Dosing &
Management
Guide

Please see Important Safety Information about PRADAXA and PRAXBIND throughout this brochure. Please see accompanying full Prescribing Information for PRADAXA, including boxed WARNING and Medication Guide, as well as full Prescribing Information for PRAXBIND.
Starting patients on PRADAXA
Assess renal function prior to initiating treatment with PRADAXA

General dosing information
- Should be taken with a full glass of water
- Taken with or without food
- No INR monitoring required
- Rapid onset—maximum plasma concentrations achieved 1–3 hours after administration
- Not metabolized by the cytochrome P450 system

Periodically assess renal function as clinically indicated and adjust therapy accordingly
- Assess more frequently in clinical situations that may be associated with a decline in renal function
- Discontinue PRADAXA in patients who develop acute renal failure and consider alternative anticoagulant therapy
- Generally, the extent of anticoagulation does not need to be assessed. When necessary, use aPTT and not INR to assess for anticoagulant activity in patients on PRADAXA

Indication-specific dosage strengths available: 75 mg, 110 mg, and 150 mg

RECOMMENDED DOSE FOR NVAF
- PRADAXA 150 mg twice daily for patients with CrCl >30 mL/min

REDUCED DOSE
- PRADAXA 75 mg twice daily for patients with CrCl 15-30 mL/min

DOSE ADJUSTMENTS
- In patients with moderate renal impairment (CrCl 30-50 mL/min):
  Reduce dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole

• In patients with CrCl <30 mL/min: Avoid concomitant use of PRADAXA and P-gp inhibitors
• For patients with CrCl <15 mL/min or on dialysis: Dosing recommendations cannot be provided

SELECT SAFETY INFORMATION ABOUT PRADAXA
WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, (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.

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**PRADAXA—dosing for DVT & PE patients**

Uniform dosing for the treatment of DVT & PE

<table>
<thead>
<tr>
<th>RECOMMENDED DOSE FOR DVT AND PE</th>
<th>PRADAXA 150 mg twice daily for patients with CrCl &gt;30 mL/min</th>
</tr>
</thead>
</table>

**DOsing INFORMATION**
- Initial treatment with parenteral anticoagulant for 5-10 days
- Patients can start PRADAXA on Day 6
- No bridging necessary

- In patients with CrCl <50 mL/min: Avoid concomitant use of PRADAXA and P-gp inhibitors
- For patients with CrCl ≤30 mL/min or on dialysis: Dosing recommendations cannot be provided

**For the reduction in risk of recurrence of DVT and PE**

<table>
<thead>
<tr>
<th>RECOMMENDED DOSE FOR DVT AND PE</th>
<th>PRADAXA 150 mg twice daily for previously treated patients with CrCl &gt;30 mL/min</th>
</tr>
</thead>
</table>

**DOsing INFORMATION**
- No parenteral anticoagulation necessary

- In patients with CrCl <50 mL/min: Avoid concomitant use of PRADAXA and P-gp inhibitors
- For patients with CrCl ≤30 mL/min or on dialysis: Dosing recommendations cannot be provided

**SELECT SAFETY INFORMATION ABOUT PRADAXA**

**CONTRAINDICATIONS**
- PRADAXA is contraindicated in patients with:
  - active pathological bleeding;
  - known serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock);
  - 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 bleeding (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 Vila 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.

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Converting patients on PRADAXA to and from other anticoagulants

**Warfarin**

**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 start of warfarin before discontinuing PRADAXA</th>
<th>Creatinine clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td>≥50 mL/min</td>
</tr>
<tr>
<td>2 days</td>
<td>30-50 mL/min</td>
</tr>
<tr>
<td>1 day</td>
<td>15-30 mL/min</td>
</tr>
</tbody>
</table>

- No recommendations can be made <15 mL/min

- 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 TO WARFARIN**

**Parenteral anticoagulants**

**CONVERTING FROM PARENTERAL ANTICOAGULANTS**

Administration of parenteral anticoagulant

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

Before initiating treatment with a parenteral anticoagulant:

**CONVERTING TO PARENTERAL ANTICOAGULANTS**

<table>
<thead>
<tr>
<th>Wait 12 hours after last dose of PRADAXA</th>
<th>Wait 24 hours after last dose of PRADAXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥30 mL/min</td>
<td>CrCl &lt;30 mL/min</td>
</tr>
</tbody>
</table>

**SELECT SAFETY INFORMATION ABOUT PRADAXA**

**WARNINGS & PRECAUTIONS**

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 dexamethasone 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 common adverse reactions reported with PRADAXA were related to gastritis-like symptoms and 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).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

The limited available data on PRADAXA use in pregnant women are insufficient to determine drug-associated risks for adverse developmental outcomes.

**Lactation**

Breastfeeding is not recommended.

**Geriatric**

Risk of bleeding increases with age.
Assessing anticoagulation activity of PRADAXA

GENERAL GUIDELINES

• INR is relatively insensitive to dabigatran exposure and cannot be interpreted the same way for warfarin monitoring
• When assessment is necessary, use aPTT and not INR to assess for anticoagulant activity in patients on PRADAXA
  – PRADAXA prolongs aPTT at therapeutic doses
• When possible, determine time of last dose of PRADAXA relative to time of blood sampling²

ANTICOAGULANT EFFECT

• aPTT provides an approximation of anticoagulant effect
  – Prolongation of aPTT occurs with increasing PRADAXA plasma concentration²
  – In the RE-LY® Trial, median (10th to 90th percentile) trough aPTT in patients receiving PRADAXA 150 mg was 52 (40 to 76) seconds
• The degree of anticoagulant activity can also be assessed by the ECT—a more specific measure of dabigatran effect

Average time course for effects of dabigatran on aPTT in patients with various degrees of renal impairment*†

- While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, curves in the aPTT time course can be used to estimate time to reach a particular level of aPTT recovery—even when time since the last dose of PRADAXA is not precisely known*
  – Plasma concentration levels decline relatively quickly following discontinuation in patients with normal renal function²

RE-LY=Randomized Evaluation of Long-term anticoagulant therAPy; ECT=ecarin clotting time; BID=twice daily; PK=pharmacokinetic; PTT=partial thromboplastin time.
*Curves represent mean levels without confidence intervals; variations should be expected when measuring aPTT.
**Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RE-LY Trial; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Roche Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between various established methods for aPTT assessment.

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Discontinuing PRADAXA before scheduled surgery and interventions

**HALF-LIFE**
- Healthy subjects: 12-17 hours

**BEFORE INVASIVE OR SURGICAL PROCEDURES**
- Due to an increased risk of bleeding, PRADAXA should be discontinued before invasive or surgical procedures, if possible:

<table>
<thead>
<tr>
<th>Discontinue 1-2 days before procedure</th>
<th>Discontinue 3-5 days before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥50 mL/min</td>
<td>CrCl &lt;50 mL/min</td>
</tr>
</tbody>
</table>
- Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal epidural catheter or port, in whom complete hemostasis may be required

**ADDITIONAL GUIDANCE**

- **Risk of bleeding**
  - If surgery cannot be delayed, there is an increased risk of bleeding
  - This risk of bleeding should be weighed against urgency of intervention
  - Use the specific reversal agent Praxbind® (idarucizumab) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed
  - Refer to the prescribing information for PRAXBIND for additional information
  - Restart PRADAXA as soon as medically appropriate

- **Discontinuation and increased risk of thrombotic events**
  - 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, consider coverage with another anticoagulant and restart PRADAXA as soon as medically appropriate

Additional instructions for patients

- Tell patients to take PRADAXA exactly as prescribed
- Remind patients not to discontinue PRADAXA without talking to the healthcare provider who prescribed it
- Instruct patients to remove only 1 capsule from the opened bottle at the time of use. The bottle should be immediately and tightly closed
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone
- Advise patients that the capsule should be taken with a full glass of water
- If GI symptoms develop, consider having the patient take PRADAXA within 30 minutes after a meal or adding a PPI

**Storage & handling of PRADAXA**

- Bottles and blister packs:
  - Store at 25°C (77°F)
  - Excursions permitted to 15°-30°C (59°-86°F)
  - Store in original package to protect from moisture
  - Patients should not place product in pill boxes or pill organizers

- Bottles only:
  - Patients should only open 1 bottle at a time
  - Keep the bottle tightly closed
  - Must be used within 4 months of opening

GI=gastrointestinal; PPI=proton pump inhibitor; NDC=national drug code.

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Accidents can happen—anytime, anywhere

Management of medical emergency*

- For emergency surgery/urgent procedures
  - Discontinue Pradaxa® (dabigatran etexilate)
  - Clinical evaluation of the need for reversal of anticoagulant effects in patients taking PRADAXA
  - Initiate use of PRAXBIND
  - Consider standard supportive measures as medically appropriate:
    - Surgical hemostasis
    - Volume replacement
    - Transfusion (e.g., pRBCs, platelets)

- In life-threatening/uncontrolled bleeding

• Additional considerations
  1. Determine reversal strategies as medically appropriate:
     - Blood products (prothrombin complex concentrates or recombinant Factor VIIa)†
     - PRADAXA—the only OAC that is dialyzable (~50% of dabigatran can be cleared from plasma over 4 hours)‡
     - Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of PRADAXA
     - Half-life of PRADAXA in healthy subjects is 12-17 hours
     - Anticoagulant effect and half-life of PRADAXA are increased in patients with renal impairment
     - If surgery cannot be delayed, there is an increased risk of bleeding and this risk should be weighed against the urgency of the intervention
  2. PRADAXA can be restarted as soon as medically appropriate

PrXBIND—ready-to-use agent for immediate reversal

Praxbind® (idarucizumab) 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

Immediate and complete reversal of PRADAXA with no procoagulant effects

In the RE-VERSE AD™ Trial,§

Median maximum reversal in evaluable patients was 100% in the first 4 hours¶

Most patients achieved complete reversal as measured by ECT (82%) or dTT (99%)||

1Based on determination for dTT or ECT.
2In a limited number of patients, elevated coagulation parameters (e.g., aPTT or ECT) have been observed 12-24 hours post-dose.

Study design: Multicenter, prospective, open-label study

Patients: Final study analysis included 503¶ patients taking PRADAXA who were administered PRAXBIND. The patients were divided into 2 groups:
• Group A (n=301): Patients who presented with life-threatening or uncontrolled bleeding
• Group B (n=202): Patients who required emergency surgery or urgent procedures

Study treatment: All patients were to receive 5 g of intravenous PRAXBIND, which was administered as two 50-mL bolus infusions, each containing 2.5 g of PRAXBIND, no more than 15 minutes apart

Primary endpoint: To determine the maximum percentage reversal of the anticoagulant effect of PRADAXA within 4 hours of administration of PRAXBIND, based on central laboratory determination of dTT or ECT in patients who presented with PRADAXA-related life-threatening or uncontrolled bleeding (Group A) or who required emergency surgery or urgent procedures (Group B)
- Reversal was evaluable only for those patients showing prolonged coagulation times prior to PRAXBIND treatment

SELECT SAFETY INFORMATION ABOUT PRAXBIND

WARNINGS & PRECAUTIONS

Thromboembolic Risk

• Dabigatran-treated patients have underlying diseases predisposing them to thromboembolic events. Reversing dabigatran therapy exposes patients to thrombotic risk.
  Consider resumption of anticoagulant therapy as soon as medically appropriate.

pRBCs=packed red blood cells; OAC=oral anticoagulant; dTT=diluted thrombin time. Coagulation factors and dialysis have not been evaluated in clinical trials and clinical experience for the management of medical emergencies is limited.

† Coagulation factors and dialysis have not been evaluated in clinical trials and clinical experience for the management of medical emergencies is limited.
‡ Accurate as of 5/31/19, based on the current information provided to Boehringer Ingelheim Pharmaceuticals, Inc. The company cannot guarantee the availability of the specific reversal agent treatment at all facilities in every state.
¶ Median age was 78 years and median CrCl was 53 mL/min. Approximately 62% of patients in Group A and 62% of patients in Group B had been treated with PRADAXA 110 mg BID.

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SELECT SAFETY INFORMATION ABOUT PRAXBIND

WARNINGS & PRECAUTIONS

Re-elevation of Coagulation Parameters

- Elevated coagulation parameters (eg, 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.

ETP=endogenous thrombin potential.

SELECT SAFETY INFORMATION ABOUT PRADBAXA and PRAXBIND throughout this brochure. Please see accompanying full Prescribing Information for PRADAXA, including boxed WARNING and Medication Guide, as well as full Prescribing Information for PRAXBIND.

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PRAXBIND—flexible administration for immediate reversal

Ready to use immediately

- One recommended dose for all Pradaxa® (dabigatran etexilate) patients
- No reconstitution needed

Intravenously administer the dose of 5 g (2 vials, each containing 2.5 g/50 mL) as:

- Do not mix with other medicinal products
- A pre-existing intravenous line may be used for administration of PRAXBIND. The line must be flushed with sterile 0.9% Sodium Chloride Injection, USP solution prior to infusion
- No other infusion should be administered in parallel via the same intravenous access

PRAXBIND has shown no procoagulant effect

- Measured as ETP

PRADAXA can be reinitiated after 24 hours

FIRST & ONLY specific reversal agent for a NOAC available nationwide*1

PRAXBIND is available in 3300+ institutions across all 50 states*1

For more information or to locate PRAXBIND in your state, visit PRAXBIND.com

*Accurate as of 5/31/19, based on the current information provided to Boehringer Ingelheim Pharmaceuticals, Inc. The company cannot guarantee the availability of PRAXBIND at all facilities in every state.

SELECT SAFETY INFORMATION ABOUT PRAXBIND

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions

- There is insufficient clinical experience evaluating risk of hypersensitivity to idarucizumab, but a possible relationship could not be excluded. Risk of hypersensitivity (eg, 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 (eg, hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure, and death) may occur.
PRAXBIND is available in 3300+ institutions across all 50 states*1

Ready-to-use agent for immediate reversal with no procoagulant effects

Quick, flexible administration

• Fast-acting reversal in a single 5-g dose (2 vials, each containing 2.5 g/50 mL)†
  – One recommended dose for all PRADAXA patients
  – Can be administered as an infusion OR bolus injection
• PRADAXA can be reinitiated after 24 hours

PRAXBIND orders are generally filled or restocked within 24-48 hours, and Boehringer Ingelheim offers a seamless return process for all expired products

SELECT SAFETY INFORMATION ABOUT PRAXBIND

ADVERSE REACTIONS

• The most frequently reported adverse reaction in ≥5% of idarucizumab-treated healthy volunteers was headache (5%). The most frequently reported adverse reactions in ≥5% of patients were constipation (7%) and nausea (5%).
• Treatment-emergent antibodies with low titers were observed in 4% of healthy subjects and 2% of patients treated with idarucizumab.

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

• PRAXBIND should be given to a pregnant woman only if clearly needed. Caution should be exercised when PRAXBIND is administered to a nursing woman.

CL-PB-100001 April 2018

*Accurate as of 5/31/19, based on the current information provided to Boehringer Ingelheim Pharmaceuticals, Inc. The company cannot guarantee the availability of PRAXBIND at all facilities in every state.
†There are limited data to support administration of an additional 5 g of PRAXBIND.

References:

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