



Dabigatran, an oral direct thrombin inhibitor, is approved by the TGA for:

- 'Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement)' for which it is also PBS listed.
- 'Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.'

It is not currently listed on the Queensland Health List of Approved Medicines (LAM).

Although dabigatran has only been on the Australian market for less than 2 years, there have been recent incident reports of haemorrhage and deaths in Queensland, nationally and internationally. This has prompted the need for specific guidelines for the management of patients presenting to hospital who are already taking the drug.

Risk factors for adverse events with dabigatran include: age older than 75 years, low body weight (less than 50kg), and **moderate or severe renal impairment** (CrCl less than 50mL/min). Dabigatran is primarily renally excreted and is **contraindicated if creatinine clearance (CrCl) is less than 30mL/min**. Note: Calculation of CrCl should be determined using ideal body weight with the Cockcroft Gault equation (see below) as it is more accurate than eGFR for patients who are elderly or who have low body weight.

	Cockcroft Gault equation CrCl = $\frac{\{(140 - \text{Age}) \times \text{wt (kg)} \times F\}}{(\text{Serum creatinine} \times 0.8136)}$
	Where F = 1 if male, and 0.85 if female
	Ideal body weight: Female (kg) = $45.5 + 0.9 \times [\text{height (cm)} - 152]$
	Male (kg) = $50 + 0.9 \times [\text{height (cm)} - 152]$

Monitoring / Pathology testing

There is currently no assay available for dabigatran levels in Queensland Health facilities. Advice should be sought from local laboratories on availability of coagulation tests. Monitoring with INR is not recommended. The following tests are qualitative indicators and can be influenced by concomitant use of other anticoagulants:

- **Activated partial thromboplastin time (APTT)** is moderately sensitive to dabigatran, but it becomes increasingly insensitive with higher levels. A trough (when the next dose is due) APTT of 1.5 times the baseline value is seen with 150mg twice daily of dabigatran in patients with normal renal function. Trough APTT values greater than 80 seconds are associated with increased bleeding risk.
- **Thrombin time (TT)** is very sensitive to dabigatran, and a normal TT (14–19 seconds) excludes the presence of significant dabigatran levels but is not useful for monitoring or dose adjustment.

Routine testing is generally not conducted during treatment with dabigatran because it has a predictable pharmacokinetic profile enabling a fixed-dose regimen. Laboratory testing is currently limited but may be helpful in the following situations:

- in the **peri-operative setting**
- for **acute coronary syndrome (ACS)**
- in the **event of bleeding**
- when **renal function is deteriorating**
- when **parenteral anticoagulants are being considered for a patient taking dabigatran**
- for **patients at high risk of bleeding** (e.g. age older than 75 years, weight less than 50kg, renal impairment with CrCl less than 50mL/min).

Drug interactions

Close clinical monitoring is recommended (watch for signs of bleeding or anaemia) during concomitant administration of the following agents, especially if risk factors (see introduction section) are present:

Other Anticoagulants (rivaroxaban, warfarin, lepirudin, heparin, enoxaparin, fondaparinux)

Antiplatelets (aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine)

Non-steroidal anti-inflammatory drugs (NSAIDs) - Monitor for risks of bleeding if dabigatran is used with NSAIDs, especially those with half-lives greater than 12 hours (e.g. naproxen, piroxicam). NSAIDs with short half-lives less than 12 hours (e.g. ibuprofen) have not been shown to be associated with increased bleeding risk.

P-glycoprotein efflux transporter inhibitors and inducers

As the prodrug dabigatran exilate is a substrate of this transporter, avoid use in combination with the following:

Inhibitors which may increase levels of dabigatran:

- calcium channel blockers (diltiazem, nifedipine, verapamil)
- immunosuppressants (cyclosporin, tacrolimus)
- macrolides (clarithromycin, erythromycin)
- azoles (itraconazole, ketoconazole)
- protease inhibitors (ritonavir, saquinavir)
- others (amiodarone, dipyridamole, hydrocortisone, progesterone, propranolol, quinine, tamoxifen).

Studies to date have not shown clinically relevant interactions with amiodarone, atorvastatin, clarithromycin, ketoconazole, or verapamil.

Inducers which may reduce levels of dabigatran:

- rifampicin
- St John's wort.

Management of bleeding

Currently, there is no available antidote for dabigatran. Prothrombin complex concentrates have been shown to be ineffective (in contrast to rivaroxaban studies). Vitamin K and fresh frozen plasma infusion have not been shown to be effective. The effect of Factor VIIa (Novoseven®) is currently unknown.

Dabigatran associated bleeding

If a patient is bleeding, discontinue dabigatran therapy and investigate for site of bleeding.

Initiate symptomatic treatment and optimise renal function.

Review all medications and discontinue all anticoagulants, anti-platelets and NSAIDs. Check for possible drug interactions (see above).

Check coagulation screen (APTT, TT and fibrinogen assay); indicate time of last dose on request form.

Check full blood count, renal function and electrolytes (including calcium).

Organise blood group and hold, and blood group antibody screen.

Mild bleeding	Moderate to severe bleeding*	Life threatening†
<ul style="list-style-type: none"> • Withhold next dose of dabigatran or discontinue treatment as appropriate. • Apply local measures and treat any underlying infection. 	<ul style="list-style-type: none"> • Discontinue dabigatran. • Consult Haematology Service. • Mechanical compression, or consider surgical intervention or wound packing. • Fluid replacement to maintain good urine output as dabigatran is renally excreted. • Consider platelets if levels less than $70-80 \times 10^9/L$ or patient on anti-platelet agent. • Consider anti-fibrinolytic agent, tranexamic acid IV 15-30mg/kg, possibly followed by a continuous infusion at 1mg/kg/hr and continue until bleeding under control. • Oral charcoal application if dabigatran ingested in last 2 hours. 	<ul style="list-style-type: none"> • Implement all measures for moderate to severe bleeding, and: • Recombinant factor VIIa (Novoseven®) IV bolus 50microg/kg may be trialled if critical. Seek Haematology guidance.* Note factor VIIa half life is significantly shorter than dabigatran; may require further dosing of factor VIIa. • Haemodialysis (especially if renal failure present) may remove approximately 60% of dabigatran. • Charcoal haemofiltration.

* **Moderate to severe bleeding:** reduction in Hb of greater than or equal to 20g/L, transfusion of greater than or equal to 2 units of red blood cells, or symptomatic bleeding in critical area or organ.

† **Life-threatening bleeding:** symptomatic intracranial bleed, reduction in Hb of greater than or equal to 50g/L, transfusion of greater than or equal to 4 units of red blood cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

♦ NB: Individual Patient Approval should be obtained as per hospital or District procedure for recombinant factor VIIa 'For the management of life-threatening bleeding and coagulopathy in non-haemophilic patients who have failed to respond to conventional therapy.' (QH LAM, see Appendix 9).

Management peri-operatively

Semi-acute or elective surgery

- Assess the risk of bleeding against the risk of thrombosis as dabigatran may not need to be discontinued for minor procedures.
- If dabigatran needs to be withheld, plan ahead as there is no treatment available for immediate reversal.
- Consider bridging anticoagulant therapy if there is a high risk of thrombosis (see *Bridging or switching to or from other anticoagulants*).

Dabigatran is primarily renally excreted, therefore renal function will determine the time frame to withhold the medication prior to surgery. Renal function should be checked pre-admission and the patient provided with instructions about when to withhold dabigatran pre-operatively. **In situations where complete haemostasis is required, APTT and TT should be checked pre-operatively.**

Renal function (CrCl, mL/min) NB. Use Cockcroft Gault equation with ideal body weight (see page 1)	Dabigatran half-life (range)	Withholding time of dabigatran prior to surgery after last dose	
		Standard bleeding risk	High bleeding risk ^a
Greater than 80	13 (11–22) hrs	48 hrs	4–5 days
51–80	15 (12–34) hrs	48 hrs	4–5 days
31–50	18 (13–23) hrs	At least 72 hours	4–5 days
Equal to or less than 30	27 (22–35) hrs	5 days - do not restart	Greater than 5 days - do not restart

^a Types of surgery associated with high risk of bleeding include cardiac surgery, neurosurgery, abdominal surgery, surgery involving a major organ, or in major surgery where complete haemostasis may be required. Other procedures such as spinal anaesthesia may require complete haemostasis. Other risk factors for bleeding include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of anti-platelet therapy.

Urgent surgery

Stop dabigatran.

- Check full blood count, electrolytes (including calcium), renal function and coagulation screen (APTT, TT and fibrinogen assay); indicate time of last dabigatran dose on request form.
- Consider delaying surgery, if appropriate, until coagulation screen is normal or until sufficient time for drug clearance (4 half-lives).
- Where urgent life-saving surgery cannot be delayed, consult with Haematology Service over measures to control bleeding prior to and during surgery.
- Epidural or spinal anaesthesia is contraindicated.

Cross-match blood.

Recommendations regarding epidural and spinal catheter

Epidural or spinal anaesthesia is contraindicated, unless dabigatran has been eliminated as indicated by a normal TT (14–19 seconds).

Dabigatran should not be recommenced in patients who have an epidural or spinal catheter in place.

Dabigatran should not be restarted within 12 hours of removal of spinal or epidural catheter. Delay for at least 24 hours if multiple punctures or traumatic insertion of spinal or epidural catheter.

Restarting dabigatran after surgery

Discuss with Haematology Service regarding individual patients, based on nature of surgery, urgency of restarting anticoagulant therapy, and haemostatic state.

- Do not restart dabigatran in severe renal impairment (i.e. CrCl equal to or less than 30mL/min).
- In elective surgery where haemostasis is satisfactory, it is suggested that dabigatran is restarted with a single capsule (110 mg or 150 mg depending on the indication) after at least 12 hours and when surgeon considers it safe to do so.
- If haemostasis is not satisfactory and clinically significant wound losses are present, a delay in restarting dabigatran is appropriate.
- Consider using an alternative reversible anticoagulant if the risk of thrombosis is greater than the risk of wound bleeding.

Venous Thromboembolism (VTE) prophylaxis

Do not commence pharmacological VTE prophylaxis (e.g. heparin, enoxaparin) if patient is taking dabigatran.

If dabigatran is ceased, and VTE prophylaxis is indicated, start pharmacological prophylaxis when APTT is less than 60 seconds.

Bridging or switching to or from other anticoagulants

Conversion from dabigatran to a parenteral anticoagulant

- For conversion from dabigatran to unfractionated heparin (UFH) infusion, loading doses of UFH should not be given.
- Only use UFH. Low molecular weight heparins such as enoxaparin should not be used.

Unfractionated Heparin Dosing

- The *Queensland Health Heparin Intravenous Infusion Order and Administration - Adult* form should be used as a guide for dose adjustment only.
- Measure APTT at 12 hours after last dabigatran dose.
 - If APTT is less than 60 seconds, start UFH infusion without loading dose. Measure APTT 6 hours after UFH infusion has started, then every 4–6 hours.
 - If APTT is greater than 60 seconds, repeat APTT every 6 hours until APTT is less than 60 seconds, then start UFH infusion without loading dose. Measure APTT 6 hours after UFH infusion has started, then every 4–6 hours.

Conversion from a parenteral anticoagulant to dabigatran

Do not restart dabigatran with severe renal impairment (i.e. CrCl equal to or less than 30mL/min).

- For conversion from an UFH infusion to dabigatran, start dabigatran when infusion ceased.
- For conversion from enoxaparin to dabigatran, start dabigatran 12 hours after the last dose of enoxaparin.

Conversion from dabigatran to warfarin

- For conversion from dabigatran to warfarin, adjust the starting time of warfarin based on renal function (see table below) and start dosing as per the *Queensland Health Guidelines for Anticoagulation Using Warfarin - Adult*.

Creatinine clearance (CrCl)	Initiate warfarin:
Greater than 50 mL/min	3 days before discontinuing dabigatran
31 to 50 mL/min	2 days before discontinuing dabigatran
Less than 30mL/min	Dabigatran is contraindicated - discontinue and start warfarin

- As dabigatran can contribute to an elevated INR, the INR will better reflect the effect of warfarin after dabigatran has been ceased for 2 days.
- If patient has previously been on warfarin, restart on usual dose.

Conversion from warfarin to dabigatran

- For conversion from warfarin to dabigatran, discontinue warfarin and start dabigatran when INR is below 2.

Acute coronary syndrome (ACS)

ST Elevation Myocardial Infarction (STEMI)

- For parenteral anticoagulation for ACS in dabigatran treated patients, unfractionated heparin (UFH) is preferred to enoxaparin.
- For patients receiving dabigatran, primary percutaneous coronary intervention (PCI) is preferred (if available) to thrombolysis.
- Similar to patients on warfarin, anticoagulation with dabigatran is a relative, not absolute, contraindication to thrombolysis. The decision to thrombolysise should be based on an assessment of the perceived benefit (e.g. anterior versus inferior myocardial infarction, time to presentation) versus the perceived risk of a bleeding complication (e.g. elderly, reduced renal function, presence of other relative contraindications).
- If thrombolysis is administered, do not start UFH within 12 hours of last dabigatran dose or longer if impaired renal function (see likely half life-lives with renal impairment in the table in Management peri-operatively).
- Loading doses of UFH should not be given.
- See section above for table showing Unfractionated Heparin Dosing**

Non-ST Elevation Acute Coronary Syndrome (NSTEMI)

(e.g. Non-ST Elevation Myocardial Infarction (NSTEMI) and Unstable Angina)

- For parenteral anticoagulation for ACS in dabigatran treated patients, unfractionated heparin (UFH) is preferred to enoxaparin.
- Do not start UFH within 12 hours of the last dose of dabigatran or longer if impaired renal function (see likely half life-lives with renal impairment in the table in Management peri-operatively).
- See section above for table showing Unfractionated Heparin Dosing**