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**Volume 27, Issue No. 1** **February, 2010**

# NEW ORAL ANTICOAGULANTS

As of 2009, two new anticoagulants have been approved in Canada – Pradax™ (dabigatran etexilate) and Xarelto® (rivaroxaban). The new agents are conveniently dosed once daily, have few dosage adjustments and do not require regular INR monitoring like the typical vitamin K antagonist warfarin. Another advantage of the new anticoagulants is oral administration which avoids the hassle of injections associated with the heparins. The agents have an immediate onset of anticoagulation[1,2] unlike warfarin which takes around 5 days to achieve full anticoagulation. Both dabigatran and rivaroxaban have received approval in Canada for the prophylaxis of venous thromboembolism (VTE) following elective total hip or knee replacement surgery.

## Dabigatran etexilate

### How does dabigatran work?

Dabigatran is supplied as a prodrug – dabigatran etexilate – that is rapidly absorbed after oral administration and is quickly converted to the active moiety in the plasma and liver.[1] Dabigatran exerts its effect by directly inhibiting thrombin (factor IIa).[1] Thrombin is the coagulation factor responsible for converting fibrinogen to fibrin which leads to clot formation.

### When is dabigatran indicated?[1]

Dabigatran is indicated for the prevention of VTE in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.

### Dose/Administration[1]

The recommended dose of dabigatran is 220 mg once daily, taken with or without food. Treatment should be initiated with a single dose of 110 mg within 1-4 hours after completion of surgery and achievement of hemostasis and continued with 220 mg once daily thereafter. If treatment is started on any day other than the day of surgery, initiate dabigatran at 220 mg once daily. Dose reduction is recommended in moderate – severe renal impairment (CrCL 30-50 mL/min) as 85% of the dabigatran dose is renally eliminated. Treat for 10 days following TKR and 28 -35 days following THR surgeries.

### Efficacy

Three large phase III trials have been conducted to evaluate safety/efficacy of dabigatran vs. enoxaparin for VTE prophylaxis following hip/knee surgery. Dabigatran appears to be as effective and as safe as enoxaparin for VTE prevention when compared to the European enoxaparin dose (40 mg once daily).[3] However, the one study comparing dabigatran to the Canadian-approved enoxaparin dose (30 mg twice daily) found dabigatran to be less effective; the Common Drug Review has recommended dabigatran not be listed on formularies.[4]

### Cost/Availability

Pradax™ is approved for use in Canada and is available at most wholesalers. However, it is currently not on the Saskatchewan formulary or covered by EDS.[5]
Pradax™ 75 mg (30capsules) ≈ $126[6] Pradax™ 110 mg (30 capsules) ≈ $126[6]

### Safety/Risk-benefit Profile[1]

Rates of bleeding were similar between dabigatran and enoxaparin in the major trials

conducted comparing the two agents. Dabigatran was otherwise well tolerated.
*Drug Interactions*: dabigatran is not metabolized by the CYP450 enzymes, although the parent compound – dabigatran etexilate -- is a substrate of the p-glycoprotein (P-gp) transporter. Co-administration with potent P-gp inhibitors/inducers may affect dabigatran levels in the blood.

**Rivaroxaban (Xarelto®)**

**How does rivaroxaban work?**

Rivaroxaban is a competitive, selective, direct factor Xa inhibitor.[2] Factor Xa is responsible for the conversion of prothrombin to thrombin.

**When is rivaroxaban indicated?**

Rivaroxaban is indicated for the prevention of VTE in patients who have undergone elective THR or TKR surgery. [2]

**Dose/Administration:** [2]

The recommended dose of rivaroxaban is 10 mg once daily taken orally with or without food. Treatment with rivaroxaban should be initiated within 6-10 hours after surgery, once hemostasis has been achieved. Treatment should be continued for a total of 14 days for TKR surgery and 35 days for THR surgery.

**Efficacy:**

From the data of five trials, rivaroxaban appears to be slightly more effective at preventing VTE post-knee/hip replacement surgery than enoxaparin; four of these trials compared the European dose of enoxaparin but one used the Canadian-approved dose.[7]

**Cost/Availability:**

Xarelto® is available at most wholesalers at a cost of $474/50 tablets.[6]
Xarelto® has EDS status on the Saskatchewan Formulary with the following criteria:

a) for prophylaxis following total knee arthroplasty for up to 14 days following the procedure[5]
b) for prophylaxis in patients undergoing total hip replacement for up to 14 days following the procedure[5]

*Note: While the manufacturers recommend duration of 35 days VTE prophylaxis following total hip replacement surgery, the Canadian Expert Drug Advisory Committee (CEDAC) felt there was insufficient evidence to recommend prophylaxis beyond 14 days.*[7]

**Safety:** [2]

Rates for bleeding between rivaroxaban and enoxaparin were not found to be statistically different. Rates of major bleeding for rivaroxaban vs. enoxaparin were 0.3% vs. 0.2% respectively. Rivaroxaban was otherwise well tolerated with a low incidence of adverse effects.
*Drug Interactions:* rivaroxaban is a CYP 3A4 and P-gp substrate. Strong inhibitors of *both* CYP 3A4 and P-gp are contraindicated (ie. azole antimycotics and ritonavir). Strong inhibitors of only one of p-GP or CYP 3A4 are not expected to alter rivaroxaban concentrations to a significant degree. Strong CYP 3A4 inducers may reduce rivaroxaban concentrations to subtherapeutic levels and should only be used in combination with caution.

**In the works…**

Studies are underway to evaluate the long-term safety and efficacy of these new oral anticoagulants. There is hope that one day they may be found to be safe and effective enough to replace warfarin for indications such as atrial fibrillation. Until such time, they should only be used for their proven indications of VTE prophylaxis following elective THR or TKR surgery.

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