Pharmacy Bulletin
Dabigatran - new anticoagulant

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Dabigatran **(Pradaxa®)** is an alternative anticoagulant to warfarin funded since 1st July 2011 and licensed to prevent stroke in patients with atrial fibrillation, and as an alternative to low molecular weight heparin in venous thromboembolism prophylaxis post major orthopaedic surgery.

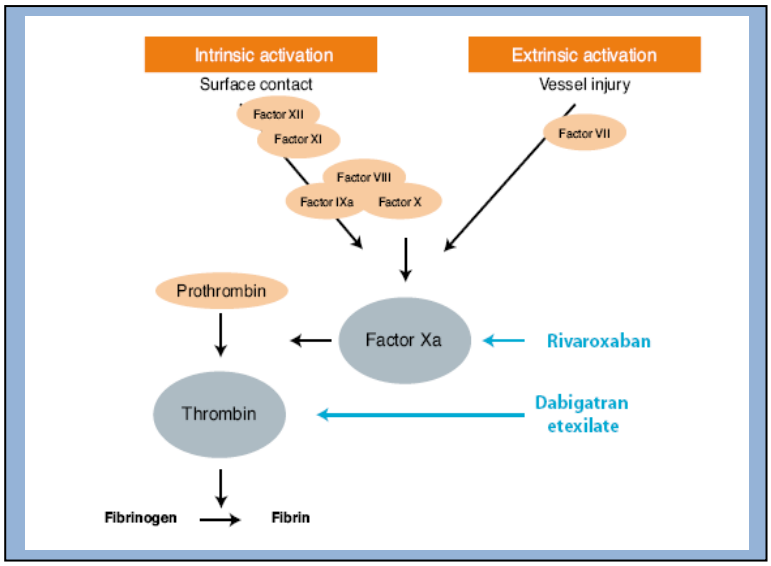
This bulletin provides a summary of the properties of dabigatran. Please refer to data sheet for full information.

Mode of Action

Dabigatran etexilate is a new oral direct thrombin inhibitor. It is a prodrug that is metabolised by the liver to its active component, dabigatran.

Properties

The pharmacokinetics and pharmacodynamics of dabigatran are more predictable than those for warfarin[1]. This means it has a more predictable dose-response relationship than warfarin i.e. there is less intra and inter-patient variation in respect to response to dose [1,2]. For this reason, dabigatran does not require *routine* monitoring. If monitoring is needed aPTT or TT are options[3,4].



Site of action of new anticoagulants (Diagram from Aust Prescriber[4])

Table 1. Summarises some of the comparatives properties of warfarin and dabigatran etexilate:

Property	Warfarin	Dabigatran etexilate
Onset of anticoagulant effect	36-72 hours	Within 30 minutes (max effect 0.5-2 hrs)
Duration of anticoagulant effect	48-96 hours	24-36 hours
Elimination half-life	20-60 hours	7-9 hours (young adults), 12-18 hours (older adults)
Predictable pharmacokinetics	No	Yes
Monitoring	Routine INR monitoring	No routine monitoring required
Dosing	Individualised according to INR	Fixed according to clinical condition
Use in severe renal impairment	No dose adjustments required	Increased drug plasma levels. Contraindicated if CrCl < 30ml/min
Use in liver failure	Contraindicated or cautioned	Possibly safe, but caution advised
Reversibility after cessation	Several days Antidote available – vitamin K	24-48 hours, dependant on renal function and elimination half life. **No antidote available – vitamin K not effective**
Interactions with food & alcohol	Yes	Low potential
Medication interactions	Numerous	Not as common. See table below

Table adapted from Australian Prescriber[5]

Precautions to use

The **risk of bleeding** is **similar to warfarin**, therefore the **benefit vs risk** of therapy still needs to be assessed, taking into account that although dabigatran has a much shorter half life than warfarin, there is **no antidote** available to reverse its effects (i.e. vitamin K is not effective.)

Table 2. Factors that can increase bleeding risk with dabigatran include[3]:

Any factors that increase dabigatran plasma levels	Moderate renal impairment (30-50 ml/min CrCl) P-glycoprotein drug interactions (see interactions table)
Disease/procedures with bleeding risk	Includes: coagulation and platelet disorders, ulcerative or bleeding GI conditions, surgery, intracranial haemorrhage, recent biopsy, major trauma, bacterial endocarditis
Age	≥ 75 years

Contraindications to use include:

- Severe renal impairment (CrCl < 30ml/min)
- Known hypersensitivity to dabigatran etexiliate or excipients
- Active bleeding or risk of significant bleeding
- Haemorrhagic stroke within last 6 months
- Co-prescribing with ketoconazole
- Prosthetic heart valve replacement [10,11]

There is no data available on dabigatran in pregnancy, breast feeding, age < 18 years, or liver impairment (patients with liver enzymes > 2 x upper limit of normal were excluded from studies). Use **not recommended** in these situations.

Common Adverse Effects

- Generally related to anticoagulation effect and in the range similar to warfarin
- Except for gastrointestinal (GI) disorders which are higher for dabigatran[3] with dyspepsia being reported by approximately **12%** of patients compared to 5.8% for warfarin[1].
- **Long term safety data not yet available**.

Drug interactions

Dabigatran has less drug and food interactions than warfarin. Part of the bioconversion to the active metabolite occurs in the liver, however the cytochrome p450 system is not involved[1]. P-glycoprotein inhibitors may potentially increase dabigatran concentrations.

Table 2. Summarises some known interactions:

Interacting medication	Comment	Recommendation
P-glycoprotein inhibitors	May ↑ concentrations of dabigatran Includes cyclcosporin, clarithromycin, ketaconazole, itraconazole, ritonavir, saquinavir, tacrolimus	Use cautiously & monitor for signs of bleeding Ketaconazole - contraindicated
P-glycoprotein inducers	May ↓ concentrations of dabigatran Includes rifampicin (↓ dabigatran levels up to 67%), carbamazepine, St John's Wort	Use cautiously Avoid rifampicin if possible Avoid St John's Wort
Amiodarone	P-glycoprotein inhibitor	No dose adjustment in AF, use the 150mg daily dose of dabigatran for VTE prophylaxis
Verapamil	P-glycoprotein inhibitor	Avoid combination if possible, see manufacturer's recommendations[7]

IMPORTANT

Any medications that increase bleeding risk - such as aspirin, clopidogrel, NSAIDs, heparins and possibly SSRIs -will, similar to warfarin, increase the risk of bleeding with dabigatran.

Dabigatran in prevention of VTE

Dabigatran is considered to be an acceptable alternative to enoxaparin 40mg once daily for the prevention of thromboembolism after elective hip or knee replacement. Three large studies conducted by the manufacturer compared the use of dabigatran with enoxaparin in prevention of VTE post orthopaedic surgery. Two studies (one post hip and one post knee replacement) demonstrated 'noninferiority' for dabigatran 150mg and 220mg once daily compared to enoxaparin once 40mg daily, with major bleeding being similar[2]. One study concluded that dabigatran was 'inferior' to enoxaparin after knee replacement surgery, however the dose of enoxaparin used was 30mg bd[6] . Evidence-based guidelines from NICE report broadly similar efficacy for dabigatran vs low molecular weight heparins after hip or knee replacement[7].

Dabigatran vs Warfarin in AF

The RE-LY study[8] involved more than 18,000 patients with non valvular AF for the prevention of stroke. Two doses of dabigatran (110mg bd and 150mg bd) were compared with warfarin (target INR 2-3); median follow-up 2 years. It was a non-inferiority study with primary outcomes of stroke or systemic embolism. Summarised findings were:

- dabigatran 150mg bd resulted in lower risk of stroke/systemic embolism compared to warfarin and similar risk of major bleeding. Slightly higher risk of **MI** was associated with this higher dabigatran dose.
- dabigatran 110mg bd was associated with similar rates of stroke/systemic embolism and lower rates of major bleeding compared to warfarin.

Overall, dabigatran appears to be similar in efficacy and safety to warfarin. It offers an advantage in that it does not require routine monitoring, however its **higher rate of GI adverse effects** may limit its use in some patients. It may be a preferable option in patients where monitoring is difficult.

Patients who should remain on warfarin?[9]

- Severe renal impairment (<30ml/min creatinine clearance)
- Mechanical heart valve replacement
- Severe valvular disease requiring anticoagulation
- On long term treatment for deep vein thrombosis (DVT) and pulmonary embolism (PE)

Patients who you could consider prescribing dabigatran to?[9]

- Diagnosis of AF and at increased thromboembolic risk who should be on warfarin, but currently on either no treatment or inadequate treatment
- On warfarin for AF but having trouble managing the monitoring regimen or not achieving control (or who wish to change for convenience)
- Short term treatment for prophylaxis of VTE post major orthopaedic surgery

Administration of capsules

- Absorption in the stomach and small intestine is dependent on an acid environment and the capsule is formulated with tartaric acid. Advise patient to swallow capsule whole with or without food – **do not open capsules or sprinkle on food.**
- Once opened. bottles of Pradaxa ® must be used within 30 days. The manufacturers are investigating a blister packaging capsule option to lengthen the shelf-life of the capsules.

Dosing Information

Table 3

Indication	Dose[3]	CrCl 30-50ml/min**	CrCl < 30ml/min
VTE prevention post knee replacement	**110 mg** within 1-4 hours of surgery, then **220 mg** once daily for 10 days*	Reduce dose to **150 mg** once daily	Avoid
VTE prevention post hip replacement	**110 mg** within 1-4 hours of surgery, then **220 mg** once daily for 28-35 days*	Reduce dose to **150 mg** once daily	Avoid
Prevention of stroke/embolism in AF	**150 mg twice daily** (life long) Patients ≥ 80 yrs: **110 mg twice daily** Patients at increased bleeding risk: consider **110mg twice daily** and monitoring coagulation	Recommend reducing dose to **110mg twice daily**	Avoid

***** Refer to data sheet for guidance if haemostasis not secured post surgery
** Do not rely on the laboratory reported eGFR; calculate CrCl before prescribing

Missed Dose

In prevention of *VTE post orthopaedic surgery* – do not take double dose, continue with usual dose the next day.

In prevention of *stroke/embolism in AF* – the missed dose can be taken up to 6 hours prior to next scheduled dose. From 6 hours prior to next scheduled dose - do not take the missed dose. Do not take a double dose.

Switching patient from warfarin to dabigatran

Warfarin should be stopped and dabigatran can be given as soon as the INR is < 2.0.

Please refer to specific guidance in data sheet if switching patient from **dabigatran** to **warfarin.** Dosing guidance is dependent on the patient's renal function and warfarin will need to be started before dabigatran is discontinued.

References

1. Garcia D, Libby E, Crowther MA. Review Article: The new oral anticoagulants. Blood 2010;115(1):15-20
2. Gallus A. New oral anticoagulants – clinical applications. Australian Prescriber 2010;23(2)42-47
3. Pradaxa ® datasheet. Boehringer Ingelheim (NZ) Limited. Prepared on 11 Feb 2011. Available on http://www.medsafe.govt.nz/ Viewed on 16/04/2013
4. Guidelines for testing and perioperative management of dabigatran. Pharmac Information sheet, June 2011
5. Brighton T. New oral anticoagulant drugs-mechanisms of action. Australian Prescriber 2010;33(2):38-41
6. REMOBILIZE writing committee, Ginsing JS, Davidson BL et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of VTE after knee arthroplast surgery. J Arthroplasty 2009;24:1-19
7. National Institute for Health and Clinical Excellence. Dabigatran etexilate for the prevention of venous thromboembolism after total hip or knee surgery in adults. London: NICE, 2008. http://www.nice.org.uk/nicemedia/live/12059/42032/42032.pdf,
8. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009;361(12):1139-1151
9. Dabigatran (Pradaxa ®) – Pharmac Bulletin, June 2011
10. Van de Werf et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomised, phase 11 study to evaluate the safety and phramcokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN) American Heart Journal 2012;163:931-7
11. Prescriber Update 2013;34(1):2