.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

> The proposed proprietary name, BevyxXa, is vulnerable to medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed proprietary name, BevyxXa, is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of BevyxXa, you will be requested to submit another name.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Thomas Iype, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

MID-CYCLE COMMUNICATION

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

Dear Ms. Castillo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BevyxXa™ (betrixaban) capsule, 40 mg & 80 mg.

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 7, 2017; 3:00 PM – 4:00 PM (ET)

Application Number: NDA 208383
Product Name: BevyxXa™ (betrixaban)
Indication: For extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.
Applicant Name: Portola Pharmaceuticals

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Thomas Iype, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Ann T. Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Albert Deisseroth, MD, PhD, Supervisory Associate Deputy Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Saleh Ayache, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Thomas Iype, PharmD, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPH, Statistical Team Leader
Xin Gao, PhD, Statistical Reviewer

Office of Clinical Pharmacology
Florian Jeffry, PhD, Pharmacometrics Team Leader, Division of Pharmacometrics
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology I (DCPI)
Lars Johannesen, PhD, Clinical Pharmacology Reviewer, DCPI

Office of Prescription Drug Promotion
Rachael Conklin, MS, RN, Regulatory Review Officer

Office of Surveillance and Epidemiology
Susan Camp Rimmel, PharmD, Safety Evaluator

APPLICANT ATTENDEES
Olga Bandman, MD, Senior Director, Clinical Development
Michele Bronson, PhD, Vice President, Development Operations, Project Management
Janice Castillo, Senior Vice President, Regulatory Affairs
John T. Curnutte, MD, PhD, Executive Vice President, Research and Development
Jacqueline A. Dombroski, PhD, Senior Director, Regulatory Affairs
Alexander M. Gold, MD, Senior Vice President, Clinical Development
Shoba Gopalan, PhD, Director, Project Management
Janet Leeds, PhD, Senior Director, DMPK, Pharmacology
William Lis, Chief Executive Officer
Shiao-ping Lu, MS, Director, Biostatistics
Anjali Pandey, PhD, Senior Vice President, Medicinal Chemistry & Chemical Development
Nancy Vinh, Executive Director Clinical Operations, Clinical Research and Development

APEX Executive Committee EC Members:
(b) (4)

Consultants
(b) (4)

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Product Quality:
No significant issues have been identified to date.

Pharmacology/Toxicology:
No significant issues have been identified to date

Clinical Pharmacology:
Your submission included an analysis of efficacy events rates on the reduced dose (40 mg betrixaban) (b) (4) Further analysis of primary efficacy events and major bleeding or clinically relevant non-major (CRNM) bleeding from APEX shows a comparable efficacy event rate between enoxaparin and 40 mg betrixaban, but an increased event rate of major bleeding or CRNM bleeding. It was also observed that bleeding (major bleeding and CRNM bleeding) was more frequent in the 40 mg betrixaban group compared to 80 mg betrixaban. These observations do not appear to be consistent with an over-correction of the betrixaban dose. Please comment about this finding.

Our analysis of the pharmacokinetic data from APEX, as well as other studies, suggests that there is an impact of renal function on betrixaban exposures that might warrant dose reduction in patients with severe renal impairment.

Statistical:
No significant issues have been identified to date.

Clinical:
No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

Product Quality:
An information request was communicated to the Applicant on February 2, 2017.

Pharmacology/Toxicology:
There are no information requests at this time.

Clinical Pharmacology:
There are no information requests at this time.

Statistical:
There are no information requests at this time.

Clinical:
We are concerned that your proposed label (b) (4) You should revise your label description of the study and its results to more accurately reflect the comparisons being made.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There is no advisory committee meeting planned for NDA 208383.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Late-Cycle Meeting with Portola: April 28, 2017; 11:00 AM – 12:00 PM (ET)

The PDUFA goal date for your application is June 24, 2017. We plan to begin labeling discussions and, if necessary, any post-marketing requirement/commitments requests by March 23, 2017. If these timelines change, we will communicate the updates to you during the course of the review.

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/s/

KATHY M ROBIE SUH
02/09/2017

From:	Wall, Laura
To:	jdombroski@portola.com
Cc:	Iype, Thomas; Wall, Laura
Subject:	NDA 208383 - FDA Information Request - Please respond as soon as possible
Date:	Thursday, January 26, 2017 11:25:50 AM

Dear Dr. Dombroski,

The clinical and statistical review teams request that you respond to the following Information Request for NDA 208383 Betrixaban:

For the ITT population, the Safety population and the PEOP in Study 11-019, for Cohort 1, Cohort 2 and All randomized patients:

Provide an analysis of the primary efficacy endpoint for events occurring: a)during double-blind, double-dummy treatment portion of study treatment (i.e., betrixaban vs enoxaparin) (from randomization to the time of parenteral study medication discontinuation) and b)during the double-blind, single dummy to end of treatment portion of study treatment (i.e., betrixaban vs betrixaban placebo) (from the time of parenteral study medication discontinuation through 7 days after discontinuation of all study medication). Provide a table summarizing the component events for this analysis. Also, submit datasets that correspond to these analyses including time-to-event endpoints.

- Provide a tabulation and summary table showing for each treatment arm how many patients received how many days (e.g., 1, 2, 3, …) of study treatment during the double-blind, double-dummy treatment portion of the study treatment and during the double-blind, single dummy to end of treatment portion of study treatment.

- Provide an analysis of the primary efficacy endpoint adjusting for duration of double-dummy period treatment

- Provide a dataset including for each patient: treatment; days of double-blind, double dummy treatment; day of hospital discharge relative to last day of double-blind, double dummy treatment; primary efficacy endpoint event (yes/no); day of primary efficacy endpoint event if applicable; major bleed (yes/no); day of major bleed if applicable.

- Provide subgroup analysis of the primary efficacy endpoint for events occurring in population who have a history of VTE.

Also,

- In the Case Report Form for Study 11-019 under 'Study Drug' section under Enoxaparin/enoxaparin placebo there is the question: "If patient was discharged from the hospital before Day 6, did the patient refuse to continue enoxaparin/enoxaparin placebo as an outpatient? (yes/no)." If 'yes', the reason for premature discontinuation was to be recorded. Please provide a summary table and a data listing by treatment group for the randomized population and for each cohort of the response to this question.

- For Study 11-019 provide a summary table and a patient Listing by treatment group for the randomized population showing:
    - Hospital day (#) of discharge
    - Study Treatment day (#) of discharge
    - Number of days of 'double dummy' treatment (i.e., receiving both oral and sc study blinded treatment)

Please send the requested information with clean and track change versions via e-mail and officially to your application as soon as possible.

Kindly confirm receipt.

Thank you,

Laura

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/s/

LAURA C WALL
01/26/2017

From:	Wall, Laura
To:	jdombroski@portola.com
Cc:	Iype, Thomas; Wall, Laura
Subject:	NDA 208383 Betrixaban ODAC is Cancelled
Date:	Thursday, January 26, 2017 10:52:26 AM

Dear Dr. Dombroski,

On behalf of Thomas Iype, I was informed that the ODAC is cancelled for NDA 208383 Betrixaban, as the review so far has not uncovered issues that require public discussion.

Kindly confirm receipt.

Thank you,

Laura

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/s/

LAURA C WALL
01/26/2017

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	Janice Castillo
Subject:	NDA 208383 (Betrixaban) – Information Request – 12/27/2016
Date:	Tuesday, December 27, 2016 9:15:00 AM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/27/2016

1. Submit the analysis results of "other subgroups of PEOP regardless of cohort membership" specified in the SAP (version 1.6, page 45).
2. In the Section 11.1.2.2 of the CSR, you reported that the patients in cohort 2 or overall with missing D-dimer values by the local lab were excluded from the stratified analysis (RR, RRR and p-value). Of these excluded patients, two had adjudicated primary efficacy outcomes, and both of them were randomized to the enoxaparin arm. You claimed that excluding these patients from the stratified analysis was therefore conservative. Please provide more details of these two patients, including patient ID, efficacy endpoints status, etc.
3. Add an analysis as follows. Define an analysis population consisting of all randomized patients who have adequate assessment on one or more primary or secondary components. Based on this population, perform the efficacy analysis for cohort 1, cohort 2, and all randomized patients. Submit the analysis results, analysis dataset, and SAS program code.
4. Please provide literature references for the tipping point analysis you performed for handling of dropouts or missing data.

For the above requested items, if you have already performed such analyses, please submit the analysis results or clarify where you included them in the NDA submission, and respond to the items **by 12/30/2016**. If not, please perform such analyses, and respond to the item **by 1/3/2017**.

Kind regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

THOMAS N IYPE
12/27/2016

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	Janice Castillo
Subject:	NDA 208383 (Betrixaban) – Information Request – 12/23/2016
Date:	Friday, December 23, 2016 4:05:00 PM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/23/2016

Please provide a point by point response to the information request below **by no later than January 11, 2017** via email and an amendment to the NDA.

Regarding Study 11-019:

1. The reference to Appendix 16.1.7 does not appear to provide information on the number of patients screened. Please provide a summary of the number of patients screened but not enrolled at each participating site including reasons for screening failure where applicable and note under which protocol amendment screening was done. Also provide a summary of patients (if any) who were multiply screened and whether or not they were enrolled.

2. For the patients enrolled before implementation of Amendment 3 and those enrolled after implementation of Amendment 3, please provide tables analogous to the following tables listed in your Study 11-019 Report: Tables 17 through 41 and Tables 45 through 59.

3. The Schedule of study events indicates that compliance (pill/syringe counts) will be assessed at Day of hospital discharge (no later than Day 14 after randomization) and at Day 35 (+7 days). However, Listing 16.2.4.3 Study Drug Accountability Safety Population only shows 'Date dispensed' and 'Number of capsules/Syringes Remaining' for each patient with no other information or context. Please provide raw data and calculated data to show percentage compliance for each patient at both time points. Note that for the first 14-day period each patient should reflect double dummy (i.e., have 2 values for each patient --one for the injection and one for the oral). The Day 35 compliance assessment should have only one value per patient (oral).

4. Study 11-019 Figure 14.2.36 appears damaged in our EDF files. (The Note is missing some lines of text). Page numbering appears overlapping/superimposed for pages between 1754 and 1763. Please examine the group of pages affected and provide any corrections/clarifications.

5. Please provide a listing of patients assigned to the low dose of betrixaban/betrixaban placebo due to concomitant strong P-gp use. Include name of concomitant P-gp inhibitor, dose and duration of use.

6. For the subpopulation of patients assigned to the 40 mg dose of betrixaban/betrixaban placebo, provide an analysis of primary efficacy outcome (include tables comparable to Tables 25, 26 and 27 in your Study Report).

7. For the subpopulation of patients assigned to the 80 mg dose of betrixaban/betrixaban placebo, provide an analysis of primary efficacy outcome (include tables comparable to Tables 25, 26 and 27 in your Study Report.

8. For the subpopulation of patients assigned to the 40 mg dose of betrixaban/betrixaban placebo, provide an overview of bleeding events (include a table comparable to Tables 65 in your Study Report.

9. For the subpopulation of patients assigned to the 80 mg dose of betrixaban/betrixaban placebo, provide an overview of bleeding events (include a table comparable to Tables 65 in your Study Report).

10. Your study database appears to include about 500 healthy subjects and others who received betrixaban in a variety of clinical studies (e.g., PK/PD, food effect, bioavailability). Please provide an integrated summary, analysis and discussion of the safety data and information from these studies. Relevant safety findings from these studies should be incorporated in the Adverse Reactions section (6) of the proposed label.

11. We note also that safety data are available from about 380 patients who received betrixaban in an atrial fibrillation trial and from about 170 who received betrixaban in a study in patients undergoing hip replacement. Relevant safety data, particularly for bleeding, from these studies should be discussed and incorporated in the Adverse Reactions section (6) of the proposed label.

Kind regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us via email response to the sender or at the telephone number listed above.

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/s/

THOMAS N IYPE
12/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

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

Dear Ms. Castillo:

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

We also refer to your submissions dated November 8, 9, 22, and 29; and December 12 and 13 (2), 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 24, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 23, 2017.

In addition, the planned date for our internal mid-cycle review meeting is January 19, 2017. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. The proposed indication "for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE" is very broad and does not appear to reflect the population that was studied in the submitted single pivotal trial (the APEX Study). The main inclusion criteria in the pivotal trial were age ≥ 40 years (≥90%of patients were age ≥ 65 years), anticipated to be severely immobilized for at least 24 hours after randomization and anticipated to be severely or moderately immobilized for ≥4 days after randomization and expected to be hospitalized for ≥ 3 days after randomization. However, your proposed indication is not restricted to hospitalized patients or severely to moderately immobilized patients or elderly. Wording of the indication will be a review issue.

2. You claim that, although there were no significant differences between the prespecified primary efficacy between the two arms of the trial, the prespecified exploratory analyses provide evidence suggesting a clinical benefit from extended prophylactic treatment with betrixaban in prevention of venous thromboembolism (VTE). Adequacy of the support for efficacy from single pivotal trial will be a review issue.

3. There appear to be imbalances between patients' compliance among patients in US vs non-US (compliance was lower in US than non-US, in the betrixaban 62% vs 84.7%, in the enoxaparin 84.7 % vs 95.8%, respectively). Impact of these imbalances on outcomes will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

Highlights (HL)

1. The Boxed Warning (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*.

2. Delete the (b) (4).

3. 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.

Full Prescribing Information (FPI)

4. 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 is:

    - Advise the patient to read the FDA-approved patient labeling (Medication Guide).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 11, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application in pediatric patients less than 2 years of age. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application for pediatric patients 2 to less than 12 years of age and adolescent patients 12 to less than 18 years of age. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

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

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/s/

ALBERT B DEISSEROTH
12/22/2016

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Cc:	"Janice Castillo"
Subject:	NDA 208383 (Betrixaban) – Information Request – 12/20/2016
Date:	Tuesday, December 20, 2016 10:37:00 AM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/20/2016

Please provide a response to the information request below **by no later than December 30, 2016** via email and an amendment to the NDA.

1. Please perform subgroup analyses by age (< 65 years vs. ≥ 65 years) for cohort 1, cohort 2, PEOP, and mITT. Please also perform subgroup analyses by geographic region including U.S. vs. non-U.S. for PEOP and mITT. Please submit the subgroup analyses results along with the analysis datasets and SAS code to the Agency for review.

2. The Agency noticed that not all versions of the SAP were submitted in the package, and the current submitted SAP were not tracked with changes. Please submit all versions of the SAP with tracked changes.

Kind regards,

Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
12/20/2016

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (Betrixaban) – Information Request – 12/20/2016
Date: Tuesday, December 20, 2016 2:18:00 PM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/20/2016

Please provide a response to the below information request **by December 22, 2016** via email and an amendment to the NDA.

1. Verify the site contact information and the number of randomized patients in each site in the Table below.

Clinical Investigator Sites for inspection	**Protocol #/ Site #/ # of Subjects**
Krievins, Dainis Pauls Stradins Clinical University Hospital, Pilsonu Street 13, Riga, LV-1002, Latvia Phone: +37129450000 Fax: +37167069604 Email: (b) (6)	Protocol 11-019 Site# 44 Randomized Subjects=229
De Pellegrin, Annamaria Presidio Ospedaliero di Vittorio Veneto Via Forlanini, 71 31029 Vittorio Veneto (TV) – Italy Phone: +390438665510 Fax: +390438665757 Email: annamaria.depellegrin@ulss7.it	Protocol 11-019 Site# 93 Randomized Subjects=103
Valavicius, Arvydas Klaipeda University Hospital Department of Internal diseases Liepojos str. 41 LT-92288 Klaipeda Lithuania Phone: +370(6) 982 891 x2 Fax: +370(4) 639 669 x5 Email: (b) (6)	Protocol 11-019 Site# 104 Randomized Subjects=65
Welker, Jim Anne Arundel Health System 2001 Medical Parkway, Suite 203 Annapolis, MD 21401	Protocol 11-019 Site# 260

Phone: (443) 481-1407 Fax: (443) 481-5896 Email: jwelker@aahs.org	Randomized Subjects=44

2. Submit the following study subject data listing information for each clinical sites listed above, **as separated pdf file for each site**.

    1) Study efficacy endpoint raw data (each component of composite endpoint).
    2) Subject discontinuations (date of first dose/last dose, date of discontinuation, reason for discontinuation).
    3) Protocol deviations/violations
    4) Concomitant medication list (i.e., non-study medications).
    5) All adverse events, both during treatment or post-treatment AEs, as submitted to the NDA (preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event [yes/no], death [yes/no]).

Kind regards,

Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
12/20/2016

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Subject:	NDA 208383 (Betrixaban) – Information Request – 12/20/2016 (3)
Date:	Tuesday, December 20, 2016 4:26:00 PM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/20/2016 (3)

Please provide a response to the below information request by December 28, 2016 via email and an amendment to the NDA.

*1. Please provide clarification of your Financial Certification and Disclosure (Module 1.3.4) for. For your document named "Box 1 Study 11-019", please clarify the meaning of the contents of the last column of the table (header '**FDF Disclosure (Y/N) (all N's will substantiate 3454 Box 1').** For your document named "Box 3 Study 11-019", please provide a detailed description and documentation of efforts to obtain the required information. Also, please describe and explain the function of the 'delegation log'.*

2. For your Audit Certificate (Module 16.1.8) please provide a detailed description and documentation of your Provide a list of any audits performed by, on behalf of, or attested to by the sponsor. Include audit type (e.g., investigator site), center number for any site audits, name of auditor and date of audit.

Kind regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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THOMAS N IYPE
12/20/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/16/2016 10:11:33 AM
To: jcastillo@portola.com
CC: laura.pogue@fda.hhs.gov, Rabiya.Laiq@fda.hhs.gov
BCC: michael.hadwiger@fda.hhs.gov, olen.stephens@fda.hhs.gov, sithamalli.chandramouli@fda.hhs.gov, Sherita.McLamore-Hines@fda.hhs.gov
Subject: Method Verification Material Request for NDA 208383

Good morning,

Please refer to the attached request for Method Verification Materials regarding NDA 208383 and promptly confirm receipt to Laura.Pogue@fda.hhs.gov.

Thank you,

Laura C. Pogue, Ph.D.
Method Verification Program (MVP) Coordinator
Division of Pharmaceutical Analysis | Office of Testing and Research
FOOD AND DRUG ADMINISTRATION - CENTER FOR DRUG EVALUATION AND RESEARCH
645 S. Newstead Ave | St Louis, MO 63110
314-539-2155 (w) | Laura.Pogue@fda.hhs.gov (e)

U.S. FOOD & DRUG ADMINISTRATION

REQUEST FOR METHOD VERIFICATION MATERIALS

NDA 208383

December 16, 2016

Janice Castillo
Senior Vice President Regulatory Affairs
jcastillo@portola.com
Portola Pharmaceuticals, Inc.
270 East Grand Avenue
South San Francisco, CA 94080

Dear Janice Castillo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BevyxXa (Betrixaban) Hard (b) (4) Capsule, 40mg & 80mg.

We will be performing method verification studies on BevyxXa (Betrixaban) Hard (b) (4) Capsule, 40mg & 80mg as described in NDA 208383.

In order to perform the necessary testing, we request the following sample materials and equipment:

Note: Naming of reference standards, drug substance, and impurities seems to vary slightly across the 3 methods listed below. Please clarify if possible, or correct our interpretation herein and provide all reference standards and impurities needed to complete the following analyses:

Method, current version

1) CRLC3998 HPLC: Assay and Related Substance by HPLC
2) CRIC2853 (b) (4): (b) (4)
3) (b) (4) CTMLP-2893: Determination of Betrixaban and Related Substances in Betrixaban Maleate Immediate Release Capsules by HPLC

U.S. Food and Drug Administration
645 S. Newstead Ave
St. Louis MO 63110
www.fda.gov

Phone 314.539.2135
FAX 314.539.2113

U.S. FOOD & DRUG ADMINISTRATION

Chemicals, Samples and Reference Standards

Requested Material	Other Names	Amount Requested
Betrixaban Drug Substance	PT01040 / PT01 / 17PT01	2 x 2g
Betrixaban Reference standard	maleate salt/PRT054021	2 x 2g
(b) (4)		2 x 1g
	(b) (4)	As needed for (b) (4) method
Betrixaban Maleate Immediate Release Capsules, 40 mg		2 x 100 capsules
Betrixaban Maleate Immediate Release Capsules, 80 mg		2 x 100 capsules
40 mg PLACEBO capsules		40 capsules
80 mg PLACEBO capsules		40 capsules

Impurity	Other names	Amount Requested
A		200 mg
C		200 mg
D		200 mg
E	(b) (4)	200 mg
F		200 mg
I		200 mg
J	(b) (4)	200 mg
K		200 mg
L		200 mg
M	(b) (4)	200 mg
Q	(b) (4)	200 mg
R		200 mg
S	(b) (4)	200 mg

Equipment

1) (b) (4)
2)
3)
4)

U.S. Food and Drug Administration
645 S. Newstead Ave
St. Louis MO 63110
www.fda.gov

Phone 314.539.2135
FAX 314.539.2113

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials as well as impurities if available.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155) or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

Laura C. Pogue -S

Digitally signed by Laura C. Pogue -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laura C. Pogue -S, 0.9.2342.19200300.100.1.1=2000606027
Date: 2016.12.16 09:03:04 -06'00'

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
645 S. Newstead Ave
St. Louis MO 63110
www.fda.gov

Phone **314.539.2135**
FAX **314.539.2113**

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (Betrixaban) – Information Request – 12/16/2016
Date: Friday, December 16, 2016 10:59:00 AM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/16/2016

Please provide a response to the below information request by Monday 12/19/2016 via email and to the NDA.

Submit the contact information of all sites including name of the PI, site number, address, phone number and e-mail.

Kind regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
12/16/2016

From:	Iype, Thomas
To:	"Jacqueline Dombroski"
Subject:	NDA 208383 (Betrixaban) – Information Request – 12/02/2016
Date:	Friday, December 02, 2016 4:16:00 PM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 12/02/2016

Please respond to the below information request via an amendment to the NDA by the dates below. Also, acknowledge receipt of this communication.

Further review of your NDA submission (NDA 208,383) has revealed that data sets are also missing for study 05-002. Please submit the data sets as SAS transport files (*.xpt) along with define files by 12/14/2016.

In addition, we are not able to locate the bioanalytical reports pertaining to results of incurred sample re-analysis for the following studies 05-002, 07-008, 07-009, 11-019. Please submit these reports to the NDA by 12/21/2016.

Kind regards,

Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
12/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

PROPRIETARY NAME ACKNOWLEDGEMENT

Portola Pharmaceuticals, Inc.
270 East Grand Avenue
South San Francisco, CA 94080

ATTENTION: Janice Castillo
Senior Vice President, Regulatory Affairs

Dear Ms. Castillo

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

We acknowledge receipt of your November 22, 2016, correspondence, received November 22, 2016, requesting a review of your proposed proprietary name, BevyxXa.

If the application is filed, the user fee goal date will be February 20, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Thomas Iype, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Latonia Ford, MBA, BSN, RN
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LATONIA M FORD
12/02/2016

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (Betrixaban) – Information Request – 11/29/2016
Date: Tuesday, November 29, 2016 3:27:00 PM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 11/29/2016

Please respond to the below information request via an amendment to the NDA by 12/09/2016. Also, acknowledge receipt of this communication.

Preliminary review of your NDA submission (NDA 208,383) has revealed that data sets have not been submitted for several studies that are likely to be important for the review of your application. Please submit the data sets as SAS transport files (*.xpt) along with define files for the following studies:

- DDI studies: PPI (07-008), digoxin (08-014), ketoconazole (07-009) and verapamil (pn010)
- Healthy subject PK/PD studies: pn002 (b) (4)
- Food effect: 09-018, pn001
- Mass balance: 06-005
- Absolute BA: 07-012

Please provide these datasets and materials.

Kind regards,
Thomas Iype, Pharm.D.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
11/29/2016

From: Iype, Thomas
To: "Jacqueline Dombroski"
Subject: NDA 208383 (Betrixaban) – Information Request – 11/08/2016
Date: Tuesday, November 08, 2016 10:31:00 AM

Dear Dr. Dombroski,

NDA 208383 (Betrixaban) – Information Request – 11/08/2016

Please provide a response to the following information request by Thursday, November 10, 2016 via email and followed by an amendment to the NDA.

Provide the following:

- Appendix 16.1.12 for Study Report 11-019
- Copies of the references 1-36 cited in Study Report 11-019

Kind regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
02/09/2017

From:	Iype, Thomas
To:	Janice Castillo; "Jacqueline Dombroski"
Subject:	NDA 208383 (Betrixaban Capsule, 40 mg & 80 mg) - Information Request - 11/03/2016
Date:	Thursday, November 03, 2016 3:03:00 PM

Good afternoon,

NDA 208383 (Betrixaban Capsule, 40 mg & 80 mg) - Information Request - 11/03/2016

Please provide a response to the following information request **by Monday, November 7, 2016 (ET)** via email followed by a formal amendment to the NDA.

Your major study includes data from non-US sites. Please direct us to where in the application you have discussed applicability of the foreign data to the US population/practice of medicine.

Kind regards,

Thomas Iype, Pharm.D.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2389
Silver Spring, MD 20993
Phone: 240-402-6861 | thomas.iype@fda.hhs.gov

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/s/

THOMAS N IYPE
11/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

NDA ACKNOWLEDGMENT

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

Dear Ms. Castillo:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: BevyxXa™ (betrixaban) capsule, 40 mg & 80 mg

Date of Application: October 23, 2016

Date of Receipt: October 24, 2016

Our Reference Number: NDA 208383

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 23, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of the labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Thomas Iype, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

THOMAS N IYPE
10/28/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072679

MEETING MINUTES

Portola Pharmaceuticals, Inc.
Attention: Jacqueline Dombroski, PhD
Senior Director Regulatory Affairs
270 East Grand Avenue
South San Francisco, CA 94080

Dear Dr. Dombroski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for betrixaban.

We also refer to the meeting between representatives of your firm and the FDA on May 11, 2016. The purpose of the meeting was to discuss the adequacy of the Phase 3 clinical data from Study 11019, entitled "*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 medially Ill Patients"* to support the planned New Drug Application submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Patricia Garvey, Lead Regulatory Project Manager, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 11, 2016; 3:00 pm – 4:00 pm (ET)
Meeting Location:	Federal Research Center at White Oak 10903 New Hampshire Avenue White Oak Bldg 22, Room Silver Spring, MD 20903
Application Number:	IND 072679
Product Name:	Betrixaban
Proposed Indication:	For extended venous thromboembolism (VTE) prophylaxis in the acutely ill medical patient population
Sponsor/Applicant Name:	Portola Pharmaceuticals, Inc.
Meeting Chair:	Kathy Robie Suh, MD, PhD
Meeting Recorder:	Patricia Garvey, RPh

FDA ATTENDEES

Office of the Center Director
Robert Temple, MD, Deputy Director for Clinical Science

Office of Hematology and Oncology Products/Division of Hematology Products
Ann Farrell, MD, Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Min Lu, MD, Clinical Reviewer
Ashley Ward, MD, Clinical Reviewer
Patricia Garvey, RPh, Lead Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Rajeshwari Sridhara, PhD, Director
Yuan-Li Shen, DrPH, Statistical Team Leader
Qing Xu, PhD, Statistical Reviewer

EASTERN RESEARCH GROUP ATTENDEE

Peggah Khorrami, Independent Assessor

SPONSOR ATTENDEES

Portola Pharmaceuticals, Inc.
Olga Bandman, MD, Senior Director, Clinical Development
Janice Castillo, Senior Vice President, Regulatory Affairs and Quality Assurance (via telephone)
John T. Curnutte, MD, PhD, Executive Vice President, Research and Development
Jacqueline Dombroski, PhD, Senior Director, Regulatory Affairs
Alexander M. Gold, MD, Senior Vice President, Clinical Development
Shelly Goodman, Senior Director, Pharmacovigilance (via telephone)
Shoba Gopalan, PhD, Director, Project Management (via telephone)
Yvonne Kim, Director, Regulatory Affairs
Janet Leeds, PhD, Senior Director, DMPK, Pharmacology
William Lis, Chief Executive Officer
Brian Wiens, PhD, Senior Director, Biometrics

APEX Executive Committee Members

(b) (4)

Additional Experts

(b) (4)

1.0 BACKGROUND

Betrixaban maleate is an orally administered inhibitor of coagulation Factor Xa being developed for extended venous thromboembolism (VTE) prophylaxis in the acutely ill medical patient population.

The purpose of this meeting is to discuss the adequacy of the Phase 3 clinical data from Study 11-019 (APEX) entitled "*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"* to support the planned New Drug Application submission.

The APEX study (**A**cute Medically Ill VTE **P**revention with **Ex**tended Duration Betrixaban Study) was designed to assess efficacy and safety of betrixaban (or matched placebo) dose for 35 to 42 days, compared with active control enoxaparin (or matched placebo) dosed for 10 $\pm$ 4 days, in a population aged 40 years or older with reduced mobility and an acute medical illness requiring hospitalization. Portola is proposing that the APEX study is adequate for review and approval of the NDA for betrixaban.

On October 2, 2015, Fast Track designation was granted to betrixaban maleate for extended venous thromboembolism prophylaxis in the acutely ill medical patient population.

Portola is planning to file a New Drug Application for betrixaban in the second half of 2016 based on the results of APEX data.

FDA sent Preliminary Comments to Portola Pharmaceuticals, Inc. on May 5, 2016.

2.0 DISCUSSION

The Sponsor presented their analyses and interpretation of the APEX study results (see attached slides) and stated they plan to submit an NDA late this summer (August). The Agency commented that the Sponsor must make a strong case for why additional analyses are justified considering the provisions of the gate-keeping procedure in place and that the trial missed on its specified primary efficacy analysis per the planned statistical analysis. The Agency pointed out that the study also had issues of missing data (missing central D-dimer assays).

The meeting questions and responses below were not specifically discussed.

2.1. Clinical

Question 1: *Does the Division agree that the findings of APEX study continue to support the fast track development approach already granted and the potential to address the unmet need for extended anticoagulant therapy in acutely ill medical patients?*

FDA Response to Question 1: Yes, pending review of your study results.

Question 2*: Given the consistency and magnitude of these findings, does the Agency agree that the borderline statistical significance of the p value for Cohort 1 as identified by local D-dimer should not prevent the appropriate evaluation of benefit/risk of betrixaban for this indication?*

FDA Response to Question 2: In general, FDA would accept a single pivotal study to support licensure if results show a highly statistically significant effect on the efficacy that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. In this case, FDA considers the primary analysis to be statistically marginal. Based on the additional analyses in your meeting package, we observed that the results are not consistent in various populations. The Agency will be examining the time course of events in the study (e.g., before and after 10 days). Ultimately, whether or not the results can support an appropriate evaluation of benefit/risk of betrixaban for the intended indication will be a review issue.

Question 3: *If the FDA review confirms the overall positive benefit-risk for therapy with betrixaban, does the Agency agree that the single, Phase 3 APEX study may support the approval of an NDA for betrixaban in extended prophylaxis of thromboembolism in acutely ill medical patients?*

FDA Response to Question 3: See response to Question 2. Whether you will need an additional Phase 3 study will be a review issue.

2.2. Regulatory

Question 4: *Does the Agency agree with the overall format and content of the NDA, based on the Table of Contents provided or wish to provide additional input?*

FDA Response to Question 4: From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comment below:-

- **Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Do not use 5.3.7 as a heading element in the index.xml. Instead, case report forms need to be referenced in the appropriate Study Tagging File (STF) to which they belong, organized by site as per the specifications and tagged as "case report form."**

Question 5: *Does the Division agree with the preliminary proposal that a Risk Evaluation Mitigation Strategy will not be required for betrixaban?*

FDA Response to Question 5: The proposal appears reasonable, pending review of your study results.

***Question 6*:** *Does the Division of Product Quality agree that these application components may be submitted no later than 30 days after the submission of the original application, if necessary?*

FDA Response to Question 6: It is acceptable to provide certificate of batch analysis and additional stability data within 30 days after the original NDA submission. Please refer to the CMC only WRO dated April 29, 2016, for information that should be submitted in the NDA.

Question 7: *Do the Divisions that require this information recommend any specific format or content for the comprehensive lists and is any other information required to support these lists?*

FDA Response to Question 7: See Section 3 below.

Comments regarding data format and content:

a. Variables used in the define datasets should be the same for all datasets so that sets can be combined or sorted as needed.

b. Provide a roadmap to locations of major topics in the submission.

c. Provide all SAS programs that were used to create all of the efficacy and safety tables and figures included in the main test portion of the CSR. Please also provide all necessary macros and SAS utility programs. All programs should be thoroughly commented and have passed Sponsor's validation procedures.

- **Ensure the SAS dataset file names are consistent with those in the SAS programs that call them, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.**
- **Annotations for all efficacy and safety tables and figures should be included in the main test portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the tables or figures.**

d. Please provide a simple and all-containing "Statistical Efficacy Analysis Data Set" for statistical reviewers, in SAS transport. There should be a reviewer-friendly dataset without the necessity to merge datasets: on demographics, baseline status, and other prognostic variables, and efficacy variables on which the statistical analyses were performed, along with patient and site/investigator identifications.

e. There should be an instruction for the reviewer for the use of variables and flags to identify the set of patients on which the primary analysis was performed. Please provide flags to identify, for example, (1) Intent-to-Treat patients set, (2) per-protocol population set and (3) safety population set.

Question 8: *Does the Division agree with Portola's proposals to comply with topics covered under the PDUFA V "Program" as stated in the background to Questions 4 through 7?*

FDA Response to Question 8: Yes.

3.0 IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. There will be no late submission.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that it is pending review of the study results. Refer to response to question 5.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

    1. Quality: Refer to response to Question 6.
        - certificate of batch analysis and additional stability data

In addition, we note that a chemistry pre-submission meeting was granted as a written response only. The written responses were provided to the Sponsor on April 29, 2016. We refer you to the April 29, 2016, written responses for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission

types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

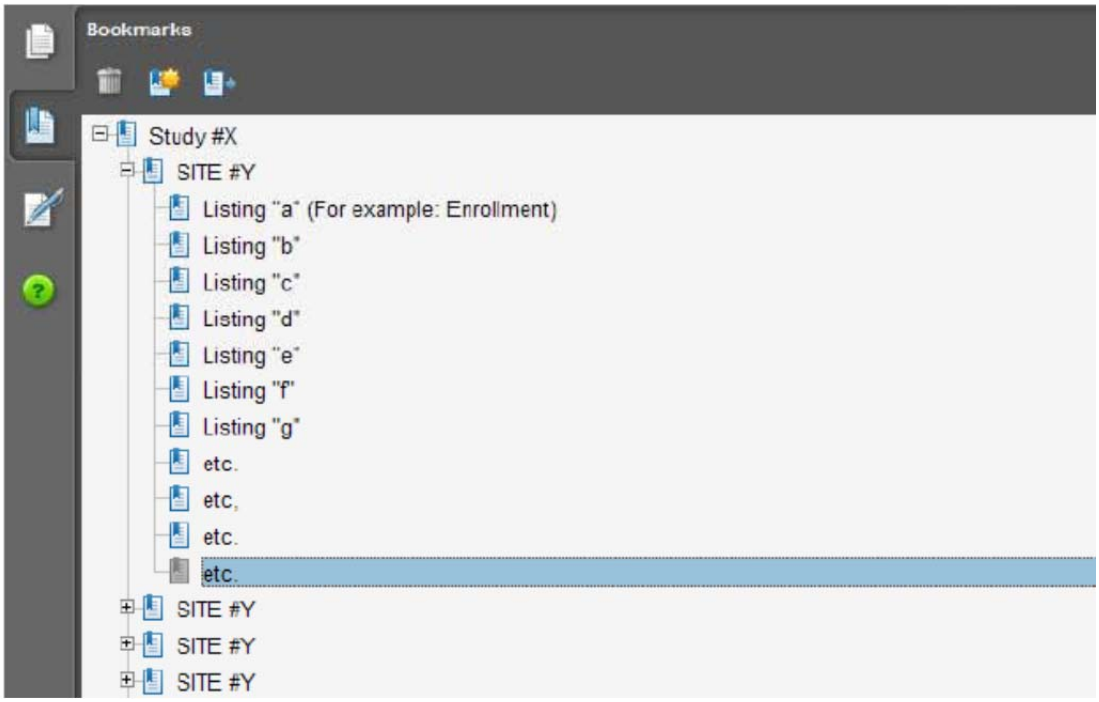
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial, provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning* (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

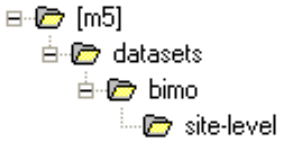
Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

During the meeting, the Agency recommended a follow-up pre-NDA meeting to discuss any analyses that Portola may not have considered for the APEX Clinical Study Report that the Agency might anticipate as being informative.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Portola's meeting presentation slides.

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/s/

KATHY M ROBIE SUH
05/27/2016

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

IND 072679

MEETING REQUEST-
WRITTEN RESPONSES

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

Dear Ms. Castillo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Betrixaban maleate.

We also refer to your submission dated March 3, 2016, containing a pre-NDA/Type B meeting request. The purpose of the requested meeting was to obtain feedback on the adequacy of the CMC data that Portola proposes will be included in the NDA.

Further reference is made to our Meeting Granted letter dated March 23, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 29, 2016 background package.

If you have any questions, call Rabiya Laiq, Pharm.D., Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Tracey L. Rogers, RPh, PhD
CMC Lead, DHP (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA (CMC)

Application Number: 072679
Product Name: Betrixaban
Indication: Extended prophylaxis of venous thromboembolic events in the acutely ill medical patient population
Sponsor Name: Portola Pharmaceuticals, Inc.

1.0 BACKGROUND

The purpose of the requested meeting was to obtain feedback on the adequacy of the CMC data that Portola proposes will be included in the NDA.

2.0 QUESTIONS AND RESPONSES

Question 1

Does the Division agree that the proposed data appear to be adequate for acceptance of the NDA for review?

FDA Response to Question 1:

The proposed information provided appears to be adequate for the acceptance of NDA for review. Refer to our response to Question 11 for stability data requirements.

Question 2

Do the data outlined appear to be adequate as the basis of approval of betrixaban (b) (4) *40 mg and 80 mg* (b) (4)

FDA Response to Question 2:

(b) (4)

Question 3

A proposed Table of Contents for Module 3 of the NDA is located in Appendix 1.

Would the Division comment on whether information about the drug substance and drug product information is located in the appropriate sections of the NDA?

The Supporting Data (Section 10.0) is organized to cover the topics listed below:

FDA Response to Question 3:
The drug substance and drug product information is located in the appropriate sections for an NDA submission. Refer to the answer to Question 13 regarding the submission of supporting stability data.

Drug Substance: Betrixaban

Question 4

(b) (4)

FDA Response to Question 4:

(b) (4)

Question 5

(b) (4)

FDA Response to Question 5:
See the answer to Question 4 above.

Question 6

Proposed starting materials for the synthesis of betrixaban, supported by proposed specifications, are described in Section 10.1.3:

Does the Division agree that [redacted] *will be acceptable as cGMP starting materials and the specifications and acceptance criteria are appropriate?*

FDA Response to Question 6:
Yes, we agree that [redacted] **are acceptable as regulatory starting materials. Data to support the starting material specifications will be evaluated during the NDA review.**

With respect to the proposed specification for [redacted] **–**

- **Provide an explanation of the test for** [redacted] **."**
- **Provide justification for the purity limit** [redacted] **%). The justification may include data from** [redacted] **studies.**

Question 7

Proposed control of polymorphic form as [redacted] is described in Section 10.1.4:

Does the Division agree that polymorphic form of betrixaban is adequately controlled by the tests and criteria described?

FDA Response to Question 7:
Yes, your approach to controlling the polymorphic form as [redacted] **appears to be adequate. Provide the method validation reports in the NDA to support the limits of detection and quantitation for the other polymorphic form** [redacted]

Question 8

The proposed specification for betrixaban drug substance is located in Section 10.1.5:
Does the Division agree with the proposed specification for betrixaban drug substance?

FDA Response to Question 8:
The proposed acceptance criteria in the drug substance regulatory specification will be evaluated during the NDA review. We recommend testing elemental impurities according to USP <232>/<233> and ICH Q3D (step 4). Unidentified impurities should be limited according to ICH Q3A to 0.10% or 1.0 mg per day intake (whichever is lower). You have

proposed specified impurity limits based on qualified levels; however, your data show [redacted] (b) (4). Consider [redacted] (b) (4) these limits.

Question 9

Stability of betrixaban, based on the body of data generated during development, is described in Section 10.1.6:

Does the Division agree that the proposed stability program will provide adequate data to support the determination of the stability of betrixaban, the long-term storage conditions and the proposed re-test period for betrixaban?

FDA Response to Question 9:

You indicated you would have limited stability data available [redacted] (b) (4) Provide an estimate of how much data will be available at the time of NDA submission. We recommend submitting at least 3 months of long-term and accelerated stability data [redacted] (b) (4)

Drug Product: Betrixaban [redacted] (b) (4) 40 mg and 80 mg

Question 10

[redacted] (b) (4)

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/s/

RABIYA LAIQ
04/29/2016

TRACEY L ROGERS
04/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072679

MEETING MINUTES

Portola Pharmaceuticals, Inc.
Attention: Janice Castillo
Vice President, Regulatory Affairs
South San Francisco, CA 94080

Dear Ms. Castillo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Betrixaban Maleate.

We also refer to the meeting between representatives of your firm and the FDA on October 25, 2011. The purpose of the meeting was to discuss:

- the betrixaban data supporting the Phase 3/registration strategy.
- the population of acutely ill medical patients who are at risk for thromboembolic complication.
- the specifics of your proposed Phase 3 protocol supporting data for the study design.
- feedback and agreement from the Agency on the questions relevant to the design, conduct and acceptability of the proposed Phase 3 protocol.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Kathy Robie-Suh, M.D., Ph.D.
Clinical Team Leader, Hematology
Division of Hematology Products
Office of Hematology and Oncology Products
"Formerly Office of Oncology Drug Products (OODP)"
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 25, 2011 / 11:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 072679
Product Name:	Betrixaban Maleate
Indication:	Acutely ill medical patients who are at risk for thromboembolic complication
Sponsor/Applicant Name:	Portola Pharmaceuticals, Inc.
Meeting Chair:	Kathy Robie-Suh, M.D., Ph.D.
Meeting Recorder:	Tyree Newman, B.S.

FDA ATTENDEES

DIVISION OF HEMATOLOGY PRODUCTS

Ann T. Farrell, M.D., Director (Acting)
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., M.P.H., Clinical Reviewer
Tyree Newman, B.S., Regulatory Health Project Manager

DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Biostatistics Reviewer
Mark D Rothmann, Ph.D., Biostatistics Team Leader

DIVISION OF SCIENTIFIC INVESTIGATIONS

Anthony Orencia, M.D., OSI Reviewer
Antoine El Hage, Ph.D., OSI Reviewer

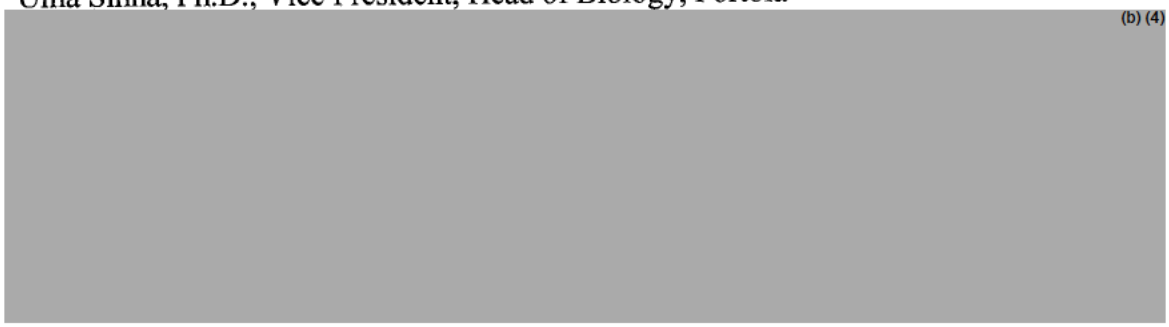
DIVISION OF PHARMACOMETRICS

Dhananjay Marathe, Ph.D., Pharmacometrics Reviewer
Anshu Marathe, Ph.D., Pharmacometrics Reviewer

SPONSOR ATTENDEES

Michael Kitt, M.D., Sr. Vice President and Chief Medical Officer, Portola
Janice Castillo, Vice President, Regulatory Affairs, Portola
William Lis, Chief Executive Officer, Portola
John Curnutte, M.D., Ph.D., Executive Vice President, Clinical Affairs and Business Strategy, Portola
Todd Lorenz, M.D., Sr. Vice President, Clinical Affairs and Business Strategy, Portola
Uma Sinha, Ph.D., Vice President, Head of Biology, Portola

(b) (4)



1.0 BACKGROUND

Portola requested a Type B meeting on August 12, 2011. On August 23, 2011, the Division sent Portola the meeting request granted letter.

On October 20, 2011, the Division emailed Portola preliminary responses to the questions contained in the meeting information package dated September 26, 2011.

2.0 DISCUSSION

2.1. Non-Clinical

Question 1: *Does the Agency agree that carcinogenicity studies will not be required for an NDA for the proposed indication, which entails 35 days of dosing, and that only a Segment III: peri- and post-natal reproductive toxicology study in the rat is necessary to complete our nonclinical package for the NDA?*

FDA Response: Yes, we agree. A final decision on the adequacy of your nonclinical package will be made after review of complete data submitted with the NDA.

Discussion: No discussion.

2.2. Clinical

Question 2A (Primary Efficacy Endpoint Analysis): *Does the Agency agree that a primary composite endpoint consisting of VTE-related death, nonfatal PE, asymptomatic proximal DVT and symptomatic (proximal or distal) DVT can be an appropriate primary efficacy endpoint to study betrixaban in the proposed indication?*

FDA Response: We recommend including all-cause death in the primary efficacy endpoint for the study.

Discussion: No discussion.

Question 2B: *Does the Agency agree with the definition of the efficacy population* (b) (4) [redacted] (b) (4) *for the analysis of the primary endpoint?*

FDA Response: Every subject should be accounted for in the analysis by either being assessed for the primary endpoint or properly accounted for if not assessed for the primary endpoint. The number of subjects not assessed for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results.

Several sensitivity analyses should be performed to account for the limitation of the data and to examine the potential impact of any missing data. Sensitivity analyses should include an appropriate method of imputation under the null. For further advice on missing data see the National Academy of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.

Discussion: **No discussion.**

Question 2C: *Does the Agency agree with inclusion of all events reported at the "Day 35 visit" (required by protocol to be conducted between days 31-39) in the primary endpoint analysis? (The only exception to this would be that patients who die by actual Day 39 who did not have a "Day 35 visit" would be counted as having an event (death) at the "Day 35 visit")?*

FDA Response: **Yes. We agree.**

Discussion: **No discussion.**

Question 3: *Does the Agency agree that if the Phase 3 clinical study results in a 'p' value of 0.01 in the primary endpoint as outlined under Clinical Question #1 it would be considered highly significant and will constitute adequate and well controlled evidence of efficacy such that a single study New Drug Application can be approved?*

FDA Response: **Two adequate and well-controlled studies are generally required to support an indication. FDA would accept a single study if results show a highly statistically significant effect on mortality that is internally consistent across subgroups. See "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" at http://www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf**

Discussion: **The Sponsor asked the Agency to clarify the requirement that the study show an effect on mortality. The Agency commented that this will be the first indication for this drug product and there is no supporting marketing experience in other anticoagulant indications and therefore, the benefit-risk will need to be well supported by the clinical database submitted for this indication. The Agency recommended the study have an efficacy endpoint incorporating all cause mortality in this population. The Sponsor stated they will do a single study and understand that the data would need to be highly persuasive, but feel seeking an outcome on mortality is not feasible for their study. The Agency provided their best advice at this time for this application. The acceptability of the NDA package is a review issue. The benefit-risk will be assessed on the totality of the data.**

Question 4A ***(Study Design -*** [redacted] (b) (4)

FDA Response: **No. We strongly recommend an efficacy assessment prior to the placebo-controlled period. You need to show that 35-day betrixaban treatment is superior to both 10-day enoxaparin and 10-day betrixaban treatment. No adjustment is needed for multiplicity.**

We refer to our previous comments regarding our concerns for the major design limitations of your phase 3 study designs.

Discussion: **No discussion.**

Question 4B: *Does the Agency agree* (b) (4) *is an appropriate approval strategy for a new fXa inhibitor?*

FDA Response: **No.** (b) (4) **In addition, you need to provide justification for an extended prophylaxis treatment in medical patients. You should consider the potential for declining benefit of betrixaban while risk of bleeding continues with the extended treatment duration in those patients.**

Discussion: **No discussion.**

Question 5A (Patient Population): *Does the Agency agree with the proposed strategy in the Phase 3 protocol* (b) (4)

FDA Response: **No. Immobilization is an important risk factor for development of VTE in medically ill patients and it should be defined and required as one of inclusion criteria for all study patients.**

Discussion: **No discussion.**

Question 5B: *Does the Agency agree with the plan to have the IDMC monitor the control event rate including a D-dimer level at baseline ≥ 2x the ULN as one of the additional VTE risk factors vs. those having two or more of the additional risk factors and dropping the D-dimer inclusion criteria if the event rate in the control group is inconsistent with the control group event rate assumptions described in the proposed protocol.*

FDA Response: **D-dimer has been used in clinical practice in assisting the diagnosis of VTE. Since assessment of VTE is not required at baseline in the study and the increased D-dimer can be caused by many other conditions, you need to provide justification to include D-dimer as a risk factor for the development of VTE.**

Discussion: **No discussion.**

Question 6A (Dose Selection): [redacted] (b) (4) *The Agency also stated that we have not provided adequate support for the dosing regimen proposed for the Phase 3 study.*

Does the Agency agree that Portola has presented, in this briefing document, evidence of a beneficial effect of betrixaban?

FDA Response: [redacted] (b) (4) **. You have not conducted a dose response phase 2 study in the medically ill patients.**

Discussion: The Sponsor stated enough is known about dosing to justify their proposed dose for the Phase 3 study. The Agency clarified that the dose is not a clinical hold issue for the proposed study. The Agency expressed concerns about larger peak-to-trough ratios in *QD* as compared to *BID* dosing as this may have possible effects in safety profiles.

Question 6B: *Does the Agency agree that the data suggest a favorable benefit: risk profile for betrixaban?*

FDA Response: See response to Question 6A.

Discussion: No discussion.

Question 6C: *Does the Agency agree with Portola's rationale and proposed dose for the Phase 3 clinical study?*

FDA Response: See response to Question 6A. The proposed 80 mg QD dose has not been studied in this population or in other population for the prophylaxis of DVT.

We believe that you have not provided sufficient justification for the proposed dose of 80mg QD. The occurrence of VTE in your Phase 2 trial (EXPERT, 05-003) was 15.4% for 40mg BID dosing. Your supportive PK/PD analysis has not compared the safety and efficacy of the 80mg QD dosing against the 40mg BID dosing. We recommend that you submit the simulation results for safety and efficacy analysis of 40mg BID vis-à-vis 80mg QD (with appropriate dose adjustments in renal impairment and Pgp-inhibition sub-groups).

Discussion: See discussion for Q.6A.

Question 7 (Durability of Response): *Does the Agency agree that a* (b) (4) *day follow-up is adequate to assess the durability of the response of VTE to betrixaban therapy?*

FDA Response: **We recommend a 30-day follow-up for mortality and cardiovascular events.**

Discussion: **No discussion.**

Question 8A (Statistical Assumptions): *In the FDA response of June 13, 2011, the Agency asked to justify our non-inferiority margi* (b) (4) *Does the Agency agree with the proposed protocol* (b) (4) *analysis of efficacy?*

FDA Response: **See response to Question 4A.**

Discussion: **No discussion.**

Question 8B: *The Agency asked to justify the* (b) (4)

(b) (4)

FDA Response: **See response to Question 4A.**

Discussion: **No discussion.**

Question 8C: *The Agency commented that the study does not allow for a comparison of*

(b) (4)

FDA Response: **No. See response to Question 4A.**

Discussion: **No discussion.**

Question 9 (Adverse Event Reporting): *Does the Agency agree to a plan* (b) (4)

FDA Response: **No. All adverse drug reactions including non-serious and serious adverse reactions should be collected, documented, and reported in the study.**

Discussion: **No discussion.**

Question 10 (Monitoring): *Does the Agency agree with a plan for* (b) (4) *in this large, multinational, multi-center Phase 3 study?*

FDA Response: Please clarify what "[redacted] (b) (4)" means. Please review the link to the draft guidance to assist you in identifying and designing monitoring practices for a given clinical trial.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>

We encourage you to consider using the recommended types of monitoring identified in the draft guidance. If you elect to perform "[redacted] (b) (4)" it will be at your own risk.

Discussion: No discussion.

Question 11 (Pediatric Deferral): *Does the Agency agree that pediatric studies can be deferred until after the results of the Phase 3 study of betrixaban in acute medically ill patients has been completed and can be performed after an initial approval is granted?*

FDA Response: Pediatric studies need not be conducted prior to your Phase 3 study. Please submit your plan for pediatric studies and the request for deferral at the time of NDA submission.

Discussion: No discussion.

Question 12 (Drug-drug Interaction Studies): Does the Agency agree that data from the drug-drug interaction studies support the planned dose of betrixaban in patients receiving a Pgp inhibitor?

FDA Response: Yes, 40 mg QD for patients receiving a P-gp inhibitor appears acceptable.

Discussion: No discussion.

Question 13 (Patients with Severe Renal Insufficiency): *Does the Agency agree with Portola's plan to enroll patients with severe renal insufficiency (i.e., < 30 mL/min CrCl) into the Phase 3 study at the reduced dose (40 mg QD) specified in the protocol?*

The proposed Phase 3 protocol reflects the US labeled dose of enoxaparin (30 mg SC QD) use in patients with severe renal insufficiency. Portola however, would like the Agency to comment on the potential use of one, globally standardized, enoxaparin dose (20 mg SC QD) in patients with severe renal insufficiency (i.e., < 30 mL/min CrCl) in this study. Portola requests the Agency's recommendation on an appropriate dose of enoxaparin for patients with severe renal insufficiency in a worldwide trial.

FDA Response: Yes, 40 mg QD for patients with severe renal impairment appears acceptable. Since your dedicated renal impairment study shows approximately 2-fold

higher exposures in patients with moderate renal impairment, you should monitor for increased bleeding events in this sub-population. A dose adjustment for moderate renal impairment should be considered in order to reduce their exposures if increased bleeding is a trend seen in this population. Please provide the evidence to suggest that enoxaparin 20mg in patients with severe renal insufficiency has similar exposure to enoxaparin 40mg in patients with no underlying renal insufficiency.

Discussion: **No discussion.**

Question 14 (Cardiac Safety and the QT Interval): *Does the Agency agree that Portola has demonstrated that the proposed dose of 80 mg QD (as well as the 40 mg QD dose adjustment for concomitant use of strong inhibitors of Pgp and patients with a CrCl ≤ 30 ml/min) does not result in QT prolongation (See Thorough QT Study* ***Section 4.2.1.5****) and therefore the collection of baseline and periodic on-therapy ECGs in the proposed Phase 3 study in accordance with clinical practice is sufficient (Guidance for Industry, E14 Clinical Evaluation of QT/QTc)?*

FDA Response: **Yes. We agree.**

Discussion: **No discussion.**

Question 15A (Antidote for fXa in Bleeding Patients): *Does the Agency agree that Portola's recombinant fXa inhibitor antidote could be studied in the latter half of the betrixaban Phase 3 trial?*

FDA Response: **You should incorporate the evaluation of efficacy and safety of the antidote in your phase 3 trials at the beginning to obtain sufficient data.**

Discussion: **No discussion.**

Question 15B: *Does the agency agree that this would not affect the efficacy and safety analysis of the Phase 3 study?*

FDA Response: **See response to Question 15A.**

Discussion: **No discussion.**

Additional Comments:

Statistical: **Only stratification variables should be included in the model for the primary efficacy analysis. Covariate adjusted analyses with pre-specified covariates may be regarded as supportive only if the primary analysis demonstrates a statistically significant result, otherwise such analyses will be regarded as exploratory.**

Clinical Pharmacology: **Collect sparse PK samples in all patients as a part of the standard assessments. Patient participation in PK sampling should not be a separate consent. The sparse PK data along with exposure-response analyses will support your dose justifications for coadministration with p-gp inhibitors and for patients with renal impairment. We also recommend that you perform exposure-response analysis for efficacy and safety end-points with the Phase 3 data.**

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided slides (attached).

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/s/

KATHY M ROBIE SUH
11/07/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 72,679

Portola Pharmaceuticals, Inc.
Attention: Daniel D. Gretler, M.D., F.A.C.P.
270 E. Grand Avenue, Ste. 22
South San Francisco, CA 94080-7000

Dear Dr. Gretler:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PRT054021.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on June 27, 2007. The purpose of the meeting was to discuss (b) (4)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 27, 2007
TIME: 10:00 AM-11:30 AM
LOCATION: White Oak Room 1417
APPLICATION: IND 72,679
DRUG NAME: PRT054021
TYPE OF MEETING: Type B; End of Phase 2

MEETING CHAIR: Dr. Rafel (Dwaine) Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Officer,
Diane Leaman, Regulatory Health Project Manager,
Tushar Kokate, Ph.D., Pharmacologist, DMIHP (HFD-160)

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Christy John, Ph.D., Clinical Pharmacology Reviewer

Office of Biometrics

Somesh Chattopadhyay, Ph.D., Statistician, Division of Biometrics V

Office of Drug Evaluation I

Robert Temple, M.D., Associate Director

Office of Drug Evaluation I, Division of Cardio-Renal Products

Abraham Karkowsky, M.D., Ph.D., Medical Team Leader
Meg Pease-Fye, M.S., Regulatory Health Project Manager

IRT, QT Team

Rajnkanth Madabushi, Ph.D., Clinical Pharmacology Reviewer
Christoffer W. Tornoe, Ph.D., Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Samuel Chan, PharmD., MBA, Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Dan Gretler, MD., Vice President, Clinical Development/Regulatory Affairs
Joe Lambing, PhD., Vice President, Pharmaceutical Development
Charles Homcy, MD., Chief Executive Officer, Head of Research and Development
(b) (4)

BACKGROUND:

PRT054021 is an orally active small molecule inhibitor of coagulation factor Xa (fXa). Inhibition of fXa with PRT054021 is anticipated to elicit anticoagulant and antithrombotic effects by decreasing the conversion of Prothrombin to proteolytically-active thrombin. (b) (4)

A QT signal was observed at higher concentration in two Phase 1 clinical studies conducted with PRT054021.

On December 14, 2005, Portola Pharmaceuticals, Inc. (Portola) met with the Division of Medical Imaging and Hematology Products (DMIHP) for a Pre-IND meeting to discuss specifics of the QT prolongation data gathered to date for the single ascending dose (SAD) escalation clinical trial (b) (4)

On October 10, 2005, Portola submitted the IND to the Agency proposing an initial single-dose food-effect study. DMIHP held a teleconference with the sponsor on November 10, 2005, to discuss the immediate drug development needs for this product to progress beyond the submitted single-dose drug interaction study in healthy subjects to multiple-dose studies in patients.

On April 26, 2007, Portola requested an End of Phase 2 meeting to discuss (b) (4) The background package was submitted May 25, 2007. A response to an information request was submitted on June 15, 2007.

MEETING OBJECTIVES:

To discuss the immediate drug development needs for this product to progress beyond the submitted single-dose drug interaction study in healthy subjects to multiple-dose studies in patients.

DISCUSSION POINTS:

The meeting started with a discussion of the proposed Thorough QTc (TQT) Study. The Agency was concerned regarding the study design and the sponsor's approach given the current results of previous studies. The Agency felt that the proposed supra-therapeutic doses did not go high enough. The range of exposures expected with the supra-therapeutic dose did not cover the range of the exposures expected with the highest dose proposed to be studied in the registration trial. Also, the critical PK features such as absolute bioavailability and metabolic fate were unknown. The Agency also recommended that the sponsor study the drug in patients with hepatic impairment. Consequently, the most appropriate dose or doses to study were unclear.

The sponsor was concerned with exposing subjects to high levels of PRT054021 (b) (4) The sponsor was concerned that exposing subjects to greater doses for the purpose of QTc effect evaluation might lead to bleeding. The sponsor also said that the QT prolongation risk at higher exposures has been quantified with the analysis submitted in the meeting package. The range of the exposures used for the analysis would not be achieved in a TQT study. (b) (4) . The sponsor is also concerned regarding the administration of the drug to hepatically impaired patients as the drug is excreted mainly through the biliary system. (b) (4) . The sponsor said that they had completed some drug-drug interaction studies including ketoconazole and have submitted the summary results. The interaction with ketoconazole resulted in a doubling of AUC and C_{max}, i.e., not a large effect. The sponsor said that they will be completing an absolute bioavailability study and are planning to complete a mass balance C^{14} study in humans before the registration trial.

The Agency said the purpose of the supra-therapeutic doses was to cover the worst-case scenarios that could be expected with the proposed therapeutic doses, but it did not appear that the proposed study would do that. Our concern was that, from previous data, the QT effect seemed delayed (hysteresis). The sponsor thought that the full QT effect was seen within 24 hours. In that case, a single dose TQT study should be able to definitively determine the QT risk. The sponsor said they submitted data in March 2007 looking at metabolites and ion channel metabolites with C^{14} in animals. The circulating levels of the metabolites are almost undetectable in the plasma. Finally, the sponsor noted that in the multiple dose study, the time course of the QT prolongation was similar on the first and the last days post-dose, indicating no substantial effect or drug accumulation of metabolites.

The Agency and the sponsor discussed whether a single-dose or multiple-dose TQT study was needed. If the sponsor shows that hysteresis can be captured within the sampling period following a single dose and can provide evidence that metabolites with long half lives are not formed, a single-dose TQT study could suffice. If the sponsor cannot provide such evidence, a single-dose TQT study may not be sufficient. The supra-therapeutic dose should be selected to cover the worst case scenarios expected at steady-state. This dose should take into account the potential increase in concentrations as a consequence of drug-drug interactions, of approximately about two-fold variability in bioavailability, changes in the PK (b) (4) and the food-effect on the new formulation and any effects related to the route of

excretion of metabolism. The Agency also pointed out that the sponsor does not need to perform studies with both supra-therapeutic and therapeutic doses. They could perform the TQT study with the supra-therapeutic dose, so long as samples collected over time will cover the range of the exposures expected to be achieved and the proposed doses to be studied in the registration trials. If a single-dose study is conducted, the single dose should be followed for two days or more based on the PK and hysteresis characterization.

The Agency recommended that the sponsor perform the studies that will give information on the expected worst-case exposures before choosing the dose for the TQT and the registration trials. They will then be able to design the TQT study and be able to manage the safety monitoring for QT prolongation (b) (4) The sponsor should submit the protocol for the TQT study for review.

The Agency suggested that the sponsor perform a food-effect study (b) (4)

(b) (4)

With respect to the proposed TQT study, the Agency recommends a blinded moxifloxacin double-dummy study design.

DECISIONS (AGREEMENTS) REACHED:

In response to the questions in the May 25, 2007, background package, the Agency has the following responses. The format provides the firm's questions in *italics* followed by DMIHP's responses in **bolded** lettering.

We have the following concerns regarding your drug program:

1. (b) (4)

2. **The proposed clinical pharmacology studies are not adequate due to the need for a study in subjects with hepatic impairment and deficiencies in the proposed QTc study. Based on animal data, PRT054021 is excreted predominantly through the biliary route and you claim (b) (4) You should conduct a study in hepatically-impaired subjects to demonstrate the exposure in such a population.**

3. **Available data indicate that, at certain doses, PRT054021 prolongs the QT interval. These data present formidable safety challenges for the development of the product. Hence, we anticipate that persuasive evidence of a favorable risk-benefit profile for**

PRT054021 will necessitate extensive evidence of safety, especially if the product is shown to provide no clinically important advantages over products already approved for the proposed indication.

4. **Please be aware that reassuring findings from your proposed QTc study are not likely to resolve the question of safety regarding cardiac effects of PRT054021. We may feel reassured if the TQT study shows no prolongation (UCI < 10 ms) at the worst case exposures for the highest proposed dose, and the percentage of outliers (>30 – 60 ms) are minimal. The findings from the QTc study must be fully supported by the outcomes from all your clinical studies. Other channels besides QT may be altered. The drug could alter cardiovascular function (negative inotrope). As such, a QT study alone may be insufficient to completely rule out risk.**

Questions

(b) (4)

(b) (4)

FDA Response:

- (b) (4)

- **Generally, two adequate and well-controlled studies are generally needed to support a new indication. There is a risk in performing a single trial that may not have convincingly positive results to support the proposed indication. The acceptance of the single study as a sufficient scientific and regulatory basis for approval of a new indication will be determined by its adequacy to support the efficacy claim based on strength of the results. See "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products" and "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials".**

- **Please submit detailed statistical analysis plans** (b) (4)

2. *Portola would like to engage the Agency in a discussion of how best to address the risk associated with QT prolongation.* (b) (4)

FDA Response:

- **We are not certain what you mean by "** (b) (4) **" but you should plan to include intensive ECG monitoring for QT prolongation. The timing and intensity of ECG monitoring necessary is dependent on the results of your 'thorough QT study' as well as a thorough understanding of your drug's pharmacokinetics.**

- **Under circumstances where there is concern regarding provocation of arrhythmic events, we usually recommend that both real time and archival ECGs be collected. The real time measurements would allow for early intervention in the case of an arrhythmic event. The archival (Holter) would allow for an accurate assessment of the nature of the arrhythmia.** (b) (4)

(b) (4)

3a. *To further characterize any QTc risk, this Briefing Document contains a proposed design for a thorough QTc study. Does the Agency concur that the design of this study is appropriate to adequately characterize the potential for PRT054021 to prolong the QTc interval?*

FDA Response:

The following are the comments with respect to the design of the proposed the 'thorough QT" (TQT) study:

(b) (4) **is not acceptable** (b) (4) **We recommend that you derive the supratherapeutic dose based on the results of the drug-drug interactions studies, an absolute bioavailability study and the mass balance study. The following are additional comments and suggestions:**

- **In the event of no significant drug-drug interaction, we recommend 120 mg bid with a loading dose of 240 mg for supratherapeutic dose. The mean C_{max} on Day 10 with 120 mg bid is 122 ng/mL and it covers the 95th percentile expected with 80 mg qd.**
- **In addition, there appears to be a hint of a hysteresis effect. As such, any set of ECGs performed in a QTc study should capture the effect of withdrawal of drug on QTc intervals. The results of the TQT and other data would, in part, dictate the diligence of ECG monitoring. (See discussion above)**
- **We note your concern about the risks of exposing normal volunteers to your product, which is an anticoagulant. Use of a cross-over design** (b) (4) **for your 'thorough QT study' will minimize the number of subjects needed to achieve the same statistical power.**
- **We recommend you administer moxifloxacin blindly using a double-dummy approach (as you did in part II of study 04-001), to minimize the possibility of bias.**
- **We recommend that you stipulate in the protocol for your TQT study that PRT054021 be administered in the fasting state since you indicate food decreases exposure.**

3b *Also, in light of the data available thus far, what would be the consequences of a negative vs. a positive thorough QT study in terms of labeling and cardiac safety monitoring in future* (b) (4) *trials?*

FDA Response:

- **The data that you have provided suggests that there is a serum concentration dependent lengthening of the QTc. The magnitude of this effect is not clear yet so we cannot comment on implications for the label. Please see our answer to your**

question 2 which indicates a need for intensive ECG monitoring (b) (4)

- **Should there be a large effect on QTc, it may be important for you to demonstrate that this increase does not lead to an increase in adverse outcomes (such as arrhythmia-related risk factors, heart failure, post myocardial infarction with large ventricular ectopy, patients with intermittent compression devices (ICDs), in general, patients at risk for sudden death and sudden death-like syndrome). If there are substantial numbers of patients with therapeutic doses that provoke large increases in QTc intervals, you may need to perform a study in patients with cardiovascular risk factors, such as concomitant medications, and demonstrate that the overall safety profile is acceptable.**

4. Is the proposed clinical pharmacology, ADME and PK/PD data package adequate to support the proposed Phase 3 clinical development plan and submission of an NDA?

   FDA Response:
   Please see our concerns regarding your drug program described on page 4. The adequacy of the clinical pharmacology studies for an NDA submission will depend upon the outcome of the planned and on-going studies. -

5. Will the proposed Phase 3 program provide an adequate safety database in support of an NDA approval?

   FDA Response:
   - **Please be aware that the sufficiency of a safety database is determined by the totality of the study findings. In general, it is not possible to *a priori* confirm that any proposed safety database will be acceptable; however, the results of your planned QTc study and clinical pharmacology studies will assist in targeting a reasonable safety database sample size.**
   - **Long-term safety data will be needed for this oral product even for a short-term indication.**
   - **In general, for oral anticoagulant products, we have suggested at least 1000 patients who have received the drug for six months and at least 500 patients who have received the drug for one year; however, in light of the QT concerns, a substantially larger database may be necessary.**

6. Does the proposed non-clinical data package provide adequate support for an NDA submission and approval?

   FDA Response:

   a. The adequacy of the non-clinical studies for an NDA submission will depend on the outcome of the planned/ongoing pre-clinical and clinical studies.

b. In a 3-month repeat-dose study in rats, dose-dependent myofiber necrosis of the skeletal muscle was observed. We recommend you closely monitor CPK, AST, LDH and troponin in clinical studies, in particular, in elderly subjects.

Sponsor Response:

The sponsor agreed to closely monitor enzymes indicative of muscle injury.

7. (b) (4) Does the Agency concur with this plan?

FDA Response:
See above comments. In general, the plan appears to be reasonable. (b) (4) **Monitor CPK and aldolase levels.**

8. (b) (4)

FDA Response: (b) (4)

Additional QT Interdisciplinary Review Team comments:

- **Biliary excretion is proposed to be the predominant pathway of PRT054021. It is not known whether the proposed supratherapeutic dose covers the increase in exposures that can be expected in hepatic impairment associated with impairment of biliary secretion. We recommend that you collective extensive ECGs in your hepatic impairment study.**
- **We believe you plan to incorporate the following elements into your assessment of the ECGs acquired during your TQT study but reiterate them to emphasize their importance:**
  - **a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation,**
  - **b. Blinding of ECG readers to subject identifiers, treatment, time, and day (*i.e.*, Day -1; Day 1),**
  - **c. Review of all ECGs from a particular subject by a single reader on one day, and**
  - **d. Assessment of inter-reader variability by having a subset of tracings interpreted by a second reader.**
- **When you submit the protocol for your TQT study report, please include the following items:**

e. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

f. Electronic or hard copy of the clinical protocol

g. Electronic or hard copy of the Investigator's Brochure

h. A completed Highlights of Clinical Pharmacology Table (the QT-IRT can not review your protocol until this item is received)

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

(Note: some information requested in the above table was submitted in the June 15, 2007 submission.)

Portola agreed to closely monitor enzymes indicative of muscle injury.

Portola agreed to submit proposals for the following studies:

- **A formal male vs female PK study in Phase 2.**
- **An absolute bioavilability study**
- **A bioequivalence study**
- **A food-effect study**
- **A C^{14} experiment for metabolites**

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Once the results of the above studies has been reviewed, further details (b) (4) can be delineated.

ACTION ITEMS:

Portola Pharmaceuticals, Inc. will submit the information, study protocols and study reports to the Agency as outlined above.

ATTACHMENTS/HANDOUTS:

See attached.

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/s/

Diane V Leaman
7/19/2007 03:19:48 PM

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

LATE-CYCLE MEETING MINUTES

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

Dear Ms. Castillo:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on April 28, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Thomas Iype, PharmD, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: April 28, 2017; 11:00 AM – 12:00 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: NDA 208383
Product Name: Betrixaban capsule
Applicant Name: Portola Pharmaceuticals, Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Thomas Iype, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, MD, Director

OHOP/Division of Hematology Products
Ann T. Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Saleh Ayache, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Thomas Iype, PharmD, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist

Office of New Drug Products/Division of New Drug Products I – Branch II
Sherita McLamore-Hines, PhD, Acting Quality Assessment Lead

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPH, Statistical Team Leader
Xin Gao, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology I
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader
Lars Johannesen, PhD, Clinical Pharmacology Reviewer

Office of Clinical Pharmacology/Division of Pharmacometrics
Florian Jeffry, PhD, Pharmacometrics Team Leader, Review Team 3

Office of Surveillance and Epidemiology (OSE)/Division of Pharmacovigilance
Page Crew, PharmD, MPH, Safety Evaluator

OSE/Division of Medication Error Prevention and Analysis
Susan Rimmel, PharmD, Safety Evaluator

APPLICANT ATTENDEES
Portola Participants:
Olga Bandman, MD, Senior Director, Clinical Development
Janice Castillo, Senior Vice President, Regulatory Affairs
John T. Curnutte, MD, PhD, Executive Vice President, Research and Development
Jacqueline A. Dombroski, PhD, Senior Director, Regulatory Affairs
Alexander M. Gold, MD, Senior Vice President, Clinical Development
Shoba Gopalan, PhD, Director, Project Management
Janet Leeds, PhD, Senior Director, DMPK, Pharmacology
William Lis, Chief Executive Officer
Shiao-ping Lu, MS, Director, Biostatistics

APEX Executive Committee EC Member:
(b) (4)

Consultants:
(b) (4)

Portola Participants (by telephone)
Shelly Goodman, RN, BSN, Senior Director, Pharmacovigilance
Anjali Pandey, PhD, Senior Vice President, Medicinal Chemistry & Chemical Development
Yvonne Kim, Director, Regulatory Affairs

APEX Executive Committee EC Member (by telephone):
(b) (4)

Consultants (by telephone):
(b) (4)

1.0 BACKGROUND

NDA 208383 was submitted on October 23, 2016 for betrixaban.

Proposed indication is betrixaban for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and/or other risk factors for VTE.

The PDUFA goal date is June 24, 2017.

FDA issued a Background Package in preparation for this meeting on April 13, 2017.

2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

   The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

2. Discussion of Minor Review Issues

   Clinical Pharmacology

   - The benefit-risk assessment for patients receiving 40 mg (either based on severe renal impairment [CrCl < 30 mL/min] or concomitant use of a P-gp inhibitor) suggests an increased risk for bleeding (major or clinically relevant non-major [CRNM] bleeding; betrixaban: 4.8% vs enoxaparin: 1.4%) without an efficacy benefit (symptomatic and asymptomatic VTE events; betrixaban 7.0% vs enoxaparin: 6.7%) compared to enoxaparin. The available data does not support that an improvement in the benefit-risk could be achieved by altering the dose for patients who prospectively received 40 mg. Given this observation in this prospectively dose-reduced subgroup, a limitation of use is proposed for use of betrixaban in patients with severe renal impairment or who require concomitant use with P-gp inhibitors.

   - The unfavorable benefit-risk in these patients might be related to an unidentified underlying patient factor(s) that is currently, at best, identified by concomitant P-gp inhibitor use. To potentially identify the underlying patient factor, additional analyses were conducted to assess whether the benefit-risk in this subgroup is altered based on duration (chronic versus acute) and timing (at randomization versus after start of trial) of P-gp inhibitor use. During this evaluation, we identified inconsistencies in how P-gp

inhibitor use was documented across APEX data sets (i.e., different number of patients reported on P-gp inhibitors in the CSR compared to the Applicant's mid-cycle communication). We request a clarification on the different methodologies used between the two analyses and an explanation on why different definitions were utilized.

Discussion:
The clinical studies provided do not support the safe (bleeding risk) use of the proposed strengths in patients with severe renal impairment or in patients with concomitant use of p-glycoprotein inhibitors. Portola is willing to provide additional data to support use in these population subsets and post marketing commitments to address this safety concern.

Clinical

- (b) (4) The treatment durations in the two treatment arms are not comparable (Betrixaban up to 35-42 days vs. Enoxaparin up to 10 ± 4 days). (b) (4) the enoxaparin control arm used in the study is adequate to establish efficacy of betrixaban, (b) (4) (b) (4)

Discussion:
Portola agrees (b) (4) **In addition, Portola also agrees that the duration of treatment for betrixaban should concur with the duration of treatment in the APEX trial.**

Statistical

- The proposed claim about extended effect cannot be confirmed. The occurrence of asymptomatic proximal DVT was detected by ultrasound and determined only on or before Day 47. Therefore, the APEX study did not provide sufficient data for adequate assessment of the time course of the treatment effect, and the beneficial effect of extended treatment (i.e., after discontinuation of enoxaparin at day 6 to 14) cannot be separated from the treatment effect during the 6 to 14 days of enoxaparin active control period.

- The primary analysis of the primary efficacy endpoint did not reach the statistical significance. Therefore all subsequent analyses are exploratory.

- The population of patients with D-dimer ≥ 2 x ULN or Age ≥ 75 years old is over sampled in the APEX study compared with general population in practice. Analysis results showed heterogeneous efficacy in the enriched population vs. the non-enriched population. Interpretation of the efficacy results may need to take the sub-cohorts of the study population into consideration.

Discussion:
FDA currently believes that the mITT population is suitable for data analysis.

Chemistry, Manufacturing and Controls (CMC)

- The proposed acceptance criteria for impurity F in the drug substance specification is NMT (b) (4)%. Impurity F has been identified as potentially mutagenic and the proposed acceptance criterion is therefore not acceptable. We refer you to Table 3.2.S.4.5-12 (Related Substance Results for Clinical Betrixaban Lots) of your original submission. In this table we note that the results for the 7 clinical batches ranged from < (b) (4)% to (b) (4)% for impurity F. Accordingly, revise the acceptance criterion for impurity F to NMT (b) (4)% based on the content of this impurity in Lot A5004, which was used in the qualification studies.

Discussion:
Portola agrees to revise the acceptance criterion for impurity F to no more than (b) (4)%. The rationale that impurity F is potentially mutagenic will be provided by the FDA to Portola.

Safety

- The CSR for APEX study did not include summary safety results for the sub-group of all patients who received a dose reduction (40 mg) for the primary and secondary safety endpoints.

- There were no analyses presented of the effect of the drug withdrawal (rebound effect).

Discussion:
There was no discussion.

3. Review Plans

Clinical Site Inspection Updates

- The final inspection classification status is pending.

Product Quality Inspection Updates

- All inspections are complete and at this time there are no outstanding issues identified that will affect the approval of this application.

Discussion:
There was no discussion.

4. Wrap-up and Action Items

- The Applicant and FDA to conclude labeling discussions by May 5, 2017.

- There is no PMR/PMC identified to date.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Discussion:
The Agency and Portola agree there will be further review of the labeling pending response from Portola with additional safety/PK data.

Action Items/Description	Owner	Due Date
The rational for impurity F to be potentially mutagenic will be provided by the FDA.	FDA	May 5, 2017
Portola to provide additional safety data in patients with severe renal impairment or patients utilizing concomitant p-glycoprotein inhibitors.	Sponsor	May 8, 2017

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/s/

KATHY M ROBIE SUH
05/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

LATE CYCLE MEETING
BACKGROUND PACKAGE

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

Dear Ms. Castillo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for betrixaban capsule, 40 mg and 80 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 28, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at thomas.iype@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Thomas Iype, PharmD, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	April 28, 2017; 11:00 AM – 12:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	NDA 208383
Product Name:	Betrixaban capsule
Indication:	Betrixaban is a factor Xa inhibitor indicated for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.
Applicant Name:	Portola Pharmaceuticals, Inc.

FDA ATTENDEES (tentative)

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, MD, Director

OHOP/Division of Hematology Products
Ann T. Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Saleh Ayache, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Thomas Iype, PharmD, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Shwu-Luan Lee, PhD, Pharmacologist

Office of New Drug Products/Division of New Drug Products I – Branch II
Anamitro Banerjee, Acting CMC Branch Chief
Sherita McLamore-Hines, PhD, Acting Quality Assessment Lead

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPH, Statistical Team Leader
Xin Gao, PhD, Statistical Reviewer

Office of Scientific Investigations/Good Clinical Practice Assessment Branch
Min Lu, MD, MPH, Medical Officer

Office of Clinical Pharmacology
Florian Jeffry, PhD, Pharmacometrics Team Leader, Division of Pharmacometrics
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology I (DCPI)
Lars Johannesen, PhD, Clinical Pharmacology Reviewer, DCPI

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

    - Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 45 minutes

Clinical Pharmacology

- The benefit-risk assessment for patients receiving 40 mg (either based on severe renal impairment [CrCl < 30 mL/min] or concomitant use of a P-gp inhibitor) suggests an increased risk for bleeding (major or clinically relevant non-major [CRNM] bleeding; betrixaban: 4.8% vs enoxaparin: 1.4%) without an efficacy benefit (symptomatic and asymptomatic VTE events; betrixaban 7.0% vs enoxaparin: 6.7%) compared to enoxaparin. The available data does not support that an improvement in the benefit-risk could be achieved by altering the dose for patients who prospectively received 40 mg. Given this observation in this prospectively dose-reduced subgroup, a limitation of use is proposed for use of betrixaban in patients with severe renal impairment or who require concomitant use with P-gp inhibitors.

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Clinical

- (b) (4) The treatment durations in the two treatment arms are not comparable (Betrixaban up to 35-42 days vs. Enoxaparin up to 10 ± 4 days). (b) (4) the enoxaparin control arm used in the study is adequate to establish efficacy of betrixaban, (b) (4) (b) (4)

Statistical

- The proposed claim about extended effect cannot be confirmed. The occurrence of asymptomatic proximal DVT was detected by ultrasound and determined only on or before Day 47. Therefore, the APEX study did not provide sufficient data for adequate assessment of the time course of the treatment effect, and the beneficial effect of extended treatment (i.e., after discontinuation of enoxaparin at day 6 to 14) cannot be separated from the treatment effect during the 6 to 14 days of enoxaparin active control period.

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Safety

- The CSR for APEX study did not include summary safety results for the sub-group of all patients who received a dose reduction (40 mg) for the primary and secondary safety endpoints.

- There were no analyses presented of the effect of the drug withdrawal (rebound effect).

3. Review Plans – 5 minutes

FDA plans to take action in accordance with the PDUFA goal data of June 24, 2017.

Clinical Site Inspection Updates

- The final inspection classification status is pending.

Product Quality Inspection Updates

- All inspection are complete and at this time there are no outstanding issues identified that will affect the approval of this application.

4. Wrap-up and Action Items – 5 minutes

- The Applicant and FDA to conclude labeling discussions by May 5, 2017.

- There are no PMR/PMC identified to date.

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/s/

ALBERT B DEISSEROTH
04/13/2017