

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208383Orig1s000

PRODUCT QUALITY REVIEW(S)



**METHOD VERIFICATION
REPORT SUMMARY**

Date: March 20, 2017

To: Sithamalli Chandramouli, Drug Substance Reviewer
Olen Stephens, Drug Product Reviewer
Sherita McLamore-Hinew, CMC Lead
Rabiya Laiq, RBPM

Through: Jason Rodriguez, Ph.D., Lab Chief, CDER/OPQ/OTR/DPA

From: Priyanka Chitranshi, Ph.D. Chemist, CDER/OPQ/OTR/DPA
Michael E. Hadwiger, Ph.D. Chemist, CDER/OPQ/OTR/DPA
Anjanette P. Smith, Ph.D. Chemist, CDER/OPQ/OTR/DPA
Laura Pogue, Ph.D., Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 208383: BevyxXa (Betrixaban) Immediate Release capsules 40 mg and 80 mg dosage units

The following methods were evaluated and are acceptable with modifications for quality control and regulatory purposes:

1. CRLC3998 HPLC: Drug substance assay and related substances by HPLC
2. CRIC2853^{(b) (4)}: Content of ^{(b) (4)}
3. CTMLP2893: Determination of Betrixaban and Related Substances in Betrixaban Maleate Immediate Release Capsules by HPLC.

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods:

1. CRLC3998 HPLC: Drug substance assay and related substances by HPLC:
 - a) ^{(b) (4)}. The observed impurities in the drug substance were determined to be well within the specifications provided by the vendor.
 - b) The procedure for preparation of a 0.05% w/w LOQ solution is unclear. If prepared as

currently written, the result would be a 0.005% w/w solution.

The preparation of this solution should be amended to (b) (4) to obtain a 0.05% solution.

2.

(b) (4)

(b) (4) The samples analyzed met the applicant's specification. We recommend the applicant to revise the analytical method with the new equation.

3. CTMLP2893: Determination of Betrixaban and Related Substances in Betrixaban Maleate Immediate Release Capsules by HPLC

a) The applicant's function for the determination of %label claim (%LC) for potency and content uniformity of the drug product does not yield correct value and requires correction. (b) (4) used in the method are not applicable (b) (4).

(b) (4)

- b) The test for content uniformity for the Betrixaban 80 mg capsules (n=10) did not meet the specifications for L1 (acceptance value (AV) (b) (4)). Additionally, 1 out of 10 samples analyzed did not meet the specifications for lower limit of L2 range (b) (4). Therefore, according to USP<905>, the next 20 units of Betrixaban 80 mg capsules were tested for content uniformity. The samples (n=30) met L1 criteria (AV= (b) (4)), however one out of the 30 samples tested did not meet the lower limit of L2 range (b) (4) (the outlier from initial 10 tested).

A check analysis for the content uniformity test for Betrixaban 80 mg capsules (n=10) was performed by another analyst. The samples for check analysis met the L1 and L2 criteria for content uniformity.

Although no determinant lab error was reported, the possibility cannot be completely discounted, therefore even though one capsule did not meet the L2 specifications for content uniformity, DPA considers the risk of obtaining a sub-potent capsule as low (i.e. 1 in 40).

c)

(b) (4)

Summary of Analysis

1. CRLC3998_HPLC: Drug substance assay and related substances by HPLC

Table 1. Summary of results of the Betrixaban maleate drug substance assay by HPLC

Specification	Observations	Results
	(b) (4)	
Purity % (area)		(Acceptance criteria: Not specified)
Identity by HPLC		Pass (Acceptance criteria: Consistent with reference standard (RRT= (b) (4)))
Total related substances		Pass (Acceptance criteria : (b) (4)%)
Each of impurities A,E,F,I,K or L		Pass (Acceptance criteria : (b) (4)%)
Impurity C		Pass (Acceptance criteria : (b) (4)%)
Impurity J		Pass (Acceptance criteria : (b) (4)%)
Each of D or R		Pass (Acceptance criteria (b) (4)%)
Each of M or Q		Pass (Acceptance criteria : (b) (4)%)
S		Pass (Acceptance criteria : (b) (4)%)
Each unknown		Pass (Acceptance criteria : (b) (4)%)
Assay (b) (4) by HPLC (%w/w)		(Acceptance criteria: Not specified)
Assay (b) (4) by HPLC		Pass (Acceptance criteria: (b) (4) w/w)

2. CRIC2853 (b) (4) Content of (b) (4)

(b) (4)

3. CTMLP2893: Determination of Betrixaban and Related Substances in Betrixaban Maleate Immediate Release Capsules by HPLC

NDA 208383

Table 3. Summary of data obtained for Betrixaban 40 mg and 80 mg dosage units

Test	Data	Specifications	Results
Potency (40 mg)	Sample 1: (b) (4) % Sample 2: (b) (4) %	(b) (4) %	Pass
Content Uniformity (USP <905>)	40 mg capsules (n=10): L1 = (b) (4) % L2= (b) (4) %	L1 = (b) (4) % (maximum allowed acceptance value)	L1 = Pass L2 = Pass
	80 mg capsules (n=30):* L1 = (b) (4) %; L2low (b) (4) % L2high= (b) (4) %	L2 = (b) (4) % (Maximum allowed deviation range for each dosage unit)	L1 = Pass L2low = Fail L2high=Pass
%related substances	Sample solution 1. (b) (4) % (total impurities) Sample solution 2. (b) (4) % (total impurities)	Total impurities: (b) (4) % Impurity J (b) (4) %	Pass

*One out of 30 units tested failed the L2 range of (b) (4) %. A check analysis for content uniformity of Betrixaban Maleate IR capsules, 80 mg was performed by another analyst (Table 4)

Table 4. Results for check analysis of Betrixaban Maleate IR capsules, 80 mg

L1	(b) (4)	Specifications: L1 = (b) (4) % (maximum allowed acceptance value)	Pass
L2low	(b) (4)	Specifications: L2 = (b) (4) % (maximum allowed deviation range)	Pass
L2high	(b) (4)		Pass

Original analyst worksheets can be viewed using this ECMS link:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88105247b>

Recommendation: APPROVAL

NDA 208383

Review #1

Drug Name/Dosage Form	Betrixban Capsules
Strength	40 and 80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Portola Pharmaceutical, Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission		All
Amendment (SD 27)	09-Mar-17	DP, DS
Amendment (SD 26)	07-Mar-17	DS
Amendment (SD 25)	07-Mar-17	DP
Amendment (SD 21)	16-Feb-17	DS, DP
Amendment (SD 20)	03-Feb-17	DP
Amendment (SD 17)	19-Jan-17	DP
Amendment (SD 30)	16-Mar-17	DP, DS
Amendment (SD 36)	05-May-17	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sithamalli Chandramouli	Benjamin Stevens
Drug Product	Olen Stephens	Anamitro Banerjee
Process	Bogdan Kurtyka	Diane Goll
Microbiology	n/a	n/a
Facility	Laura Fontan	Ruth Moore
Biopharmaceutics	Gerlie Gieser	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	Anamitro Banerjee
Laboratory (OTR)		
ORA Lead		



QUALITY ASSESSMENT



Environmental	Olen Stephens	Anamitro Banerjee
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Appears this way on original

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Compendial-Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information

						provided in the NDA	
(b) (4)	Type III	(b) (4)			N/A	No Review	Adequate information provided in the NDA
	Type III				N/A	No Review	Adequate information provided in the NDA
	Type II				N/A	No Review	Compendial-Adequate information provided in the NDA
	Type III				N/A	No Review	Adequate information provided in the NDA
	Type III				N/A	No Review	Adequate information provided in the NDA
	Type III				N/A	No Review	Adequate information provided in the NDA
	Type II				N/A	No Review	Compendial-Adequate information provided in the NDA

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	072679	Betrixaban Capsules

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 208383 for BevyxXa™ (betrixaban) capsules, 40 and 80 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored at (b) (4) and a 24-month drug product expiration period when stored a USP controlled room temperature conditions 20°C to 25°C (68°F to 77°F). There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

Betrixaban is a small molecule, factor Xa (FXa) inhibitor indicated for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE. Betrixaban is expected to provide significant improvement in therapeutic options by making a safe and effective oral prophylaxis available to reduce morbidity and mortality in this patient population. The drug product is presented as 40 and 80 mg immediate release capsules. Betrixaban was originally investigated under IND (b) (4) 72679 (b) (4). It is a NME intended to treat an unmet medical need as there is no approved or guideline-recommended anticoagulant therapy currently available. FDA granted Fast Track designation in October 2015 and priority review to address this unmet medical need.

The dosing regimen for Betrixaban consists of an initial dose of 160 mg, followed by 80 mg once daily with food. For patients receiving the P-gp inhibitors (b) (4) (b) (4) the dose should be reduced to an initial dose of 80 mg followed by 40 mg once daily with food.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 208383 and grants a (b) (4) month re-test period for the drug substance and a 24-month expiration period for the commercial drug product when stored under controlled room temperature (b) (4)

Proposed Indication(s) including Intended Patient Population	Extended venous thromboembolism (VTE) prophylaxis in an acutely ill medical population with additional risk factors for VTE
Duration of Treatment	35-42 days
Maximum Daily Dose	160 mg

Alternative Methods of Administration	None
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B. Quality Assessment Overview

Drug Substance

Betrixaban drug substance is a white to pale yellow crystalline non-hygroscopic solid with no chiral centers. Betrixaban exhibits polymorphic behavior (b) (4) was developed and the agency agreed with the control strategy proposed by the applicant during the Pre-NDA stage.

The drug substance is synthesized as the maleate salt (b) (4). The specifications for starting materials, reagents and solvents are appropriate to adequately ensure the quality of the drug substance. The process development for the manufacture of the drug substance has been strengthened by DOE studies. Five batches of betrixaban were manufactured using the proposed commercial synthesis – two on (b) (4) kg scale and three at the expected commercial scale to produce (b) (4) kg of the drug substance. The drug substance has been adequately characterized. The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control.

The applicant was asked to revise the acceptance criterion for impurity F to NMT (b) (4) % based on the content of this impurity in Lot A5004. The updated drug substance specification provided by the applicant was found acceptable (see drug substance review addendum dated 05/09/17 attached below).

The drug substance is stored in (b) (4). Stability studies demonstrate that the drug substance is stable over the proposed retest period. Accordingly, the applicant's proposed (b) (4) *month retest date* for the drug substance is granted.

Drug Product

The drug product is presented as 40 and 80 mg immediate release, hard gelatin capsules containing the active, dextrose monohydrate, croscarmellose sodium, and magnesium stearate. The 40 mg capsules are size 4 gray (b) (4)/light blue hard gelatin capsules printed with 40 in black on the body and PTLA in white on the cap. The 80 mg capsules are size 2 gray (b) (4)/blue hard gelatin capsules printed with 80 in black on the body and PTLA in white on the cap.

Betrixaban 40 and 80 mg capsules (b) (4) are manufactured, packaged and release tested by (b) (4) at a commercial batch size of (b) (4) kg (which translates to (b) (4) capsules) for the 40 mg strength and a commercial batch size of (b) (4) kg (which translates to (b) (4) capsules) for the 80 mg strength. The drug product will be packaged in HDPE bottles (b) (4) 100 count) (b) (4).

The proposed specifications for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product.

The Applicant provided twelve months of long-term and six month of accelerated stability data for the registration batches packaged in (b) (4) in HDPE bottles (b) (4). The stability protocol includes a bracket for the bottle configurations and a statistical analysis for the lots packaged in (b) (4). The applicant also included forced degradation studies. The results of the forced stability studies revealed that the product is sensitive to basic and acidic conditions. The available stability data together with the statistical analysis supports the requested ***24 month shelf-life when stored under controlled room temperature.***

Process

(b) (4)
The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

Biopharmaceutics

Bridging data were not required for this NDA as the commercial drug product has the same composition and manufacturing process as the drug product evaluated in the pivotal Phase 3 Clinical trial (APEX) and the primary stability batches. The drug substance has high solubility/low permeability and the drug product is very rapidly dissolving in the QC dissolution medium with no evidence of pH-dependent dissolution. The reviewer noted that changes in various drug substance manufacturing process and other quality attributes had no impact the dissolution profile of the drug product. The proposal to (b) (4) is not expected to impact the performance of the drug product.

The proposed dissolution method (USP Apparatus 2 (paddle) at 75 rpm,) is acceptable.

Facilities

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208383 are found to be acceptable.

Environmental Assessment

The applicant is submitting a New Drug Application pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, which if approved, will increase the use of the active moiety, betrixaban. However, a claim for categorical exclusion from conducting an environmental impact statement (EIS) or environmental assessment (EA) is made

under 21 Code of Federal Regulations (CFR) Sections 25.31(b) on the basis that estimated concentration of the active moiety into the aquatic environment is less than 1 part per billion (ppb).

The claim of categorical exclusion from an environmental assessment is valid since the estimated increase usage of the active moiety is well below the allowable EIC of 1 part per billion (ppb).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)



Sherita
McLamore

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DRUG SUBSTANCE

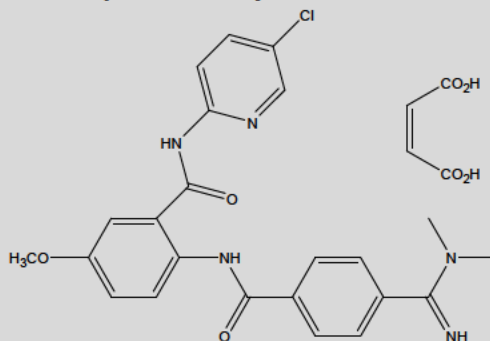
Product Background: BevyxXa™ (betrixaban capsules 40 and 80 mg) is a treatment for extended prophylaxis of venous thromboembolism (VTE) in acutely ill medical population. It will be marketed as a prescription product. It has been granted priority review status. The recommended dose of BevyxXa™ is an initial single dose of 160 mg followed by 80 mg once daily. The recommended duration of treatment is 35 to 42 days. The active pharmaceutical ingredient is betrixiban (United States Adopted Name) as the maleate salt (molecular weight 567.98). The manufacturer of betrixaban is (b) (4)

Betrixaban is a small molecule inhibitor of human plasma-derived factor Xa (fXa) that has a benzamidine portion in its structure.

The drug development information can be found IND 072679

NDA/ANDA: NDA 208383

Chemical Name and Structure: N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide maleate



DMF # (if applicable): NA

Applicant Name/DMF Holder: Portola Pharmaceuticals Inc.

Review Summary: The drug substance is synthesized in (b) (4). The specifications for starting materials, reagents and solvents are appropriate to adequately ensure the quality of the drug substance. The process development for the manufacture of the drug substance has been strengthened by DOE studies. Five batches of betrixaban have been manufactured using the proposed commercial synthesis – two on (b) (4) kg scale and three at the expected commercial scale to produce (b) (4) kg of the drug substance. The drug substance has been adequately characterized. The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control. The stability studies show the drug substance to be stable over the proposed retest period.

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Ben
Stevens

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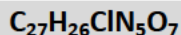
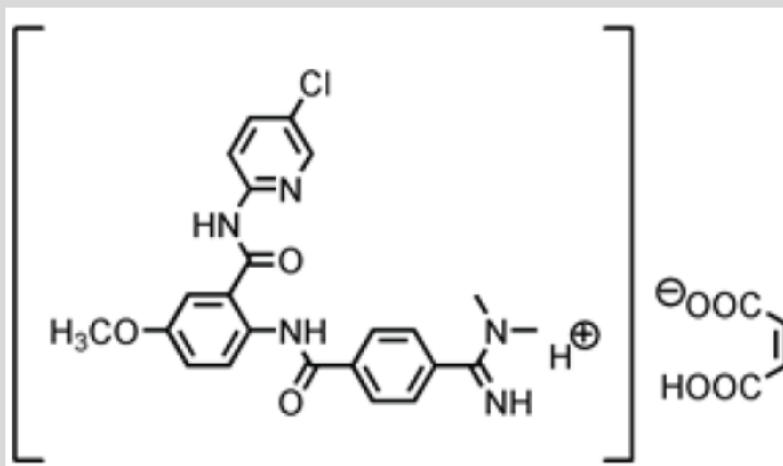


Sithamalli
Chandramouli

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DRUG PRODUCT**Product Background:**

Betrixaban is a factor Xa (fXa) inhibitor indicated for extended venous thromboembolism (VTE) prophylaxis in an acutely ill medical population with additional risk factors for VTE. Betrixaban was granted Fast Track Designation 2-Oct-15; betrixaban has the chemical name N-(5-chloropyridin-2-yl)-2-[4-(N,N-dimethylcarbamimidoyl)-benzoylamino]-5-methoxybenzamide maleate; the laboratory codes are PRT054021, MLN1021, MK-4448, and CT054021; the USAN and INN is betrixaban. Betrixaban drug substance is an off-white to yellow solid, (b) (4). The drug substance does not contain chiral centers and (b) (4) polymorphic forms have been produced; (b) (4) is used for formulating the commercial drug product and was used in the Phase 3 clinical studies. The applicant claims only (b) (4) and the drug substance reviewer has confirmed this claim (refer to the drug substance review). Additionally, the applicant claims the polymorphic form and particle size does not impact dissolution profiles (refer to the biopharmaceutics review for confirmation). No hydrates or solvates have been observed. Betrixaban is not significantly hygroscopic. The drug substance is soluble in pH ranges 1.5 – 6.5.



MW = 451.91 g/mol (free base)

MW = 567.98 g/mol (maleate salt)

CAS: 330942-05-7

BevyxXa™ (betrixaban) 40 and 80 mg capsules are submitted under NDA 208-383, which cross references IND 72,679 for developmental data. The 40 mg capsules are gray (b) (4) /light blue (b) (4) size 4 hard gelatin capsules with “40” printed in black, axially on the body and “PTLA” printed in white, axially on the cap. The 80 mg capsules are gray (b) (4) light blue (b) (4) size 2 hard gelatin capsules with “80” printed in black, axially on the body and “PTLA” printed in white, axially on the cap. (b) (4)



Anamitro
Banerjee

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Olen
Stephens

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LABELING

R Regional Information

1.14 Labeling

(b) (4)

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Reviewer's Assessment: Adequate with changes.

Reviewer's Assessment: NA

List of Deficiencies:

1.
2.

(b) (4)

3. *In the Package Insert under section 11, include the hard gelatin capsule as one of the inactive ingredients.*

The applicant responded 16-Feb-17 in amendment 0021,

(b) (4)

The artwork utilized an artwork template that has since been updated. Updated mock-ups will be provided with representative artwork using a current artwork template in a future regulatory submission to NDA 208383 Section 1.14.2."

Edits to the carton and container and package insert were communicated through the clinical division. These comments are generally not sent until after the OPQ review is due. These changes to the labels will be finalized in conjunction with the clinical division

Primary Labeling Reviewer Name and Date: Olen M. Stephens; 1-Feb-17

Secondary Reviewer Name and Date: Anamitro Banerjee; 13-Mar-17



Anamitro
Banerjee

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Olen
Stephens

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PROCESS**Product Background:****NDA: 208383****Drug Product Name / Strength: Betrixaban Capsules, 40 mg and 80 mg****Route of Administration: Oral****Applicant Name: Portola Pharmaceuticals Inc.*****Review Summary:*****List Submissions being reviewed (table):**

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Sequence 0001: Original NDA	10/24/2016
Sequence 0021: Quality/Response to IR	02/16/2017

Highlight Key Outstanding Issues from Last Cycle: N/A**Concise Description Outstanding Issues Remaining:**

(b) (4)

P.3 Manufacture

(b) (4)



Bogdan
Kurtyka

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Diane
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ASSESSMENT OF THE FACILITIES

Product Background:

NDA: 208383

Drug Product Name / Strength: Betrixaban hard gelatin capsules, 40 mg and 80 mg

Route of Administration: Oral

Applicant Name: Portola Pharmaceuticals Inc.

Review Summary:

All facilities are acceptable for the responsibilities listed in NDA 208383.

List Submissions being reviewed (table): NDA 208383 ORIG-1

2.3.S.2 Drug Substance Manufacture

Summary of Facility Information:

(b) (4)



Ruth
Moore

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Laura
Fontan

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BIOPHARMACEUTICS**Product Background:****NDA:** 208383-ORIG-1**Drug Product Name / Strength:** BevyxXa™ (betrixaban maleate) Oral Capsule, Hard Gelatin (40 mg, 80 mg)**Route of Administration:** Oral**Applicant Name:** Portola Pharma, Inc.**Review Summary:**

- The approved dissolution method and the agreed upon dissolution acceptance criterion for BevyxXa™ (betrixaban maleate) Oral Capsules are summarized in the table below.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddles) with sinker	75 rpm	0.01 N HCl, pH 2 (with addition of pepsin if gelatin crosslinking is suspected) (37 ± 0.5°C)	900 mL	$Q = \frac{(b), (4)}{(4)}\%$ at <u>15 min</u>

- Bridging data were not needed because the to-be-marketed drug product has the same composition and manufacturing process as the drug product evaluated in the pivotal Phase 3 Clinical trial (APEX), and the primary stability batches. The drug substance is highly soluble and the drug product is very rapidly dissolving in the QC dissolution medium with no evidence of pH-dependent dissolution. In addition, changes in various drug substance manufacturing process/other quality attributes did not impact the dissolution profile of the drug product. The proposal to (b) (4) is not therefore anticipated to impact the performance of the drug product.

From a Biopharmaceutics perspective, NDA 208-383 for BevyxXa™ (betrixaban maleate) Oral Capsule is recommended for APPROVAL.

List Submissions being reviewed:

SDN-1, 10/24/2016 (Original NDA Submission)

SDN-21, 2/16/2017 (Response to FDA Information Request 2/1/2017)

Highlight Key Outstanding Issues from Last Cycle:

Not Applicable (First Cycle Review)

Concise Description of Outstanding Issues:

None

BCS Designation**Reviewer's Assessment:**

A BCS designation was not formally requested for the proposed drug product, although the Applicant considers betrixaban as a BCS-3 (high solubility/low permeability) drug substance. Betrixaban maleate is a highly soluble drug substance, i.e., at least 1.45 mg/mL dissolves in various pH media at room temperature. Thus, the highest dose strength 80 mg (as well as the maximum betrixaban [160 mg once daily] dose of the proposed BevyxXa® capsule is anticipated to completely dissolve in 250 mL volume of dissolution media (across the physiologic pH range) at 37 °C. BevyxXa® capsules exhibit very rapid dissolution, i.e., at least 85% of the labeled amount of the drug is dissolved in the QC dissolution medium (0.01 N HCl).

Solubility: Per BCS criteria, the drug substance exhibits *high solubility* across the physiologic pH range. At least 1.45 mg/mL of betrixaban maleate dissolves over pH 1 – 7.4 at room temperature; see Table 3.2.S.3.1-6.

Permeability: The proposed labeling states that only 34% of the orally administered (80 mg) dose was absorbed. Per the Applicant, the Caco-2 apical-to-basolateral permeability (P_{app}) of betrixaban is 1×10^{-6} cm/s.

Dissolution: At batch release, all pivotal clinical trial batches and primary stability lots exhibited *very rapid dissolution*, i.e., at least 85% of the drug dissolves within 15 minutes in the proposed QC dissolution medium (0.01N HCl).

Dissolution Method and Acceptance Criterion**Reviewer's Assessment:****Dissolution Method - ACCEPTABLE**

(b) (4)

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Dissolution Acceptance Criteria – ACCEPTABLE

Based on dissolution profile data of historical drug product batches that had passed dissolution testing by Stage 2 testing, the Applicant's proposed QC dissolution acceptance criterion is 'Q = (b) (4) % at (b) (4) min' at batch release and during stability testing.

Based mainly on the *in vitro* dissolution profile data of the pivotal Phase 3 clinical lots, as well as that of a Phase 2 clinical lot with comparable *in vivo* PK, the Reviewer's recommended QC dissolution acceptance criterion is 'Q = (b) (4) % at 15 min' for the routine QC testing at batch release and during shelf-life of BevyxXa® capsules 40 mg and 80 mg. Note that the Reviewer's recommended dissolution specification time point of 15 minutes (but not the Applicant's proposed specification time point of (b) (4) min) for the Q of (b) (4) % would be adequate to fail at batch release the aberrant developmental batch # A08820-25 which was manufactured (b) (4) (b) (4) see Figure 1 above).

All Phase 3 clinical lots [as well as primary stability lots] exhibited 'very rapid dissolution', i.e., with at least 85% [or 83%] mean cumulative dissolution at 15 min in QC dissolution medium without added enzyme; n = 6 to 12 units) at batch release and up to 36 months [or up to 12 months] of long-term (25°C/60%RH) storage.

In the 3/7/2017 response to the Biopharmaceutics information request dated 3/2/2017, the Applicant agreed to revise the QC dissolution acceptance criterion to 'Q = (b) (4) % at 15 min' at batch release and during stability testing of both strengths of the betrixaban capsules. The Finished Drug Product Specification Table, and other pertinent NDA documents were revised accordingly.

Bridging of Formulations**Reviewer's Assessment: ADEQUATE**

Bridging data are not needed. The proposed commercial drug product has the same formulation (#5), manufacturing process (#2), manufacturer (b) (4) container-closure system, and used the same API (b) (4) as the capsules [40 mg- J7102, J7123, and L7159; 80 mg - J7103, J7124, and L7160] used in the pivotal Phase 3 Clinical trial (APEX), and the primary stability batches [40 mg -M7182, M7184, and M7186; 80 mg - M7183, M7185, and M7187]. Note that the two capsule strengths are (b) (4). For the PK parameters of the Phase 3 clinical drug product, i.e., following single dose administration of the 80 mg capsule in healthy subjects, refer to the findings of Study 15-020 in the Clinical Pharmacology review.

Note that during the 2012 End-of-Phase 2 CMC meeting, FDA agreed that the addition of (b) (4) on the proposed commercial capsule is not expected to impact drug release and other stability data. This Reviewer agrees that bridging data to support this (b) (4) (b) (4) are not needed, when considering that (1) the drug substance is highly soluble across the physiologic pH range, (2) the drug product is very rapidly dissolving, i.e., >85% dissolves within 15 min in the QC dissolution medium (0.01 N HCl), as well as in simulated gastric fluid; dissolution media pH did not impact the dissolution profile of the betrixaban maleate (b) (4) and (3) more potentially critical quality attribute changes (b) (4) were not shown to alter the 'very rapid dissolution' profile of the drug product in the QC dissolution medium.

Two of the 3 drug substance lots used in the manufacture of the primary registration lots were used for the manufacture of the Phase 3 clinical lots.

Biowaiver Request

Reviewer's Assessment: NOT APPLICABLE

Both 40 mg and 80 mg strengths of the proposed drug product were evaluated in pivotal Phase 3 clinical trials. Thus, a biowaiver request is not needed for any of the proposed commercial strengths.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (3/8/2017)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Okpo Eradiri, PhD (3/8/2017)



Gerlie
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