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 ≥ 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.

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