Formulary Drug Review: Betrixaban

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Abstract

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Keywords

anticoagulants, formulary management/P&T, critical care

Generic Name: Betrixaban
Proprietary Name: *Bevyxxa* (Portola Pharmaceuticals)
Approval Rating: 1P
Therapeutic Class: Factor Xa Inhibitors
Similar Drugs: Apixaban, Dabigatran, Edoxaban, Enoxaparin, Rivaroxaban
Sound-/Look-Alike Names: Apixaban, Baricitinib, Edoxaban

Indications

Betrixaban is approved by the US Food and Drug Administration (FDA) for 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 other risk factors for VTE.[1,2] The safety and effectiveness of betrixaban in patients with prosthetic heart valves have not been evaluated.[1] Betrixaban may also have a role in stroke prevention in patients with atrial fibrillation, and in VTE prevention following total hip or knee replacement.[3,4,5]

Table 1 summarizes the approved indications for the various oral factor Xa inhibitors.[1,6,7,8,9]

Clinical Pharmacology

Betrixaban is a direct factor Xa inhibitor anticoagulant. Betrixaban exerts its antithrombotic effect by inhibiting free and prothrombinase-bound factor Xa, an important validated target in the blood coagulation pathway, in a concentration-dependent manner.[1,3,10] Inhibition of factor Xa results in decreased thrombin generation.[1]

Pharmacokinetics

Peak plasma concentrations occur within 3 to 4 hours after oral administration of betrixaban. The oral bioavailability after a dose of betrixaban 80 mg is 34%. Absorption is affected by fatty food; peak concentration and area under the curve were decreased an average of 70% and 61%, respectively, when administered with a low-fat meal, and 50% and 48%, respectively, when administered with a high-fat meal.[1,3]

The primary route of elimination is hepatobiliary into the gut (82%-89%).[3] Following oral administration, approximately 85% of betrixaban was recovered in the feces and 11% in the urine. Metabolism by cytochrome P450 (CYP-450) enzymes is very low (less than 1%). The effective half-life is 19 to 27 hours. Apparent volume of distribution is 32 L/kg. Protein binding is 60%.[1]

Table 2 provides a comparison of select pharmacokinetic parameters for the oral factor Xa inhibitors.[1,6,7,8,9]

Comparative Efficacy

Indication: Extended-Duration Prophylaxis of VTE in Acute Medically Ill Patients

Guidelines

Guideline: Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel report

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Table 1. Approved Indications for Oral Factor Xa Inhibitors.[1,6,7,8,9]

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Brand name (manufacturer)	*Bevyxxa* (Portola)	*Eliquis* (Bristol-Myers Squibb)	*Pradaxa* (Boehringer Ingelheim)	*Savaysa* (Daiichi Sankyo)	*Xarelto* (Janssen)
Approved indications					
Prophylaxis of 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 other risk factors for VTE	X				
To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation		X	X	X	X
Prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery		X			X
Prophylaxis of DVT and PE in patients who have undergone hip replacement surgery			X		
To reduce the risk of recurrence of DVT and PE in patients who have previously been treated		X	X		X
Treatment of DVT		X			X
Treatment of PE		X			X
Treatment of DVT and PE following initial therapy			X	X	

Note. VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism.

Table 2. Select Pharmacokinetic Parameters for Oral Factor Xa Inhibitors.[1,6,7,8,9]

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Time to peak concentration	3-4 h	3-4 h	1 h	1-2 h	2-4 h
Effect of food	Decreased bioavailability	No effect	No effect	No effect	No effect with 10 mg dose Increased absorption with 20 mg dose
Metabolism via CYP-450	<1%	Major route	None	Minimal	CYP3A4/5, CYP2J2, and hydrolysis
Renal clearance	11%	27%	80%	50%	36%
Half-life	19-27 h	12 h	12-17 h	10-14 h	5-9 h
Volume of distribution (apparent)	32 L/kg	21 L	50-70 L	107 L	50 L
Protein binding (plasma)	60%	87%	35%	55%	92%-95%

Reference: American College of Chest Physicians[11]

Comments: An American College of Chest Physicians guideline and expert panel report regarding antithrombotic therapy for VTE in noncancer patients states that direct oral anticoagulants (ie, apixaban, edoxaban, dabigatran, rivaroxaban) are favored over vitamin K antagonist therapy for long-term (3 months) and extended treatment of VTE. Initial parenteral anticoagulation (ie, low-dose unfractionated heparin, low-molecular-weight heparin) should be given prior to dabigatran and edoxaban, but is

not required before administering rivaroxaban or apixaban. If a decision is made to extend treatment in VTE patients with risk factors for recurrence, the direct oral anticoagulants are effective in reducing the incidence of recurrent VTE; the same anticoagulant used for long-term treatment should be used for extended-duration treatment unless patient circumstances warrant a change in anticoagulant therapy. Betrixaban was not available when these guidelines were created.

Studies

Drug: Betrixaban versus Enoxaparin

Reference: Cohen AT, et al 2014; Cohen AT, et al 2016 (APEX trial)[1,12,13]

Study Design: Randomized, double-blind, double-dummy, active-controlled, multicenter, international study

Study Funding: Portola Pharmaceuticals

Patients: 7,513 patients 40 years and older hospitalized for a specified acute medical illness (eg, heart failure, infectious disease, respiratory failure, rheumatic disease, ischemic stroke) and who had additional risk factors for VTE were expected to be severely immobilized for 24 hours during hospitalization and moderately and/or severely immobilized for at least 4 days after study enrollment, and had an anticipated survival of at least 8 weeks. Key exclusion criteria included hospitalization for more than 96 hours prior to randomization; inability to take enteral feeding; increased risk of bleeding or history of intracranial bleeding; need for major surgery or invasive procedure; contraindications to anticoagulant therapy; and elevated liver function tests, active liver disease, or cirrhosis. Average patient age was approximately 76 years, with approximately 68% of patients aged 75 years or older; 45% were male; 93% were white; mean weight was approximately 80 kg; body mass index was approximately 29.4 kg/m^2; and median duration of hospitalization was 10 days. Two cohorts were established within the overall population: Cohort 1 included patients with elevated baseline D-dimer level at least 2 times the upper limit of normal (n = 3870), and cohort 2 included patients meeting criteria for cohort 1 plus those 75 years of age and older (n = 5735). The overall study population cohort included patients from cohorts 1 and 2 who were included in the primary efficacy outcome analysis (n = 6286).

Intervention: Patients were randomized (1:1) to receive oral betrixaban plus subcutaneous enoxaparin placebo or subcutaneous enoxaparin plus oral betrixaban placebo using a double-blind, double-dummy design. On day 1, all patients received 2 capsules of either betrixaban 80 mg or placebo orally, followed by one 80-mg capsule orally once daily for the remainder of the study (35-42 days). Patients receiving a concomitant strong P-glycoprotein (P-gp) inhibitor or who had severe renal insufficiency (creatinine clearance [CrCl] more than 15 mL/min and less than 30 mL/min) received a reduced dose of betrixaban 80 mg initially and 40 mg once daily thereafter. Enoxaparin (or matching placebo) was administered at a dose of 40 mg subcutaneously daily for 6 to 14 days (patients with CrCl more than 15 mL/min and less than 30 mL/min received enoxaparin 20 mg). The median duration of treatment was 36 days in the betrixaban group and 9 days in the enoxaparin group.

Results

Primary End Point(s)

- Composite of asymptomatic proximal DVT between days 32 and 47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between days 1 and 42:
  - Cohort 1: 6.9% of patients in the betrixaban group and 8.5% in the enoxaparin group (relative risk [RR], 0.81; 95% confidence interval [CI], 0.65-1; $P = .054$).
  - Cohort 2: 5.6% of patients in the betrixaban group and 7.1% in the enoxaparin group (RR, 0.8; 95% CI, 0.66-0.98; $P = .03$).
  - Overall population cohort: 5.3% of patients in the betrixaban group and 7% in the enoxaparin group (RR, 0.76; 95% CI, 0.63-0.92; $P = .006$).
- In the overall safety population (n = 7432), major bleeding at any point up to 7 days after discontinuation occurred in 0.7% of the betrixaban group and 0.6% of the enoxaparin group (RR, 1.19; 95% CI, 0.67-2.12; $P = .55$).

Secondary End Point(s)

- Composite of symptomatic VTE through day 42 (death from VTE, nonfatal PE, or symptomatic DVT) occurred in 0.9% of patients in the betrixaban group and 1.5% in the enoxaparin group (RR, 0.64; 95% CI, 0.42-0.98; $P = .04$).
- Composite of primary efficacy outcome plus death from any cause (instead of death from VTE) for the overall population changed to an occurrence of 9.2% in the betrixaban group and 10.8% in the enoxaparin group (RR, 0.85; 95% CI, 0.73-0.98; $P = .02$).
- Net clinical benefit (composite of the primary efficacy outcome and the primary safety outcome) occurred in 5.8% of the betrixaban group and 7.3% of the enoxaparin group (RR, 0.78; 95% CI, 0.65-0.95; $P = .01$).
- Major or clinically relevant nonmajor bleeding occurred in 3.1% of the betrixaban group and 1.6% of the enoxaparin group (RR, 1.97; 95% CI, 1.44-2.68; $P < .001$).
- New ischemic stroke occurred in 0.5% of patients in the betrixaban group and 0.9% in the enoxaparin group (RR, 0.53; 95% CI, 0.3-0.94; $P = .03$). Incidence for the development of any type of stroke was 0.6% in

the betrixaban group and 1.1% in the enoxaparin group (RR, 0.59; 95% CI, 0.35-0.97; $P = .03$).[13] A subgroup analysis also found that betrixaban decreased the risk of all-cause stroke and ischemic stroke in patients whose index event for enrollment was congestive heart failure or ischemic stroke.[14]

Comments: The study was conducted in North America, Europe, South America, South Africa, Asia, and Australia. This pivotal study was evaluated for betrixaban's approval in the United States; the information included in the betrixaban prescribing information is based on the overall study population and not the subgroup cohorts. The study was designed to assess the safety and efficacy of extended-duration oral betrixaban compared with standard-duration enoxaparin for thromboprophylaxis in patients with acute medical illness. Testing for superiority was done using a fixed hierarchical sequence: superiority for primary end point in cohort 1, followed by cohort 2, then the overall study population followed by sequential analysis for various secondary end points. Superiority was not established for cohort 1, so the results for the other primary and secondary end points can only be considered exploratory. The inability to meet superiority may have been influenced by the smaller number of patients in cohort 1 compared with cohort 2 and the overall modified intention-to-treat (mITT) efficacy population. Efficacy was assessed using the mITT population (n = 7441) (ie, patients who received at least 1 dose of study medication and had an adequate assessment of VTE). Sensitivity analysis was conducted using imputation to account for missing data and found similar results. Subgroup analysis of full- versus reduced-dose betrixaban found that the 80-mg dose achieved higher serum concentrations than the 40-mg dose and was associated with improved efficacy across all cohorts relative to enoxaparin.[15] Post hoc analysis found that extended-duration betrixaban had an approximately 30% reduction in fatal or irreversible ischemic or bleeding events compared with standard-duration enoxaparin.[16]

Limitations: Superiority was not established for cohort 1, so the results for the other primary and secondary end points can only be considered exploratory. A new analysis process was used, in which the first primary end point evaluated was in patients with higher risk, and subsequent statistical analysis was based on a fixed hierarchical sequence; if the between-group difference of the previous analysis (ie, the first primary end point) was not significant, then subsequent end points were considered only exploratory. If the overall mITT population and cohort 2 had been used as the first 2 data sets for this study, it would have been considered a success and these 2 end points would not have been classified as exploratory.

Contraindications, Warnings, and Precautions

Contraindications

The contraindications for betrixaban are similar to those of other oral factor Xa inhibitors: active pathological bleeding and severe hypersensitivity reactions to the drug and its inactive ingredients (ie, dextrose monohydrate, croscarmellose sodium, magnesium stearate, hard gelatin capsule; see Table 3).[1,6,7,8,9]

Use of dabigatran is contraindicated in patients with mechanical heart valves; safety and efficacy of factor Xa inhibitors, including betrixaban, have not been evaluated in this population. Contraindications to use of the factor Xa inhibitors are summarized in Table 3.[1,6,7,8,9]

Warnings and Precautions

The warnings and precautions associated with betrixaban therapy are similar to those of other oral factor Xa inhibitors (see Table 3).[1,6,7,8,9]

Betrixaban prescribing information includes a boxed warning regarding the risk of spinal or epidural hematomas, which may occur after neuraxial anesthesia or spinal puncture. Frequently monitor patients for signs and symptoms of neurological impairment (eg, numbness or weakness of legs, bowel or bladder dysfunction). The risk of these events may be increased by the use of indwelling epidural catheters or by concomitant use of medical products affecting hemostasis. Do not remove an epidural catheter earlier than 72 hours after the last administration of betrixaban. Do not administer the next betrixaban dose earlier than 5 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of betrixaban for 72 hours. Hematomas may result in long-term or permanent paralysis. If neurological signs or symptoms are noted, urgent diagnosis and treatment are necessary.[1]

Use of oral factor Xa inhibitors, including betrixaban, is associated with an increased risk of bleeding, which can be fatal. Concomitant use of drugs affecting hemostasis (eg, aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], nonsteroidal anti-inflammatory drugs [NSAIDs]) increases the risk of bleeding. Patients should be evaluated for signs or symptoms of blood loss, and therapy should be discontinued in patients with active pathological bleeding. There is no established way to reverse the anticoagulant effects of betrixaban; effects of hemodialysis are unknown, and protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse betrixaban's anticoagulant activity.[1]

Patients with severe renal impairment (CrCl 15 mL/min to less than 30 mL/min) taking betrixaban may have an

Table 3. Contraindications, Warnings, and Precautions Associated With Oral Factor Xa Inhibitors.[1,6,7,8,9]

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Contraindications					
Active pathological bleeding	X	X	X	X	X
Severe hypersensitivity reaction to the drug	X	X	X		X
Prosthetic heart valves	[a]	[a]	X	[a]	[a]
Warnings and precautions					
Risk of bleeding	X	X	X	X	X
Spinal/epidural anesthesia or puncture	X	X	X	X	X
Mechanical heart valves or moderate to severe mitral stenosis				X	
Reduced efficacy in patients with nonvalvular atrial fibrillation and CrCL greater than 95 mL/min				X	
Severe renal impairment	X				X
Hepatic impairment	X				X
Concomitant use of P-gp inhibitors	X		X		
Concomitant use of P-gp inducers			X		
Concomitant use of P-gp and strong CYP3A4 inhibitors or inducers					X
Increased risk of thrombotic events with premature discontinuation		X	X	X	X
Pregnancy	No adequate and well-controlled studies	No adequate and well-controlled studies	No adequate and well-controlled studies	No adequate and well-controlled studies	No adequate and well-controlled studies
Breastfeeding	No data	No data	No data	No data	No data
Pediatric patients	Safety and effectiveness not established	Safety and effectiveness not established	Safety and effectiveness not established	Safety and effectiveness not established	Safety and effectiveness not established
Specific agent for reversal of anticoagulant effect	No	No	Yes	No	No

Note. CrCL = creatinine clearance; P-gp = P-glycoprotein.
[a]Safety and effectiveness not established.

increased risk of bleeding events. Loading and maintenance doses of betrixaban should be reduced, and the patient should be monitored for any signs or symptoms of blood loss.[1]

Patients with hepatic impairment were not evaluated because these patients may have intrinsic coagulation abnormalities. Therefore, use of betrixaban in these patients is not recommended.[1]

Patients receiving concomitant P-gp inhibitors with betrixaban may have an increased risk of bleeding. The loading and maintenance doses should be reduced in patients receiving or starting P-gp inhibitors. If the patient has severe renal impairment and requires treatment with a P-gp inhibitor, betrixaban should not be prescribed. Monitor patients closely, and promptly evaluate any signs or symptoms of blood loss.[1]

There are no adequate and well-controlled studies regarding use of oral factor Xa inhibitors, including betrixaban, in pregnancy.[1,6,7,8,9] These drugs should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

It is unknown whether oral factor Xa inhibitors are excreted in human milk.[1,6,7,8,9] No data are available regarding the presence of betrixaban or its metabolites in human milk, or its effects of breastfeeding infants or milk production.[1]

Safety and efficacy of the oral factor Xa inhibitors, including betrixaban, have not been established in pediatric patients.[1]

Adverse Reactions

The most common adverse reaction associated with betrixaban therapy is bleeding.[1,12,13] Potential serious adverse reactions with betrixaban include bleeding, spinal or epidural hematomas (in patients receiving neuraxial anesthesia or undergoing spinal puncture), and major bleeding.[1] Tables 4 and 5 summarize the adverse reactions reported in a clinical trial (APEX) that compared betrixaban and enoxaparin.[1]

QTc prolongation is concentration dependent. The mean QTc prolongation after 80 mg was 4 ms; after a 4.7-fold increase in exposure, QTc prolongation was 13 ms.[1]

Table 4. Adverse Reactions (≥2% Incidence) in Patients With Acute Medical Illness With Risk Factors for VTE (APEX Study).[1]

Adverse reaction	Betrixaban (n = 3716)	Enoxaparin (n = 3716)
Bleeding-related event (all sources)		
Epistaxis	2%	1%
Hematuria	2%	1%
Nonbleeding event		
Urinary tract infection	3%	2%
Constipation	3%	3%
Hypokalemia	3%	2%
Hypertension	2%	2%
Headache	2%	2%
Nausea	2%	2%
Diarrhea	2%	2%

Note. VTE = venous thromboembolism.

Drug Interactions

Betrixaban is mainly excreted unchanged via biliary secretion. Betrixaban is not a CYP-450 substrate, and no drug-drug interactions with CYP-450 inducers or inhibitors are expected. Betrixaban is not an inducer of CYP1A2, 2C9, or 3A4 activity.[17] Betrixaban is not an inducer or inhibitor of CYP-450 enzymes.[3]

Betrixaban is a substrate of P-gp, and concomitant use of P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) results in increased exposure to betrixaban. Reduce the dose of betrixaban for patients receiving or starting concomitant P-gp inhibitors.[1]

Coadministration of betrixaban with anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss if the patient is being treated concomitantly with anticoagulants, aspirin, other platelet aggregation inhibitors, and/or NSAIDs.[1] Table 6 provides a comparison of the drug interactions associated with factor Xa inhibitors.[1,6,7,8,9]

Andexanet alfa binds betrixaban and reserves its anticoagulant activity.[18,19,20]

Recommended Monitoring

Renal function prior to initiation and periodically as clinically indicated; signs/symptoms of bleeding.[1]

Routine monitoring of coagulation tests is not required. Anti–factor Xa assay may be helpful (plasma concentrations and anti–factor Xa activity exhibit linear relationship) in guiding clinical decisions.[21]

Dosing

The recommended dosage for betrixaban is an initial single oral dose of 160 mg, followed by 80 mg once daily. Betrixaban should be given at the same time of day with food. The recommended duration of treatment is 35 to 42 days.[1] Table 7 provides a comparison of the dosing recommendations for the factor Xa inhibitors.[1,6,7,8,9]

No dosage adjustment is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal insufficiency (CrCl 15 to <30 mL/min) or those who are receiving or starting treatment with strong P-gp inhibitors, the recommended dose of betrixaban is an initial single dose of 80 mg followed by 40 mg once daily.[1,12]

Product Availability

A New Drug Application for betrixaban was submitted to the FDA in October 2016, with a Prescription Drug User Fee Act (PDUFA) date of June 24, 2017.[10,22] Betrixaban was approved by the FDA on June 23, 2017.[2] Table 8 provides a comparison of the product availability and storage recommendations for factor Xa inhibitors.[1,6,7,8,9]

Betrixaban is available as a 40- and 80-mg capsule in bottles of 100. It should be stored at room temperature (20°C-25°C [68°F-77°F]).[1]

Drug Safety/REMS

No Risk Evaluation and Mitigation Strategy (REMS) is required for betrixaban.[1,2]

Conclusion

Betrixaban, an oral factor Xa inhibitor (anticoagulant) for once-daily administration, is approved for prophylaxis of 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 other risk factors for VTE. Betrixaban is the only oral factor Xa inhibitor approved for this indication. The recommended duration of treatment with betrixaban is 35 to 42 days. Because betrixaban is not a

Table 5. Bleeding Events in the APEX Study Occurring ≤7 Days After Discontinuation of Study Drug.[1]

Bleeding event	Betrixaban (n = 3716)	Enoxaparin (n = 3716)	Betrixaban versus Enoxaparin relative risk
Major bleeding			
Any	0.67%	0.57%	1.19 (95% CI, 0.67-2.12) (P = .554)
Gastrointestinal bleeding	0.51%	0.24%	
Intracranial hemorrhage	0.05%	0.19%	
Intraocular bleeding	0%	0.03%	
Fatal bleeding	0.03%	0.03%	
Clinically relevant nonmajor bleeding			
Any	2.45%	1.02%	2.39 (95% CI, 1.64-3.49) (P < .001)

Table 6. Drug Interactions for Oral Factor Xa Inhibitors.[1,6,7,8,9]

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin)	X	X	X	X	
Moderate CYP3A4 inhibitors					X
P-gp plus strong CYP3A4 inhibitors		X			X
P-gp plus moderate CYP3A4 inhibitors					X
P-gp plus strong CYP3A4 inducers		X			X
Anticoagulants	X	X	[a]	X	X
Antiplatelet drugs	X	X	[a]	X	X
Thrombolytics	X	X		X	X
NSAIDs	X	X	[a]	X	X
CYP3A4 inhibitors		X			X
P-gp inducers (eg, rifampin)		X	X		X
CYP3A4 inducers		X		X	X
SSRIs	[a]	X	[a]	[a]	X
SNRIs	[a]	X	[a]	[a]	X

Note. NSAIDs = nonsteroidal anti-inflammatory drugs; P-gp = P-glycoprotein; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors.
[a]Not listed in prescribing information, but potentially could occur.

Table 7. Dosing Recommendations for Oral Factor Xa Inhibitors.[1,6,7,8,9]

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Recommended oral dose					
Loading dose	Single dose of 160 mg				
Maintenance dose	80 mg once daily	2.5-10 mg twice daily; dose depends on the indication.	150 mg twice daily	60 mg once daily	10-20 mg once daily or 15 mg twice daily; dose depends on the indication.
Can be crushed	No information	Yes	Not recommended	No information	Yes
Food	With	With or without	With or without	With or without	10-mg tablet can be taken with or without food 15- and 20-mg tablets should be taken with food.

(continued)

Table 7. (continued)

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Dosage reduction and/or recommendation to avoid use					
Concomitant use of P-gp inhibitors	X		X[a]		
CrCl 15 to <30 mL/min (severe renal impairment)	X		X[a]	X	X[a]
CrCl 30-50 mL/min (moderate renal impairment)			X[a]		
CrCl 15-50 mL/min				X	X
CrCl <15 mL/min (renal failure)				X	X[a]
CrCl >95 mL/min				X	
Serum creatinine 1.5 mg/dL or higher		X[a]			
Body weight 60 kg or less		X[a]			
Age 80 y or older		X[a]			
Strong dual inhibitors or inducers of CYP3A4 and P-gp		X			
Renal impairment and concomitant use of P-gp inhibitor			X[a]		

Note. CrCL = creatinine clearance; P-gp = P-glycoprotein.
[a]Not applicable to all indications.

Table 8. Product Availability and Storage for Oral Factor Xa Inhibitors.[1,6,7,8,9]

	Betrixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Dose form	Capsule	Tablet	Capsule	Tablet	Tablet
Strength	40 mg, 80 mg	2.5 mg, 5 mg	75 mg, 150 mg	15 mg, 30 mg, 60 mg	10 mg, 15 mg, 20 mg
Packaging	Bottles of 100	Bottles of 60 and 74, depending on strength; blister package	Bottles of 60; blister package	Bottles of 30, 90, and 500, depending on strength; blister package	Bottles of 30 and 90, depending on strength; blister package; starter pack with blister packaging
Storage	20°C-25°C (68°F-77°F)	20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).	25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) Store in the original package to protect from moisture	20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F)	25°C (77°F) or room temperature; excursions permitted to 15°C-30°C (59°F-86°F)

CYP3A4 substrate, the risk of certain drug-drug interactions with betrixaban is decreased.

Declaration of Conflicting Interests

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