



## DABIGATRAN (PRADAXA®)

### OBJECTIVE:

To provide an overview of the mechanism of action, licensed indications, dosing regimens, and side-effects of dabigatran.

### MECHANISM OF ACTION:

Dabigatran is an oral direct thrombin (factor IIa) inhibitor. By binding reversibly to the active site of thrombin, dabigatran attenuates thrombin activity and reduces fibrin formation.

### INDICATIONS:

Dabigatran is currently licensed in Canada for the following indications:

- Prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) after elective hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation who are candidates for oral anticoagulation therapy.
- Treatment of acute DVT and PE in patients who have initially received 5 to 10 days of a parenteral anticoagulant and prevention of recurrent DVT and PE.

### DOSING:

- Thromboprophylaxis after orthopedic surgery:** start with 110 mg 1-4 hours after surgery and increase to 220 mg once daily (OD) starting the day after surgery; the 220 mg OD dose is continued for at least 14 days and up to 35 days.
- Stroke prevention in atrial fibrillation:** 110 mg twice daily (BID) or 150 mg BID. Patients aged 80 years and older, or over 75 years old with 1 risk factor for bleeding should be treated with a dose of 110 mg BID. All other patients should receive 150 mg BID. There is no recommended dose adjustment for patients with moderate renal impairment (creatinine clearance [CrCl] 30 to 50 mL/min). Dabigatran is contraindicated in patients with a CrCl <30 mL/min.
- Treatment of DVT and PE:** Dabigatran 150 mg BID is started after 5 to 10 days of initial treatment with a parenteral anticoagulant. There is no recommended dose adjustment in patients with moderate renal impairment (CrCl 30 to 50 mL/min). The reduced dose of 110 mg has never been evaluated in a VTE treatment clinical trial.
  - Dabigatran should not be used in patients with a CrCl <30 mL/min, women who are pregnant or are breast-feeding, or in patients with active cancer.

## **MONITORING:**

Routine laboratory monitoring of the anticoagulant response is unnecessary. The prothrombin time/international normalized ratio (PT/INR) does not provide a reliable measure of its anticoagulant activity. The activated partial thromboplastin time (aPTT) is prolonged by dabigatran but the responsiveness of the test is reagent-dependent and the values plateau with higher dabigatran concentrations. Nonetheless, a prolonged aPTT indicates the presence of dabigatran and a normal test renders high dabigatran levels unlikely. The thrombin clotting time (TCT) is the most sensitive assay for the presence of dabigatran. It is always prolonged in the presence of dabigatran but it should not be used to monitor the anticoagulant activity. The dilute thrombin clotting time (commercially available as the Hemoclot<sup>®</sup> assay) shows a linear response with dabigatran plasma concentration. The ecarin clotting time or chromogenic assay also exhibits a linear response with dabigatran concentrations. Neither test is widely available and a therapeutic range has not been established. (See the Clinical Guide: New/Novel Oral Anticoagulants (NOACs): Coagulation Tests).

Although no routine laboratory monitoring is required for long-term dabigatran use, periodic clinical assessment is important to determine and reinforce adherence, review comorbidity and provide education. Furthermore, for most patients, at least yearly assessment of creatinine clearance is recommended. The creatinine should be measured more frequently in patients with an abnormal value at baseline.

## **ADVERSE EFFECTS:**

The major adverse effect of dabigatran is bleeding; concomitant use of antiplatelet drugs increases this risk. Dabigatran should be avoided in patients with indwelling epidural catheters or traumatic spinal punctures in order to reduce the risk of epidural or spinal hematomas. Dabigatran may be associated with dyspepsia in up to 10% of users; the frequency of this complication can be reduced by having patients take the drug with meals. Dyspepsia usually resolves with time and may improve with the use of an anti-ulcer medication such as a proton pump inhibitor, but caution is advised as the absorption of dabigatran is decreased when co-administered with aluminum, magnesium or calcium containing antacids.

## **PERI-PROCEDURAL MANAGEMENT:**

See Clinical Guide: New/Novel Oral Anticoagulants (NOAC): Peri-Operative Management

## **SPECIAL CONSIDERATIONS:**

**Administration and storage:** Dabigatran may be taken with or without food. Capsules should be swallowed whole. The capsule should not be crushed, chewed or opened before swallowing. Capsules should be stored in their blister package to protect them from moisture.

**Bleeding:** Idarucizumab, a humanized antibody fragment against dabigatran, is now available as an antidote for dabigatran. Idarucizumab, which is given as an intravenous bolus at a dose of 5 grams,

rapidly reverses the anticoagulant effect of dabigatran. Approaches to the management of bleeding can be found in the Clinical Guide: New/Novel Oral Anticoagulants (NOACs): Management of Bleeding.

**Drug Interactions:** Dabigatran absorption is decreased by agents that increase gastric pH (i.e. magnesium or aluminum containing antacids); however there is no contraindication to concurrent use of proton pump inhibitors.

Selective serotonin re-uptake inhibitors (SSRIs) increased bleeding by 50 to 100% and selective serotonin norepinephrine re-uptake inhibitors (SNRIs) increased bleeding by 100% in atrial fibrillation patients in the RELY trial. Concomitant use of these drugs should be avoided.

Because dabigatran etexilate is a substrate of the P-glycoprotein transport system, potent inhibitors or inducers are expected to impact exposure to dabigatran.

a) *Inhibitors of P-glycoprotein:* Drugs that inhibit this transport system can increase systemic exposure to dabigatran. Concomitant use of the strong P-glycoprotein inhibitors (e.g. ketoconazole, dronedarone) is contraindicated. Caution is advised if taken with moderate inhibitors (e.g. cyclosporine, itraconazole, ritanovir, and tacrolimus). Patients who are taking the P-glycoprotein inhibitors quinidine and verapamil, the latter of which is commonly used in patients with atrial fibrillation, should take the dabigatran dose 2 hours prior to a dose of verapamil or quinidine. No dosage adjustment to dabigatran is recommended for patients concurrently taking these interacting medications for atrial fibrillation or VTE treatment, but dose reduction to 150 mg once daily is recommended by the manufacturer for thromboprophylaxis in hip or knee replacement.

b) *Inducers of P-glycoprotein:* Drugs that induce P-glycoprotein can decrease the systemic exposure to dabigatran. Co-administration with potent inducers such as carbamazepine, phenytoin, rifampin and Saint John's wort, should be avoided.

**Renal and hepatic dysfunction:** Dabigatran is contraindicated in patients with CrCl <30 mL/min. Dose modification is not needed in patients with hepatic impairment but dabigatran should be used with caution in those with cirrhosis or baseline coagulopathy who are at high risk of bleeding.

**Mechanical heart valves:** Dabigatran is contraindicated in patients with mechanical heart valves.

**Pregnancy and breast feeding:** Dabigatran crosses the placenta and should not be used in pregnancy. It is unknown whether dabigatran passes into the breast milk; therefore, dabigatran should not be used in nursing mothers.

**Pediatrics:** Dabigatran is not recommended for use in children until ongoing studies establish the pharmacokinetics, pharmacodynamics, safety, and efficacy of dabigatran in neonates and children.

## **OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- New/Novel Oral Anticoagulants (NOACs): Comparison and Frequently Asked Questions
- New/Novel Oral Anticoagulants (NOACs): Coagulation Tests
- New/Novel Oral Anticoagulants (NOACs): Management of Bleeding
- New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management
- Pediatrics: New Anticoagulants
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery

#### **REFERENCES:**

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**Date of Version:** 2015Oct10

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