HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEVYXXA safely and effectively. See full prescribing information for BEVYXXA.

BEVYXXA ™ (betrixaban) capsules, for oral use
Initial U.S. Approval: 2017

WARNING: SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.

Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.2)

INDICATIONS AND USAGE

BEVYXXA is a factor Xa (FXa) inhibitor indicated 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 other risk factors for VTE. (1)

Limitations of Use:
Safety and efficacy of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied. (1)

DOSAGE AND ADMINISTRATION

The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food. The recommended duration of treatment is 35 to 42 days. (2.1)

- Reduce dose for patients with severe renal impairment. (2.2)
- Reduce dose for patients on P-glycoprotein (P-gp) inhibitors. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 40 mg and 80 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding. (4)
- Severe hypersensitivity reaction to betrixaban BEVYXXA. (4)

WARNINGS AND PRECAUTIONS

- Risk of Bleeding: Can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Severe Renal Impairment: Increased risk of bleeding events; reduce BEVYXXA dose (2.2, 5.3)
- Concomitant P-gp Inhibitors: Increased risk of bleeding events; reduce BEVYXXA dose (2.3, 5.4)

ADVERSE REACTIONS

Most common adverse reaction (incidence >5%) is bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals at 1-855-767-7167 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- P-gp inhibitors increase the blood levels of betrixaban. Reduce BEVYXXA dose. (7.1)
- Anticoagulants: Avoid concomitant use. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if potential benefit outweighs the potential risk to the mother or fetus (8.1)
- Renal Impairment: Reduce dose. (8.6)
- Hepatic impairment: Avoid use (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2017

FULL PRESCRIBING INFORMATION: CONTENTS *

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

FULL PRESCRIBING INFORMATION

WARNING: SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

BEVYXXA is indicated 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 other risk factors for VTE *[see Clinical Studies (14)]*.

Limitations of Use:

The safety and effectiveness of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily. Daily oral doses should be given at the same time of day with food.

The recommended duration of treatment is 35 to 42 days.

2.2 Severe Renal Impairment

For patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min computed by Cockcroft-Gault using actual body weight) the recommended dose of BEVYXXA is an initial single dose of 80 mg followed by 40 mg once daily *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), Clinical Pharmacology (12.3]*. The recommended duration of treatment is 35 to 42 days.

2.3 Use with P-gp Inhibitors

For patients receiving or starting concomitant P-gp inhibitors the recommended dose of BEVYXXA is an initial single dose of 80 mg followed by 40 mg once daily *[see Warnings and Precautions (5.4), Drug Interactions (7.1), Clinical Pharmacology (12.3)]*. The recommended duration of treatment is 35 to 42 days.

2.4 Missed Dose

If a dose of BEVYXXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. The BEVYXXA dose should not be doubled to make up for a missed dose.

3 DOSAGE FORMS AND STRENGTHS

40 mg and 80 mg capsules

- 80 mg, size 2 hard gelatin capsules are light grey with 80 printed in black, and have a blue cap with PTLA printed in white.
- 40 mg, size 4 hard gelatin capsules are light grey with 40 printed in black, and have a light blue cap with PTLA printed in white.

4 CONTRAINDICATIONS

BEVYXXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Severe hypersensitivity reaction to betrixaban *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

BEVYXXA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss *[see Adverse Reactions (6.1)]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.2)]*.

Advise patients of signs and symptoms of blood loss and to report them immediately and seek emergency care. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue BEVYXXA in patients with active pathological bleeding.

There is no established way to reverse the anticoagulant effect of BEVYXXA, which can be expected to persist for at least 72 hours after the last dose. It is unknown whether hemodialysis removes BEVYXXA. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of BEVYXXA.

5.2 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, 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.

Do not remove an epidural catheter earlier than 72 hours after the last administration of BEVYXXA. Do not administer the next BEVYXXA dose earlier than 5 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of TRADENAME for 72 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.3 Use in Patients with Severe Renal Impairment

Patients with severe renal impairment (CrCl $\geq$ 15 to < 30 mL/min computed by Cockcroft-Gault using actual body weight) taking BEVYXXA may have an increased risk of bleeding events. Reduce dose of BEVYXXA, monitor patients closely, and promptly evaluate any signs or symptoms of blood loss in these patients *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6.1), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5.4 Use in Patients on Concomitant P-gp Inhibitors

Patients on concomitant P-gp inhibitors with BEVYXXA may have an increased risk of bleeding. Reduce dose of BEVYXXA in patients receiving or starting P-gp inhibitors. Monitor patients closely and promptly evaluate any signs or symptoms of blood loss in these patients *[see Dosage and Administration (2.3), Warnings and Precautions (5.1), Adverse Reactions (6.1), Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Avoid use of BEVYXXA in patients with severe renal impairment receiving concomitant P-gp inhibitors *[see Warnings and Precautions (5.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Risk of Bleeding *[see Warnings and Precautions (5.1, 5.3, 5.4)]*.
- Spinal/Epidural Anesthesia or Puncture *[see Boxed Warning and Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

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

The safety of BEVYXXA was evaluated in the Acute Medically Ill Prevention with Extended Duration Betrixaban (APEX) Study *[see Clinical Studies (14)]*, including 3,716 patients treated with BEVYXXA for a median of 36 days compared to 3,716 patients treated with enoxaparin for a median of 9 days. Patients in both treatment groups were followed for safety, including bleeding events, for up to 77 days.

Patients randomized to the BEVYXXA arm received BEVYXXA 160 mg orally on Day 1, then 80 mg once daily for 35 to 42 days AND enoxaparin subcutaneous *placebo* once daily for 6 to 14 days. Patients randomized to the enoxaparin arm received enoxaparin 40 mg subcutaneously once daily for 6 to 14 days AND BEVYXXA *placebo* orally once daily for 35 to 42 days.

Patients with severe renal impairment (creatinine clearance ≥ 15 and < 30 mL/min) received reduced doses of study medications (BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily) along with corresponding placebo.

Patients taking a concomitant P-gp inhibitor received BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 40 mg subcutaneously once daily for 6 to 14 days along with corresponding placebo.

Hemorrhage

The most common adverse reactions with BEVYXXA were related to bleeding (> 5%) with major bleeding occurring in less than 1% of patients (see Table 1).

Overall, 54% of patients receiving BEVYXXA experienced at least one adverse reaction vs. 52% with enoxaparin. The frequency of patients reporting serious adverse reactions was similar between BEVYXXA (18%) and enoxaparin (17%). In the APEX trial, the most frequent reason for treatment discontinuation was bleeding, with an incidence rate of 2.4% for BEVYXXA vs. 1.2% for enoxaparin.

The primary and secondary safety outcomes in APEX were bleeding-related events.

A summary of major and clinically relevant non-major (CRNM) bleeding events in the overall safety population is shown in Table 1. Most CRNM events (86%) were mild to moderate in severity, and the majority (62%) did not require medical intervention.

The incidence of fatal bleeding was the same in the BEVYXXA and enoxaparin treatment groups (1 in each group).

Table 1: Bleeding Events in APEX through 7 days after Discontinuation of All Study Drugs (Safety Population)

Parameter	BEVYXXA (N=3,716)	Enoxaparin (N=3,716)	BEVYXXA vs. Enoxaparin RR (95% CI)
Major Bleeding [a]	25 (0.67)	21 (0.57)	1.19 (0.67, 2.12) p = 0.554
Gastrointestinal (GI)	19 (0.51)	9 (0.24)	
Intracranial Hemorrhage	2 (0.05)	7 (0.19)	
Intraocular	0 (0)	1 (0.03)	
Fatal Bleeding	1 (0.03)	1 (0.03)	
Clinically Relevant Non-Major Bleeding [b]	91 (2.45)	38 (1.02)	2.39 (1.64, 3.49) p < 0.001

[a] Major bleeding event was defined as clinically overt bleeding that met one of the following criteria: a reduction in hemoglobin of a least 2 g/dL within 48 hours of an overt bleeding event; a transfusion of at least two units of whole blood or packed red blood cells; a critical area; e.g., intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular, pericardial, or a fatal outcome. Retinal hemorrhages secondary to diabetic retinopathy or conjunctival bleeds did not qualify as a major bleeds.

[b] CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary/permanent) cessation of the study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

A summary of major and CRNM bleeding events by dose is shown in Table 2 and Table 3.

Table 2: Summary of Adjudicated Major, CRNM, Major or CRNM Bleeding Events through 7 Days after Discontinuation for Patients Receiving 80 mg

Parameter	TRADENAME 80 mg (N=2,986) n (%)	Enoxaparin 40 mg (N=2,991) n (%)
Major	15 (0.50)	16 (0.53)
RR (95% CI)	0.94 (0.47, 1.90)	
Clinically Relevant Non-Major (CRNM)	66 (2.21)	33 (1.10)
RR (95% CI)	2.00 (1.32, 3.03)	
Major or CRNM	81 (2.71)	49 (1.64)
RR (95% CI)	1.66 (1.17, 2.35)	

Table 3: Summary of Adjudicated Major, CRNM, Major or CRNM Bleeding Events through 7 Days after Discontinuation for Patients Receiving 40 mg

	Severe Renal Impairment		Concomitant use of P-gp Inhibitor	
Parameter	**BEVYXXA 40 mg (N=150) n (%)**	**Enoxaparin 20 mg (N=125) n (%)**	**BEVYXXA 40 mg (N=542) n (%)**	**Enoxaparin 40 mg (N=527) n (%)**
Major	3 (2.00)	1 (0.80)	6 (1.11)	4 (0.76)
RR (95% CI)	2.5 (0.26, 23.74)		1.46 (0.41, 5.14)	
Clinically Relevant Non-Major (CRNM)	6 (4.00)	2 (1.60)	20 (3.69)	3 (0.57)
RR (95% CI)	2.5 (0.51, 12.17)		6.5 (1.94, 21.68)	
Major or CRNM	9 (6.00)	3 (2.40)	26 (4.80)	7 (1.33)
RR (95% CI)	2.5 (0.69, 9.04)		3.6 (1.58, 8.25)	

The most common adverse reactions occurring in ≥ 2% of patients are shown in Table 4.

Table 4: Adverse Reactions in APEX Occurring in ≥ 2% of Patients

Adverse Reaction	BEVYXXA N=3,716 (n%)	Enoxaparin N=3,716 (n%)
Bleeding-Related (all sources)		
Epistaxis	58 (2)	24 (1)
Hematuria	62 (2)	28 (1)
Non Bleeding Adverse Reaction		
Urinary Tract Infection	123 (3)	87 (2)
Constipation	110 (3)	102 (3)
Hypokalemia	93 (3)	84 (2)
Hypertension	89 (2)	80 (2)
Headache	74 (2)	59 (2)
Nausea	67 (2)	56 (2)
Diarrhea	64 (2)	61 (2)

Other Adverse Reactions

Hypersensitivity reactions: one patient experienced a serious adverse reaction of moderate hypersensitivity

7 DRUG INTERACTIONS

7.1 Inhibitors of P-gp

BEVYXXA is a substrate of P-gp and concomitant use of P-gp inhibitors (e.g., amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) results in an increased exposure of BEVYXXA *[see Clinical Pharmacology (12.3)]*.

Reduce the dose of BEVYXXA for patients receiving or starting concomitant P-gp inhibitors *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

7.2 Anticoagulants, Antiplatelets, and Thrombolytics

Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with anticoagulants, aspirin, other platelet aggregation inhibitors, and/or NSAIDs *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with the use of BEVYXXA in pregnant women, but treatment is likely to increase the risk of hemorrhage during pregnancy and delivery *(see Clinical Considerations)*. Betrixaban was studied in reproductive and developmental toxicology studies in rats and rabbits during the period of organogenesis at exposures up to 44 times the recommended clinical dose of 80 mg daily. Although betrixaban was not associated with adverse developmental fetal outcomes in animals, maternal toxicity (i.e., hemorrhage) was identified in these studies *(see Data)*. BEVYXXA should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Embryo-fetal development studies were conducted in pregnant rats and rabbits during the period of organogenesis. In rats, no adverse embryofetal or teratogenic effects were seen when betrixaban was administered orally at doses up to 200 mg/kg/day, or 44 times the human dose of 80 mg/day when based on AUC. In rabbits, no adverse embryofetal or teratogenic effects were seen at doses up to 45 mg/kg/day, or 35 times the human exposure at a dose of 80 mg/day when based on AUC. Pregnant rabbits administered the highest dose of 150 mg/kg/day were terminated prematurely due to excessive maternal toxicities. Upon post-mortem examination, early and/or late resorptions and fetal deaths were observed at the 150 mg/kg dose, which may be linked to hemorrhage observed in various organs including the reproductive tract.

In a rat pre-and post-natal developmental study, betrixaban was administered orally during the period of organogenesis and through lactation day 20 at doses up to 200 mg/kg/day. Maternal toxicities (including decreased body weight gain and food consumption and red/brown perivaginal substance) were observed at 200 mg/kg/day, which is approximately 44 times the human exposure when based on AUC. At a maternal dose up to 200 mg/kg/day, betrixaban did not have adverse effects on sexual maturation, reproductive performance, and behavioral development of the F1 generation.

Clinical Considerations

Maternal Adverse Reactions

Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. Consider the risks of bleeding and of stroke in using BEVYXXA in this setting.

8.2 Lactation

Risk Summary

No data are available regarding the presence of betrixaban or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BEVYXXA and any potential adverse effects on the breast-fed child from BEVYXXA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the APEX clinical study 90% were 65 years and over, while 68.6% were greater than or equal to 75 years. No clinically significant differences in safety or effectiveness were observed between older and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min computed by Cockcroft-Gault using actual body weight) may have an increased risk of bleeding events. Reduce the BEVYXXA dose for patients with severe renal impairment. Monitor patients closely and promptly evaluate any signs or symptoms of blood loss in these patients *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]*. No dose adjustment is needed for mild or moderate renal impairment (CrCl > 30 mL/min, computed by Cockcroft-Gault using actual body weight).

8.7 Hepatic Impairment

BEVYXXA has not been evaluated in patients with hepatic impairment, because these patients may have intrinsic coagulation abnormalities. Therefore, the use of BEVYXXA is not recommended in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

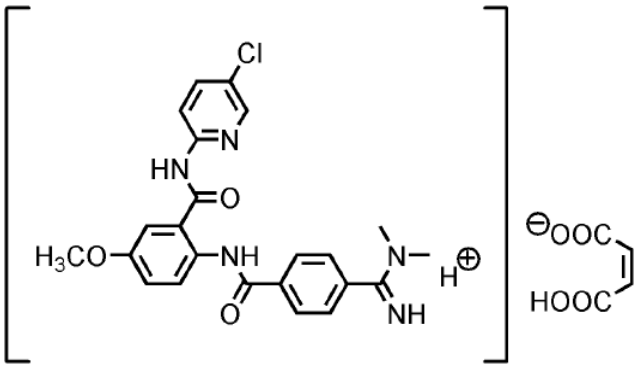
10 OVERDOSAGE

Overdose of BEVYXXA increases the risk of bleeding *[see Warnings and Precautions (5.1)]*.

A specific reversal agent for BEVYXXA is not available. There is no experience with hemodialysis in individuals receiving betrixaban. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of betrixaban.

11 DESCRIPTION

Betrixaban, a factor Xa (FXa) inhibitor, is chemically described as N-(5-chloropyridin-2-yl)-2-[4-(N,N-dimethylcarbamimidoyl)-benzoylamino]-5-methoxybenzamide maleate. Its molecular formula (as maleate salt) is $C_{27}H_{26}ClN_5O_7$, which corresponds to a molecular weight of 567.98. Betrixaban (maleate salt) has the following structural formula:



BEVYXXA capsules are available for oral administration in strengths of 80 mg and 40 mg of betrixaban with the following inactive ingredients: dextrose monohydrate, croscarmellose sodium, magnesium stearate, and a hard gelatin capsule.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Betrixaban is an oral FXa inhibitor that selectively blocks the active site of FXa and does not require a cofactor (such as Anti-thrombin III) for activity. Betrixaban inhibits free FXa and prothrombinase activity. By directly inhibiting FXa, betrixaban decreases thrombin generation (TG). Betrixaban has no direct effect on platelet aggregation.

12.2 Pharmacodynamics

Inhibition of FXa by betrixaban results in an inhibition of thrombin generation at clinically relevant concentrations, and the maximum inhibition of thrombin generation coincides with the time of peak betrixaban concentrations.

Cardiac Electrophysiology

In a study that evaluated the effect of betrixaban on the QT interval, a concentration-dependent increase in the QTc interval was observed. Based on the observed concentration-QTc relationship a mean (upper 95% CI) QTc prolongation of 4 ms (5 ms) is predicted for 80 mg betrixaban and 13 ms (16 ms) for a 4.7-fold increase in exposure *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics

Within the anticipated therapeutic dose range a two-fold increase in dose resulted in a three-fold increase in exposure in the single ascending dose study. A two-fold increase in betrixaban exposure was observed after repeat dosing, and the time to steady-state is 6 days (without an initial loading dose).

Absorption

The oral bioavailability of betrixaban for an 80 mg dose is 34%, and peak concentrations occurred within 3 to 4 hours. Betrixaban is also a substrate of P-gp.

Effect of Food

When administered with a low-fat (900 calories, 20% fat) or high-fat (900 calories, 60% fat) meal, C_{max} and AUC were reduced as compared to the fasting state by an average of 70% and 61% for low-fat and 50% and 48% for high-fat, respectively. The effect of food on betrixaban PK could be observed for up to 6 hours after meal intake.

Distribution

The apparent volume of distribution is 32 L/kg. *In vitro* plasma protein binding is 60%.

Elimination

The effective half-life of betrixaban is 19 to 27 hours.

Metabolism

Unchanged betrixaban is the predominant component found in human plasma. Two inactive major metabolites formed by CYP-independent hydrolysis comprise the other components in plasma, accounting for 15 to 18% of the circulating drug-related material. Less than 1% of the minor metabolites could be formed via metabolism by the following CYP enzymes; 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4.

Excretion

Following oral administration of radio-labeled betrixaban approximately 85% of the administered compound was recovered in the feces and 11% recovered in the urine. In a study of

intravenous betrixaban a median value of 17.8% of the absorbed dose was observed as unchanged betrixaban in urine.

Specific Populations

Male and Female Patients

No clinically significant changes in betrixaban pharmacokinetics were observed between males and females.

Patients with Renal Impairment

In a dedicated renal impairment study mean AUC_{0-24} on day 8 was increased by 1.89, 2.27 and 2.63-fold in mild ($eGFR_{MDRD} \geq 60$ to < 90 mL/min/1.73 m^2), moderate ($eGFR_{MDRD} \geq 30$ to < 60 mL/min/1.73 m^2) and severe renal ($eGFR_{MDRD} \geq 15$ to < 30 mL/min/1.73 m^2) impaired patients respectively compared to healthy volunteers *[see Use in Specific Populations (8.6)]*.

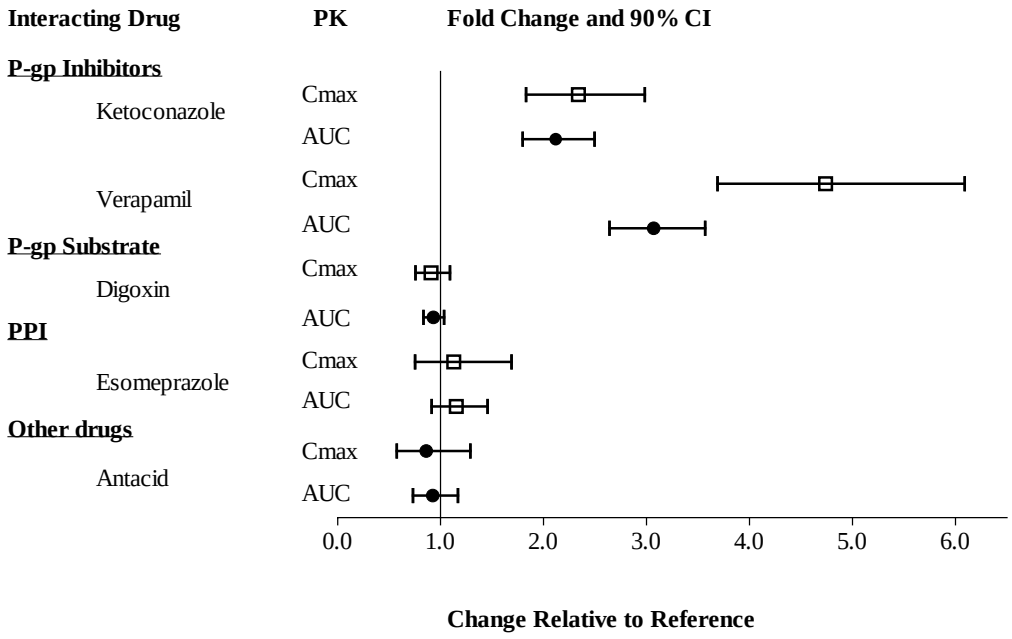
Patients with Hepatic Impairment

Studies with betrixaban in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to betrixaban has not been evaluated *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

The effects of coadministered drugs on the pharmacokinetics of betrixaban exposure based on drug interaction studies are summarized in Figure 1.

Figure 1: Effect of Coadministered Drugs on the Pharmacokinetics of Betrixaban



Dedicated Phase 1 studies evaluated the effect of co-administration of other drugs on the PK properties of betrixaban. The reference value in this case is the betrixaban PK parameter (Cmax or AUC) in the absence of the co-administered drug. The only drugs that affected betrixaban concentrations were P-gp inhibitors.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with betrixaban have not been performed.

Betrixaban was not mutagenic in bacteria (Ames-Test) or clastogenic in Chinese hamster ovary cells *in vitro* or in the rat micronucleus test *in vivo*.

In a study to assess fertility and early embryonic development to implantation, oral doses of betrixaban were administered to male and female rats. There was no evidence that betrixaban up to 150 mg/kg/day adversely affected male or female fertility, reproductive performance, or embryo-fetal viability.

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BEVYXXA is derived from the APEX clinical trial [NCT01583218]. APEX was a randomized, double-blind, multinational study comparing extended duration BEVYXXA (35 to 42 days) to short duration of enoxaparin (6 to 14 days) in

the prevention of venous thromboembolic events (VTE) in an acutely medically ill hospitalized population with risk factors for VTE.

Eligible patients included adults who were at least 40 years of age, hospitalized for an acute medical illness, at risk for VTE due to moderate or severe immobility, and had additional risk factors for VTE (described below). Expected duration of hospitalization was at least 3 days and patients were expected to be moderately or severely immobilized for at least 24 hours. The causes for hospitalization included heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke. At study initiation eligible patients were required to have one of the following additional risk factors for VTE:

a. ≥ 75 years of age,
b. 60 through 74 years of age with D-dimer ≥ 2 ULN, or
c. 40 through 59 years of age with D-dimer ≥ 2 ULN and a history of either VTE or cancer.

A total of 7,513 patients were randomized 1:1 to:

- BEVYXXA arm (BEVYXXA 160 mg orally on Day 1, then 80 mg once daily for 35 to 42 days AND enoxaparin subcutaneous *placebo* once daily for 6 to 14 days),

  OR

- Enoxaparin arm (enoxaparin 40 mg subcutaneously once daily for 6 to 14 days AND BEVYXXA *placebo* orally once daily for 35 to 42 days).

Patients with severe renal impairment (creatinine clearance ≥ 15 and < 30 mL/min) received reduced doses of study medications (BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily) along with corresponding placebo.

Patients taking a concomitant P-gp inhibitor received BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 40 mg subcutaneously once daily for 6 to 14 days along with corresponding placebo.

Baseline characteristics were balanced between the treatment groups. The population was 55% female, 93% White, 2% Black, 0.2% Asian, and 5% others. The most prevalent acute medical illness at hospitalization was acutely decompensated heart failure (45%), followed by acute infection without septic shock (29%), acute respiratory failure (12%), acute ischemic stroke (11%) and acute rheumatic disorders (3%). The mean and median ages were 76.4 and 77 years, respectively, with 68% of patients ≥ 75 years of age, 97% were severely immobilized at study entry, and 62% had D-dimer ≥ 2 x ULN.

While the APEX Study was ongoing (after 35% enrollment), the study was amended to restrict further enrollment to patients ≥ 75 years of age or with D-dimer values ≥ 2 x ULN. The APEX trial excluded patients whose condition required prolonged anticoagulation (e.g., concurrent VTE, atrial fibrillation, cardiac valve prosthesis), were at increased risk of bleeding, had liver dysfunction, were on dual antiplatelet therapy, or patients who had both severe renal insufficiency (CrCl 15-29 ml/min) and required the concomitant use of a P-gp inhibitor.

The efficacy of BEVYXXA was based upon the composite outcome of the occurrence of any of the following events up to Day 35 visit:

- Asymptomatic proximal Deep Vein Thrombosis (DVT) (detected by ultrasound),
- Symptomatic proximal or distal DVT,
- Non-fatal Pulmonary Embolism (PE), or
- VTE-related death.

Efficacy analyses were performed based on the modified Intent-to-Treat (mITT) population. The mITT population consisted of all patients who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy outcome components. A total of 7,441 patients (N=3,721 for BEVYXXA and N=3,720 for enoxaparin) were included in the mITT population.

The efficacy results for the APEX trial are provided in Table 5 below.

Table 5: Efficacy Outcomes in APEX Trial (mITT Population)

	BEVYXXA N=3,721 n (%) [1]	**Enoxaparin** N=3,720 n (%) [1]	**Relative Risk** (95% CI) [2]
Composite Outcome	165 (4.4)	223 (6.0)	0.75 (0.61, 0.91)
Asymptomatic Event	133 (3.6)	176 (4.7)	
Symptomatic DVT	14 (0.4)	22 (0.6)	
Non-fatal PE	9 (0.2)	18 (0.5)	
VTE-related Death	13 (0.3)	17 (0.5)	
Symptomatic Events [3]	35 (0.9)	54 (1.5)	0.64 (0.42, 0.98)

[1] Percentages and event rates are based on the total number of patients and events included in each treatment group.

[2] Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[3] Symptomatic events include symptomatic DVT, non-fatal PE or VTE-related death.

For patients with D-dimer ≥ 2 ULN at baseline, the event rate is 5.7% in the BEVYXXA arm vs. 7.2% in the enoxaparin arm (relative risk = 0.79, 95% CI [0.63, 0.98]).

For patients with D-dimer ≥ 2 ULN at baseline or age ≥ 75 years, the event rate is 4.7% in the BEVYXXA arm vs. 6.0% in the enoxaparin arm (relative risk = 0.78, 95% CI [0.64, 0.96]).

Results for the primary efficacy analysis for subjects that were stratified at randomization to the 80 mg BEVYXXA dose group in the mITT population are shown in Table 6 below.

Patients who were randomized to receive 40 mg BEVYXXA (those with severe renal impairment or receiving P-gp inhibitors), had VTE rates similar to the enoxaparin arm (6 to 14 days followed by placebo) shown in Table 7 below.

Table 6: Efficacy Outcomes in APEX Trial (mITT Population) – Patients Stratified to 80 mg BEVYXXA Dose [4]

	BEVYXXA N=2,878 n (%) [1]	**Enoxaparin** N=2,926 n (%) [1]	**Relative Risk** (95% CI) [2]
Composite Outcome	120 (4.2)	180 (6.2)	0.68 (0.55, 0.86)
Asymptomatic Event	100 (3.5)	146 (5.0)	
Symptomatic DVT	11 (0.4)	17 (0.6)	
Non-fatal PE	4 (0.1)	14 (0.5)	
VTE-related Death	8 (0.3)	12 (0.4)	
Symptomatic Events [3]	22 (0.8)	41 (1.4)	0.55 (0.33, 0.92)

[1] Percentages and event rates are based on the total number of patients and events included in each treatment group and stratified to 80 mg dose.

[2] Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[3] Symptomatic events include symptomatic DVT, non-fatal PE, or VTE-related death.

[4] Analysis excludes patients with severe renal impairment or were receiving P-gp inhibitors.

Table 7: Efficacy Outcomes in APEX Trial (mITT Population) – Patients Stratified to 40 mg BEVYXXA Dose

	Severe Renal Impairment			Concomitant use of P-gp Inhibitor		
	BEVYXXA N=174 n (%) [1]	**Enoxaparin** N=149 n (%) [1]	**Relative Risk** (95% CI)	**BEVYXXA** N=669 n (%) [1]	**Enoxaparin** N=645 n (%) [1]	**Relative Risk** (95% CI)[2]
Composite Outcome	12 (6.9)	10 (6.7)	1.0 (0.45, 2.23)	33 (4.9)	33 (5.1)	1.0 (0.63, 1.60)
Asymptomatic Event	9 (5.2)	7 (4.7)		24 (3.6)	23 (3.6)	
Symptomatic DVT	0	1 (0.7)		3 (0.4)	4 (0.6)	
Non-fatal PE	2 (1.1)	2 (1.3)		3 (0.4)	2 (0.3)	
VTE-related Death	2 (1.1)	0		3 (0.4)	5 (0.8)	
Symptomatic Events [3]	4 (2.3)	3 (2.0)		9 (1.3)	10 (1.6)	

[1] Percentages and event rates are based on the total number of patients and events included in each treatment group by dosing criteria.

[2] Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[3] Symptomatic events include symptomatic DVT, non-fatal PE, or VTE-related death.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

BEVYXXA (betrixaban) capsules are available as listed below.

The 40 mg size 4 capsules are light grey with 40 printed in black, and have a light blue cap with PTLA printed in white.

- Bottles of 100 (NDC 69853-0202-1)

The 80 mg size 2 capsules are light grey with 80 printed in black, and have a blue cap with PTLA printed in white.

- Bottles of 100 (NDC 69853-0201-1)

Storage and Handling

Store at room temperature; 20°C to 25°C (68°F to 77°F).

17 PATIENT COUNSELING INFORMATION

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

Risk of Bleeding

Advise patients that it might take longer than usual for bleeding to stop, and that they may bruise or bleed more easily when treated with BEVYXXA. Instruct patients to report any unusual bleeding to their physician *[see Warnings and Precautions (5.1)]*.

Instruct patients to tell their physicians and dentists that they are taking BEVYXXA, and/or any other products known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken *[see Warnings and Precautions (5.1, 5.4)]*.

Use in Patients with Severe Renal Impairment

Advise patients that the risk of bleeding is higher in people who have severe kidney problems (severe renal impairment) *[see Warnings and Precautions (5.3)]*.

Spinal/Epidural Hematoma

Advise patients having neuraxial anesthesia or spinal puncture to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel, or bladder dysfunction *[see Warnings and Precautions (5.2)]*. Instruct patients to contact their physician immediately if any of these symptoms occur.

Pregnancy and Lactation

Advise female patients to inform their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with BEVYXXA *[see Use in Specific Populations (8.1, 8.2)]*.

How to Take BEVYXXA

Instruct patients to take BEVYXXA with food, and instruct patients on what to do if a dose is missed *[see Dosage and Administration (2.2)]*.

Manufactured for:

Portola Pharmaceuticals, Inc.

South San Francisco, California 94080 USA

BTX-US-V.1.0

MEDICATION GUIDE
BEVYXXA™ (BEV vix a)
capsules

What is the most important information I should know about BEVYXXA?
BEVYXXA can cause serious side effects, including:

- **Bleeding problems.** BEVYXXA can increase the risk of bleeding, which can be serious and may lead to death. This is because BEVYXXA is a blood thinner medicine that reduces blood clotting. The risk of bleeding is higher in people who have severe kidney problems (severe renal impairment).
  You may have a higher risk of bleeding if you take BEVYXXA and take other medicines that increase your risk of bleeding, including:
  - aspirin or aspirin containing products
  - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (Coumadin®, Jantoven®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to prevent or treat blood clots
  - P-glycoprotein (P-gp) inhibitors

  Tell your healthcare provider if you take any of these medicines. Ask your healthcare provider or pharmacist if you are not sure if your medicine is one listed above.
  While taking BEVYXXA:
  - you may bruise more easily
  - it may take longer than usual for any bleeding to stop

  Call your healthcare provider or get medical help right away if you have any of these signs or symptoms of bleeding when taking BEVYXXA:
  - unexpected bleeding, or bleeding that lasts a long time such as:
    - unusual bleeding from the gums
    - nosebleeds that happen often
    - menstrual bleeding or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - red, pink, or brown urine
  - red or black stools (looks like tar)
  - cough up blood or blood clots
  - vomit blood or your vomit looks like coffee grounds
  - unexpected pain, swelling, or joint pain
  - headaches, feeling dizzy or weak
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like BEVYXXA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

  If you take BEVYXXA and receive spinal anesthesia or have a spinal puncture, your healthcare provider should watch you closely for symptoms of spinal or epidural blood clots. Tell your healthcare provider right away if you have back pain, tingling, numbness (especially in your legs and feet), muscle weakness, or loss of control of the bowels or bladder (incontinence).

See **"What are the possible side effects of BEVYXXA?"** for more information about side effects.

What is BEVYXXA?
TRADENAME is a prescription medicine used to help prevent blood clots in adults who are hospitalized for an acute illness, and are at risk of getting blood clots because of the loss of or decreased ability to move around (mobility) and other risks for getting blood clots.

- It is not known if BEVYXXA is safe and effective in people with artificial heart valves.
- It is not known if BEVYXXA is safe and effective in children.

Do not take BEVYXXA if you:

- have bleeding problems. Tell your healthcare provider if you have or at risk for bleeding problems.
- are allergic to betrixaban or to any of the ingredients in BEVYXXA. See the end of this Medication Guide for a complete list of ingredients in BEVYXXA.

Before taking BEVYXXA, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems
- have ever had bleeding problems
- have an artificial heart valve
- are pregnant or plan to become pregnant. It is not known if BEVYXXA will harm your unborn baby. Taking BEVYXXA may increase the risk of bleeding during pregnancy and delivery.
- are breastfeeding or plan to breastfeed. It is not known if BEVYXXA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take BEVYXXA.

Tell all of your healthcare providers and dentists that you are taking BEVYXXA. Talk to the healthcare provider who prescribed BEVYXXA for you, before you have **any** surgery, medical, or dental procedure.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way BEVYXXA works. Certain medicines may increase your risk of bleeding when taken with BEVYXXA. See "**What is the most important information I should know about BEVYXXA?"** and **"What is BEVYXXA?"**

How should I take BEVYXXA?

- **Take BEVYXXA exactly as prescribed by your healthcare provider**.
- Take BEVYXXA 1 time a day with food.
- Your healthcare provider will decide how long you should take BEVYXXA. Do not change your dose or stop taking BEVYXXA unless your healthcare provider tells you to.
- If you miss a dose of BEVYXXA, take it as soon as you remember on the same day. Take your next dose at your usual time the next day. Do not take more than 1 dose of BEVYXXA at the same time to make up for a missed dose.
- If you take too much BEVYXXA, go to the nearest hospital emergency room or call your healthcare provider right away.

Call your healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your healthcare provider may need to check you.

What are the possible side effects of BEVYXXA?

BEVYXXA can cause serious side effects.

- See **"What is the most important information I should know about BEVYXXA?"**

The most common side effect of BEVYXXA is bleeding.

These are not all of the side effects of BEVYXXAE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BEVYXXA?

- Store BEVYXXA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep BEVYXXA and all medicines out of the reach of children.

General information about the safe and effective use of BEVYXXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BEVYXXA for a condition for which it was not prescribed. Do not give BEVYXXA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BEVYXXA that is written for health professionals.

What are the ingredients in BEVYXXA?

Active ingredient: betrixaban

Inactive ingredients: dextrose monohydrate, croscarmellose sodium, magnesium stearate, and a hard gelatin capsule

Manufactured for: Portola Pharmaceuticals, Inc., South San Francisco, California 94080 USA, Copyright© Portola Pharmaceuticals.
For more information, call 1-855-707-8052 or go to www. BEVYXXA.com

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 6/2017

BTX-US-MG-V.1.0