CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208383Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	208383
PDUFA Goal Date	June 24, 2017
OSE RCM #	2016-2478, 2016-2481
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader (Acting)	Doris Auth, Pharm.D., Associate Director (Acting)
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	March 23, 2017
Subject	Evaluation of Need for a REMS
Established Name	Betrixaban
Trade Name	Bevyxxa
Name of Applicant	Portola Pharmaceuticals, Inc.
Therapeutic Class	Factor Xa inhibitor
Formulation(s)	40 mg and 80 mg capsules
Dosing Regimen	160 mg orally one dose, then 80 mg orally once daily

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EXECUTIVE SUMMARY

This review by Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Bevyxxa (betrixaban) is necessary to ensure the benefits outweigh its risks. Portola Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 208383 for betrixaban with the proposed indication for the prophylaxis of venous thromboembolism (VTE) in adult patients during hospitalization 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 risks associated with betrixaban include serious and potentially fatal bleeding. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Hematology Product (DHP) agree that a REMS is not needed to ensure the benefits of betrixaban outweigh its risks. Betrixaban, if approved, will be the fourth-in-class, factor Xa inhibitor, after rivaroxaban, apixaban, and edoxaban. Betrixaban, as with other factor Xa inhibitors, can cause serious and potentially fatal bleeding. The risk of bleeding with betrixaban is consistent with the other drugs in the same class.

The risk of bleeding associated with the use of betrixaban is communicated in the Warnings and Precautions (Section 5) of the proposed labeling. The risk of epidural or spinal hematomas in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture will be communicated in a boxed warning, consistent with labeling in the other factor Xa inhibitors. Based on clinical experiences with the existing three factor Xa inhibitors, prescribers most likely to prescribe betrixaban should be familiar with the reported safety risks associated with this class of drug products.

The factor Xa inhibitors rivaroxaban and apixaban, as well as the direct thrombin inhibitor dabigatran, were approved with REMS that were subsequently released based on post marketing safety and acceptable REMS assessment reports. Edoxaban, the third factor Xa inhibitor was approved in January 2015 without a REMS.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Bevyxxa (betrixaban) is necessary to ensure the benefits outweigh its risks. Portola Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 208383 for betrixaban with the proposed indication for the prophylaxis of venous thromboembolism (VTE) in adult patients during hospitalization 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. This application is under review in the DHP. The applicant did not submit a proposed REMS for risk management plan with this application.

2. BACKGROUND

2.1 PRODUCT INFORMATION

Bevyxxa (betrixaban) is an NME,[a] with the proposed indication for the prophylaxis of VTE in adult patients during hospitalization 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. This application is under review in the DHP. Betrixaban is available as 40 mg and 80 mg capsules to be given orally once daily for 35-42 days.[b] The recommended dose of betrixaban is an initial single dose of 160 mg, followed by 80 mg once daily. Betrixaban is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for [Application/Number] relevant to this review:

- January 22, 2014: Type C meeting for phase 3 APEX study of betrixaban (IND 072679)
- October 2, 2015: Fast track designation granted.
- May 11, 2016: pre-NDA meeting.
- October 20, 2016: NDA 208383 submitted.
- December 20, 2016: Priority review granted, PDUFA goal date is June 24, 2017.
- February 7, 2017: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data; there were no safety issues that require a REMS for betrixaban. There is no plan for an Advisory Committee meeting.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Venous thromboembolism (VTE) is categorized by the United States General as a major public health problem. VTE is relatively common and associated with reduced survival and substantial health-care costs, and recurs frequently. Hospitalized medical patients have a high risk for VTE. Recent studies[1] suggest that 5-15% of medical patients who do not receive appropriate prophylaxis develop objectively confirmed deep venous thrombosis (DVT). Up to 75% of fatal pulmonary embolism (PE) cases occur in hospitalized medical patients, and VTE is associated with considerable long-term morbidity and substantial consumption of hospital resources.

3.2 Description of Current Treatment Options

Options for anticoagulation have been expanding over the last few decades. In addition to heparins and vitamin K antagonists, anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have been developed. Direct thrombin inhibitors (DTIs) prevent thrombin from cleaving fibrinogen to

[a] Section 505-1 (a) of the FD&C Act*: FDAAA factor (F) Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act*: FDAAA factor (D) The expected or actual duration of treatment with the drug.*

fibrin. Parental DTIs include bivalirubin, argatroban, and desirudin. The only oral DTI available is dabigatran.[2]

Factor Xa inhibitors bind directly to factor Xa, and prevent factor Xa from cleaving prothrombin to thrombin. There are no parental factor Xa inhibitors in clinical use, however, several oral agents are available. Table 1 summarizes information on the approved the oral direct thrombin and factor Xa inhibitors.

Table 1 Approved oral direct thrombin and factor Xa inhibitors.

Trade Name (Generic), Approval date	Mechanism of Action	REMS	Important Safety Issues	Boxed Warning
Pradaxa (dabigatran) 10/19/2010	direct thrombin inhibitor	Medication Guide only- REMS released 4/5/2014	a) can cause serious and fatal bleeding b) Bioprosthetic heart valve: Pradaxa use not recommended	a) premature discontinuation of pradaxa increases the risk of thrombotic events b) Spinal/Epidural Hematoma: epidural or spinal hematomas may occur in patients treated with pradaxa who are receiving neuraxial anesthesia or undergoing spinal puncture
Xarelto (rivaroxaban 11/1/2011	factor Xa inhibitor	REMS with communication plan, REMS released 2/14/2014	a) can cause serious and fatal bleeding b) Bioprosthetic heart valve: Xarelto use not recommended	a) premature discontinuation of Xarelto increases the risk of thrombotic events b) Spinal/Epidural Hematoma (same as Pradaxa)
Eliquis (apixaban) 12/28/2012	factor Xa inhibitor	REMS with communication plan, REMS released 3/17/2016	a) can cause serious and fatal bleeding b) prosthetic heart valve: Eliquis use not recommended	a) premature discontinuation of Eliquis increases the risk of thrombotic events b) Spinal/Epidural Hematoma (same as Pradaxa)
Savaysa (edoxaban) 1/8/2015	factor Xa inhibitor	no REMS	a) can cause serious and fatal bleeding b) mechanical heart valve or moderate to severe mitral stenosis: Savaysa use not recommended	a) Reduced efficacy in nonvalvular atrial fibrillation patients with creatinine clearance >95 ml/min b) premature discontinuation of Savaysa increases the risk of ischemic events c) Spinal/Epidural Hematoma (same as Pradaxa)

4 BENEFIT ASSESSMENT

The pivotal trial (APEX clinical trial) supporting this application consisted of a double-blind, placebo controlled, multicenter study which compared the safety and efficacy of extended duration of betrixaban for 35 to 42 days to short duration of enoxaparin for 6 to 14 days in the prevention of VTE in patients who are at risk for VTE due to acute medical illness. Patients were eligible if they were expected to be hospitalized for at least 3 days for a specified acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke) and anticipated to be severely immobilized for 24 hours. In addition, eligible patients needed to have any of the following

- 75 years of age or older, or
- 60 through 74 years of age with D-dimer>=2 Upper Limit of Normal (ULN), or
- 40 through 59 years of age with D-dimer >=2 ULN and a history of either VTE or cancer

A total of 7,441 patients, 3,112 in betrixaban arm and 3,174 in enoxaparin arm, were included in the primary efficacy overall population. The primary efficacy endpoint was the composite of asymptomatic proximal DVT between days 32 to 47, and symptomatic proximal or distal DVT, symptomatic nonfatal PE, or VTE-related death from day 1 to day 42. The relative risk of betrixaban arm versus enoxaparin arm was 0.697 (P value=0.002), and relative risk reduction was 0.303. The medical officer concluded that analyses showed consistent and supportive results favoring betrixaban arm.[3]

5 RISK ASSESSMENT

RISK OF BLEEDING

The safety of betrixaban was evaluated in the APEX study, including 3,716 patients treated with betrixaban for a median of 36 days compared to 3,716 patients treated with enoxaparin for a median of 9 days. The primary and secondary safety endpoints in APEX were bleeding-related events.[c] Patients in both groups were followed for bleeding events for an equal duration of approximately 43 days.

A summary of major bleed[d] and clinically relevant non-major (CRNM) bleeding[e] events in the safety population is shown in Table 2. Per medical reviewer presented at Mid-Cycle meeting, the primary safety endpoint of major bleeding was statistically insignificant between the two groups. The secondary safety endpoint of major/CRNM bleeding showed an increase in the betrixaban arm compared to the

[c] Section 505-1(a) of the FD&C Act FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

[d] Major Bleed: overt bleeding with fall in Hgb of 2 g/dL; need for RBC transfusion of >2 units; intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, intraarticular or retroperitoneal; death.

[e] Clinically relevant non-major bleeding (CRNM): Epistaxis lasting> 5 minutes; gingival bleeding lasting> 5 minutes; macroscopic hematuria; macroscopic GI bleeding or rectal bleeding of > a few spots; hemoptysis of more than a few speckles; intramuscular hematoma or subcutaneous hematoma>25 cm.

enoxaparin arm. Most CRNM events were moderate in severity, and the majority did not require or prolong hospitalization. The incidence of treatment emergent AEs in the betrixaban arm is comparable to that in the enoxaparin arm (54% versus 52%), and the mortality rate was similar in both groups (6%).

Table 2: Bleeding events through 7 days after discontinuation of all study medication

	betrixaban (N=3716)	enoxaparin (N=3716)
major		
number of patients with events/number of patients at risk	25/3716	21/3716
events rate % (95% CI)	0.67 (0.41, 0.94)	0.57 (0.32, 0.81)
P-value 0.554		
major or CRNM		
number of patients with events/number of patients at risks	116/3716	59/3716
events rate % (95% CI)	3.12 (2.56, 3.68)	1.59 (1.19, 1.99)
P-value <0.001		

Spinal/Epidural Anesthesia or Puncture

As with rivaroxaban, apixaban, and edoxaban, when neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is performed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

6 Expected Postmarket Use

Betrixaban will be administered in the in-patient setting in the beginning of treatment, (b) (4) .

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for betrixaban beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of betrixaban on the basis of the efficacy and safety information currently available.

As cited earlier in Section 4 of this review, the primary and secondary safety endpoints in APEX study were bleeding events. Betrixaban, if approved, will be the fourth-in-class factor Xa inhibitor, after rivaroxaban, apixaban, and edoxaban. Betrixaban as with other factor Xa inhibitors, is associated with the risk of bleeding and can cause serious and potentially fatal bleeding. The risk of bleeding of betrixaban is consistent with the other drugs in the same class.

The risk of bleeding is communicated in the Warning and Precautions (Section 5) of the proposed label. Based on clinical experiences with the existing three factor Xa inhibitors, prescribers most likely to prescribe betrixaban should be familiar with the reported safety risks associated with this class of drug products.

The REMS requirement for the two approved factor Xa inhibitors (rivaroxaban and apixaban) were all released. The decisions to release these product REMS were based on post marketing safety and acceptable REMS assessment reports. The REMS assessment reports demonstrated that the goals of these REMS have been adequately achieved and that there was acceptable provider understanding of the known serious risks associated with use of these products. The third-in-class factor Xa inhibitor, edoxaban, was approved in January 2016 without a REMS.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile associate with the use of betrixaban is favorable, therefore, a REMS is not necessary for betrixaban to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 REFERENCES

1 Hull RD, Extended-Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients with Recently Reduced Mobility. Ann Intern Med, 2010; 153 (1): 8-18.

2 Leung LK, Direct oral anticoagulants: Dosing and adverse effects. www.UpToDate.com, accessed March 8, 2017

3 Ayache, S. DHP, Mid-Cycle clinical presentation for betrixaban (NDA 208383), January 19, 2017

4 Proposed Prescribing Information for betrixaban (NDA APPEARS THIS WAY ON ORIGINAL

5 Yancey, CL. DRISK, REMS Review for edoxaban (NDA 206316), September 17, 2014

6 Dabigatran Prescribing Information, dated November 2015

7 Rivaroxaban Prescribing Information, dated August 2016

8 Apixaban Prescribing Information, dated July 2016

9 Edoxaban Prescribing Information, dated September 2016

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/s/

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