



# Dabigatran (Pradaxa) to be listed without restriction

Dabigatran (Pradaxa) will be listed with no restrictions later in 2011. The listing date will be confirmed in June.

Dabigatran is a direct thrombin inhibitor. It is administered orally as the prodrug dabigatran etexilate, which is rapidly absorbed and converted through esterase-catalysed hydrolysis in plasma and in the liver. The half life of dabigatran is about 12-14 hours, it is de-esterified to the active drug, and is excreted primarily in urine.

Direct thrombin and Factor Xa inhibitors are new classes of oral anticoagulants that do not require regular blood monitoring. Use of these new classes of medicines could promote better anticoagulation management, with less monitoring burden on the patient.

Three doses (75mg, 110mg and 150mg capsules) will be listed on the Pharmaceutical Schedule later this year with no Special Authority or prescriber type restriction.

# How does dabigatran compare to current standard treatments like warfarin and enoxaparin?

As dabigatran is a relatively new drug, its adverse risk profile is less well described than other standard treatments.

## *Stroke prevention in AF*

In the RE-LY trial<sup>1</sup>, warfarin therapy was compared to two doses of dabigatran: 110mg and 150mg administered twice daily. For the primary outcome of stroke or systemic embolism, rates compared to warfarin (1.69%) were non-inferior for the 110mg dose of dabigatran (1.53%;  $p < 0.001$ ) and superior for the 150mg dose of dabigatran (1.11%;  $p < 0.001$ ).

In the same trial, the rate of major bleeding when 110mg dabigatran was administered twice daily was less (2.71%) compared to those administered warfarin (3.36%;  $p = 0.003$ ). For those administered 150mg of dabigatran twice daily, similar rates of major bleeding were observed (3.11%) compared to those administered warfarin (3.36%;  $p = 0.31$ ).

Both doses of dabigatran (110mg and 150mg) were associated with significantly lower rates of intracerebral haemorrhage when compared to warfarin.

## *VTE prophylaxis following major orthopaedic surgery*

In the RE-MODEL trial<sup>2</sup>, dabigatran (150mg and 220mg administered once daily) was found to be non-inferior to enoxaparin for VTE prophylaxis after total knee replacement.

Dabigatran (150mg and 220mg administered once daily) was also non-inferior to enoxaparin for VTE prophylaxis after total hip replacement based on the RE-NOVATE trial<sup>3</sup>.

Based on the RE-MODEL and RE-NOVATE trials, there were no significant differences in major bleeding events between both doses of dabigatran (150mg and 220mg administered once daily) and enoxaparin.

## Indications for dabigatran

Dabigatran (Pradaxa) is indicated (and registered in New Zealand) for:

- Prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation (AF);
- Venous thromboembolism (VTE) prophylaxis following major orthopaedic surgery.

## Who can dabigatran be prescribed to?

You could consider prescribing dabigatran to the following patients:

- patients with AF considered at increased thromboembolic risk who should be on warfarin, but are currently on no, or inadequate treatment;
- patients already on warfarin for AF, who are having trouble managing the monitoring regime or not achieving control, or who wish to change for convenience;
- patients who need short term treatment for prophylaxis of VTE post major orthopaedic surgery.

Guidelines for management of Atrial Fibrillation may be found: on the NZ Guidelines Group website [www.nzgg.org.nz](http://www.nzgg.org.nz) (Cardiovascular risk guidelines 2009) and the European Society of Cardiology's website [www.escardio.org](http://www.escardio.org) (last revised in 2010). Tables to assess risk factors for stroke and thromboembolism are outlined in these guidelines.

## Who should remain on warfarin?

- patients with mechanical heart valves;
- patients with severe valvular disease requiring anticoagulation;
- patients on long term treatment for deep vein thrombosis (DVT) and pulmonary embolism (PE);
- patients with severe renal impairment (<30ml/min creatinine clearance).

<sup>1</sup> Connolly et al (2009) *N Engl J Med*. Sep 17; 361(12): 1139-51.

<sup>2</sup> Eriksson et al (2007) *J Thromb Haemost*. Nov; 5(11): 2178-85.

<sup>3</sup> Eriksson et al (2007) *Lancet*. Sep 15; 370 (9591): 949-56.

## How do I prescribe dabigatran?

### *For stroke prevention in AF:*

- the recommended daily dose of dabigatran is 300mg to be taken orally as 150mg twice daily;
- for elderly patients aged  $\geq 80$  years, a daily dose of 220mg taken orally as 110mg twice daily is recommended.

### *For VTE prophylaxis following major orthopaedic surgery:*

- total knee replacement, the recommended dose is 220mg once daily for 10 days;
- total hip replacement, the recommended dose is 220mg once daily for 28-35 days;
- for patients with moderate renal impairment (creatinine clearance 30-50ml/min), the lower dose of 150mg once daily is recommended.

See Medsafe datasheet [www.medsafe.govt.nz](http://www.medsafe.govt.nz) for further information on dosing.

## What are the risks associated with dabigatran use?

- dabigatran has a similar bleeding risk profile to warfarin. However, as dabigatran is a relatively new drug, its adverse risk profile is less well described than warfarin;
- dabigatran currently has no direct antidote, which is important to note for acute bleeds or for a patient undergoing emergency surgery. Further information about how to manage acute bleeds and procedures for reversal agents is being developed and will be made available before listing;
- dabigatran causes dyspepsia in approximately 11% of patients;
- twice daily dosing regime can create compliance issues for some patients;
- there is no easy way to determine whether the drug is working.

## How do I monitor patients on dabigatran?

While there is currently no direct monitoring test for dabigatran, such as INR levels for warfarin, there are some assays that can be done to assess a patient's bleeding risk. These include:

- activated partial thromboplastin time (aPTT);
- thrombin time (TT); and
- ecarin clotting time (ECT).

Further information on these tests is being developed and will be made available before listing.

## How do I transition patients to and from dabigatran?

### *Transitioning patients from warfarin to dabigatran*

Dabigatran can be prescribed once warfarin is stopped and INR is  $< 2.0$ .

### *Transitioning patients to warfarin from dabigatran*

When transitioning to warfarin from dabigatran, adjust the starting time of warfarin based on creatinine clearance as follows:

- For creatinine clearance  $> 50$  ml/min, start warfarin 3 days before discontinuing dabigatran;
- For creatinine clearance 31-50 ml/min, start warfarin 2 days before discontinuing dabigatran.

### *Transitioning patients from parenteral coagulation to dabigatran*

Dabigatran should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (for example intravenous unfractionated heparin).

### *Transitioning patients to parenteral coagulation from dabigatran*

For VTE prophylaxis following major orthopaedic surgery, wait 24 hours after the last dose before switching from dabigatran to a parenteral anticoagulant.

For stroke prevention in AF, wait 12 hours after the last dose before switching from dabigatran to a parenteral anticoagulant.

See Medsafe datasheet [www.medsafe.govt.nz](http://www.medsafe.govt.nz) for further information about beginning and discontinuing dabigatran.

## Is it safe to carry out minor surgery on patients taking dabigatran eg, oral surgery?

The risk of bleeding for minor surgeries is less well described for dabigatran, but would be similar to warfarin.



# DABIGATRAN

## Where can I find further information about dabigatran?

Further information can be found:

- In the Medsafe datasheet – [www.medsafe.govt.nz](http://www.medsafe.govt.nz);
- In guidelines for management of Atrial Fibrillation on the NZGG website [www.nzgg.org.nz](http://www.nzgg.org.nz) and ESC website [www.escardio.org](http://www.escardio.org).

Information about dabigatran outlining dangerous interactions, risk profiles of combining dabigatran with low-dose aspirin and/or clopidogrel, managing acute bleeding episodes and procedures for reversal agents will be included in a future edition of the BPJ.

The following resources will also be available to order from the BPAC and PHARMAC websites once dabigatran is listed:

- A patient information leaflet;
- A FAQ for clinicians transitioning patients onto dabigatran; and
- Anticoagulation guidance for managing bleeding episodes.



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