Boehringer Ingelheim: Leading The Evolution of Anticoagulation Care

APPROVED INDICATIONS
PRADAXA® 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.

PRAXBIND® 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.

GLOSSARY:
OAC: oral anticoagulant
NOAC: novel oral anticoagulant
NVAF: non-valvular atrial fibrillation
DVT: deep vein thrombosis
PE: pulmonary embolism
VTE: venous thromboembolism, including DVT and PE

2005
Initiation of phase III pivotal trial: PRADAXA in NVAF (RE-LY®)

2007
Initiation of phase III pivotal trial: PRADAXA in VTE (RE-COVER II™)

2008
Initiation of phase III pivotal trial: PRADAXA in VTE (RE-COVER II™)

2010
FDA approves first NOAC, PRADAXA for patients with NVAF

2011-2015
FDA approves additional NOACs in NVAF and VTE

2014
FDA approves PRAXBIND for PRADAXA patients when reversal of the anticoagulant effects of dabigatran is needed in rare emergency situations

2014
PRAXBIND granted Breakthrough Therapy Designation

2015
PRAXBIND application granted Priority Review

Please see Important Safety Information on next page and accompanying full Prescribing Information for Praxbind® and full Prescribing Information, including boxed WARNING and Medication Guide, for Pradaxa®.

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**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.

**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 acute gastrointestinal 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:** There is a specific agent that reverses the anticoagulant effect of PRADAXA in the rare event of an emergency. Hemodialysis can remove dabigatran; however clinical experience for hemodialysis as a treatment for bleeding is limited. Activated prothrombin complex concentrates, recombinant Factor VIIa, or concentrates of factors II, IX, or X may be considered but their use has not been evaluated. Prolamine 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 to PRADAXA vs. warfarin. Use of PRADAXA for the prophylaxis of thromboembolic events in patients with AFS in the setting of other forms of valvular heart disease, including bioprosthetic heart valve, has not been studied and is not recommended.

Effect of Pgp 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 (GCl 30-50 mL/min), reduce the dose of PRADAXA to 75 mg twice daily when droperidol or systemic ketoanazole is coadministered with PRADAXA.**
- **For patients with severe renal impairment (GCl <30 mL/min), avoid concomitant use of PRADAXA and P-gp inhibitors.**

**Treatment and Reduction in the Risk of Recurrence of DVT/PE**

- **For patients with GCl <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.

**NVAF**

- **Most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding & gastrointestinal (GI) events**
- **PRADAXA 150 mg resulted in higher rates of major and any GI bleeds compared to warfarin.**
- **In patients ≥75 years of age, the risk of major bleeding may be greater with PRADAXA vs warfarin.**
- **Patients on PRADAXA 150 mg had an increased incidence of GI adverse reactions.** These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, erosive hemorrhagic gastritis, and GI ulcer).

**DVT/PE**

- **Rates of any GI bleeds were higher in patients receiving PRADAXA 150 mg vs warfarin and placebo.**
- **In the active-controlled studies, there was a higher rate of clinical major cardiovascular infarction (MI) in PRADAXA patients [20 (0.66/100 patient-years)] vs warfarin [5 (0.17/100 patient-years)].** In the placebo-controlled study, there was similar rate of non-fatal and fatal clinical MI in PRADAXA patients [1 (0.32/100 patient-years)] vs placebo [1 (0.34/100 patient-years)].
- **GI adverse reactions were similar in patients receiving PRADAXA 150 mg vs warfarin.** They were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage).

Drug hypersensitivity reactions were reported in ≤ 0.1% of patients receiving PRADAXA.

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).

**PRAXBIND**

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Thromboembolic Events**

- **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.**

**Re-evaluation 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 re-evaluation of 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., anaphylactic 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 25% of idarucizumab-treated healthy volunteers was headache (12/224). The most frequently reported adverse reactions in 25% of patients were hypokalemia (9/123), dizziness (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 (0.1%).**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy and Nursing Mothers**

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

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