## 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.

## Important Safety Information

**BOXED WARNING:**

- **(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS**
- **(B) SPINAL/EPIDURAL HEMATOMA**

**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 in patients who have been previously treated.**

**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.

NOAC=novel oral anticoagulant; INR=international normalized ratio; CrCl=creatinine clearance.

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### PRADAXA: Patient Conversion Guide

#### Converting from warfarin

Discontinue warfarin and start PRADAXA when the INR is < 2.0.

Adjust the starting time of warfarin based on CrCl as follows:

<table>
<thead>
<tr>
<th>Recommended starting time of warfarin</th>
<th>Creatinine clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days before discontinuing PRADAXA</td>
<td>&gt;50 mL/min</td>
</tr>
<tr>
<td>2 days before discontinuing PRADAXA</td>
<td>30-50 mL/min</td>
</tr>
<tr>
<td>1 day before discontinuing PRADAXA</td>
<td>15-30 mL/min</td>
</tr>
<tr>
<td>No recommendations can be made</td>
<td>&lt;15 mL/min</td>
</tr>
</tbody>
</table>

- Because PRADAXA can increase INR, the INR will better reflect warfarin’s effect only after PRADAXA has been stopped for at least 2 days.

#### Converting from parenteral anticoagulants

Start PRADAXA 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

<table>
<thead>
<tr>
<th>Administration of parenteral anticoagulant</th>
<th>Recommended starting time of PRADAXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheduled dosing</td>
<td>0 to 2 hours before time of next dose</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>At the time of discontinuation</td>
</tr>
</tbody>
</table>

Wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of PRADAXA before initiating treatment with a parenteral anticoagulant.

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Please see additional Important Safety Information about PRADAXA on next page and full Prescribing Information, including boxed WARNING and Medication Guide.
IMPORTANT SAFETY INFORMATION

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 hypertension). 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 donepezil or systemic ketoconazole is coadministered with PRADAXA.
- For patients with severe renal impairment (CrCl <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 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.

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 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, hemorrhagic erosive 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 myocardial 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 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)

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 on previous page and full Prescribing Information, including boxed WARNING and Medication Guide.