Immediate PRADAXA reversal

You are cordially invited to attend a Speaker Program on:

A New Paradigm in Oral Anticoagulation:

Superior Stroke Risk Reduction vs Warfarin in NVAF Patients and the Availability of Immediate Reversal

Speaker Name
Michael Stillabower, MD

Speaker Title
Director of Cardiovascular Clinical Trials

Speaker Affiliation
Christiana Hospital

Location Name
Firebirds

Location Address
1225 Churchmans Rd

Location City/State/Zip
Newark, DE 19713

Program Date
Thursday, July 14, 2016

Program Time
6:30 PM

RSVP
RSVP by Thursday, July 7, 2016
Michael Padovani at (215) 480-7320
michael.padovani@boehringer-ingelheim.com

BIPI acts in accordance with the PhRMA Code on Interactions with Healthcare Professionals. The PhRMA code states the inclusion of a Healthcare Professional's spouse or guest at an educational program is not appropriate and your attendance at the entire session is required. Your support of these ethical guidelines will help ensure a high quality learning environment for all participating Healthcare Professionals. Thank you.

We ask that all healthcare professionals abide by all relevant state and institutional restrictions on attending off-site, company-sponsored meals. The states of Minnesota and Colorado have restrictions on meals provided to healthcare professionals. Healthcare professionals licensed in Vermont may not attend a meal program.

Pradaxa® dabigatran etexilate CAPSULES

Praxbind® idarucizumab IV INJECTION 5g

Indications and Usage

Pradaxa® (dabigatran etexilate mesylate) capsules is indicated:

- to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation;
- for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days;
- to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated;
- for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery

IMPORTANT SAFETY INFORMATION ABOUT *PRADAXA*

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of PRADAXA and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients who are or will be anticoagulated.

INDICATIONS AND USAGE

PRAXBIND is indicated in patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is needed:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

This indication is approved under accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. Continued approval for this indication may be contingent upon the results of an ongoing cohort case series study.

IMPORTANT SAFETY INFORMATION ABOUT *PRAXBIND*

WARNINGS AND PRECAUTIONS

Thromboembolic Risk

- Dabigatran-treated patients have underlying diseases predisposing them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate.

Please see Important Safety Information throughout this piece and accompanying full Prescribing Information including boxed WARNING and Medication Guide for PRADAXA and full Prescribing Information for PRAXBIND.

IMPORTANT SAFETY INFORMATION ABOUT *PRADAXA (continued)*

CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:
– active pathological bleeding;
– known serious hypersensitivity reaction (e.g., anaphylactic reaction or anaphylactic shock) to PRADAXA;
– mechanical prosthetic heart valve

WARNINGS & PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation
Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant and restart PRADAXA as soon as medically appropriate.

Risk of Bleeding
- PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding.
- Risk factors for bleeding include concomitant use of medications that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment.
- *Reversal of Anticoagulant Effect:* A specific reversal agent (idarucizumab) for dabigatran is available when reversal of the anticoagulant effect of dabigatran is needed:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding

Hemodialysis can remove dabigatran; however clinical experience for hemodialysis as a treatment for bleeding is limited. Prothrombin complex concentrates or recombinant Factor VIIa may be considered but their use has not been evaluated. Protamine sulfate and vitamin K are not expected to affect dabigatran anticoagulant activity. Consider administration of platelet concentrates where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves
The use of PRADAXA is contraindicated in patients with mechanical prosthetic valves due to a higher risk for thromboembolic events, especially in the post-operative period, and an excess of major bleeding for PRADAXA vs. warfarin. Use of PRADAXA for the prophylaxis of thromboembolic events in patients with AFib in the setting of other forms of valvular heart disease, including bioprosthetic heart valve, has not been studied and is not recommended.

Effect of P-gp Inducers & Inhibitors on Dabigatran Exposure
Concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibition and impaired renal function are major independent factors in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to increase exposure of dabigatran compared to either factor alone.

Reduction of Risk of Stroke/Systemic Embolism in NVAF
- For patients with moderate renal impairment (CrCl 30-50 mL/min), reduce the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA.
- For patients with severe renal impairment (CrCl 15-30 mL/min), avoid concomitant use of PRADAXA and P-gp inhibitors.

Treatment and Reduction in the Risk of Recurrence of DVT/PE & Prophylaxis of DVT/PE Following Hip Replacement Surgery
- For patients with CrCl <50 mL/min, avoid use of PRADAXA and concomitant P-gp inhibitors

ADVERSE REACTIONS

The most serious adverse reactions reported with PRADAXA were related to bleeding.

Other Measures Evaluated

In NVAF patients, a higher rate of clinical MI was reported in patients who received PRADAXA (0.7/100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

Please see additional Important Safety Information about PRADAXA and accompanying full Prescribing Information, including boxed WARNING and Medication Guide.

IMPORTANT SAFETY INFORMATION ABOUT *PRAXBIND (continued)*

WARNINGS AND PRECAUTIONS *(continued)*

Re-elevation of Coagulation Parameters

- Elevated coagulation parameters (e.g., activated partial thromboplastin time or ecarin clotting time) have been observed in a limited number of PRAXBIND-treated patients. If reappearance of clinically relevant bleeding together with elevated coagulation parameters is observed or if patients requiring a second emergency surgery/urgent procedure have elevated coagulation parameters, an additional full dose may be considered.

Hypersensitivity Reactions

- There is insufficient clinical experience evaluating risk of hypersensitivity to idarucizumab, but a possible relationship could not be excluded. Risk of hypersensitivity (e.g., anaphylactoid reaction) to idarucizumab or excipients needs to be weighed cautiously against the potential benefit. If serious allergic reaction occurs, immediately discontinue PRAXBIND and institute appropriate treatment.

Risk in Patients with Hereditary Fructose Intolerance

- PRAXBIND contains 4 g sorbitol as an excipient. When prescribing PRAXBIND in patients with hereditary fructose intolerance consider the total daily amount of sorbitol/fructose consumption from all sources as serious adverse reactions (e.g. hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure and death) may occur.

ADVERSE REACTIONS

- The most frequently reported adverse reaction in ≥5% of idarucizumab-treated healthy volunteers was headache (12/224). The most frequently reported adverse reactions in ≥5% of patients were hypokalemia (9/123), delirium (9/123), constipation (8/123), pyrexia (7/123) and pneumonia (7/123).
- As with all proteins there is a potential for immunogenicity with idarucizumab. In treated patients, treatment-emergent antibodies with low titers were observed (9/224).

USE IN SPECIFIC POPULATIONS

Pregnancy and Nursing Mothers

- PRAXBIND should be given to a pregnant or nursing woman only if clearly needed.

Please see additional Important Safety Information about PRAXBIND and accompanying full Prescribing Information.

Pradaxa® dabigatran etexilate CAPSULES

Praxbind® idarucizumab IV INJECTION 5g

Boehringer Ingelheim