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Waitemata District Health Board
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DABIGATRAN – SAFE PRESCRIBING – NOT A MAGIC BULLET

- INFORM PATIENTS TO REPORT ANY BLEEDING IMMEDIATELY
- BLEEDING MAY REQUIRE URGENT REFERRAL
- CHECK RENAL FUNCTION BEFORE PRESCRIBING - USE THE CORRECT DOSE
- CONSIDER POTENTIAL INTERACTIONS AND ADVERSE EFFECTS
- COMMUNICATE GOOD COMPLIANCE AND APPROPRIATE ADMINISTRATION

Dabigatran etexilate is a direct thrombin inhibitor. It is indicated for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with non-valvular atrial fibrillation. It is also indicated for the prophylaxis of venous thromboembolism (VTE) post major orthopaedic surgery, for the treatment of acute VTE and for the prophylaxis of recurrent VTE.[1] Dabigatran must not be given to patients with prosthetic heart valves.[1]

INFORM PATIENTS TO REPORT ANY BLEEDING IMMEDIATELY

As with all anticoagulants, there is a risk of bleeding.[1] Avoid giving dabigatran to patients with haemorrhagic risk factors including gastrointestinal bleeding, recent trauma, haemorrhagic stroke (within 6 months) or following brain, spinal or ophthalmic surgery.[1] Educate patients to report any signs of bleeding immediately.

The risk of bleeding may be increased with:

- Patients over 75 years old
- Patients with moderate renal impairment (Creatinine clearance (CrCl) 30-50mL/min)
- Concomitant treatment with antiplatelet agents
- Previous gastro-intestinal bleed

For these patients a dose reduction is usually recommended. See dosing information (page 3).

BLEEDING MAY REQUIRE URGENT REFERRAL

Monitor patients for signs of bleeding at each appointment and check for symptoms of anaemia. **If there is any bleeding**, discontinue dabigatran, check thromboplastin time (TT) and activated partial thromboplastin time (aPTT), note when the last dose was taken, and discuss further with a haematologist or cardiologist.[1] A combination of intensive interventions may be required to contain the situation. A dabigatran reversal agent called **idarucizumab** (Praxbind®) is available in the hospital setting for those patients requiring urgent reversal for bleeding or who require urgent surgery/procedures within 8 hours.

Although the relationship between TT and bleeding risk for patients taking dabigatran is unknown, a normal TT indicates an absence of dabigatran anticoagulant effect and could be used to exclude dabigatran as a cause of haemorrhage.[2]

The aPTT doesn't have a linear association with the dose of dabigatran and may underestimate the level of thrombin inhibition.[2] The prothrombin time (PT) is insensitive to dabigatran.[2]

Because frequent monitoring is not required, regular review should be arranged for patients with comorbidities or renal insufficiency.[3] Fatal haemorrhage associated with dabigatran is more prevalent in older patients.[4]

CHECK RENAL FUNCTION BEFORE PRESCRIBING – USE THE CORRECT DOSE

Dabigatran is predominantly cleared by the kidneys, and will accumulate if renal function is compromised. Dabigatran **must not** be given to patients with severe renal impairment (CrCl less than 30mL/min) because there is no data to support use in these patients.[1] Discontinue dabigatran if acute renal failure develops during treatment.[1]

Patients who have moderate renal impairment (CrCl 30-50mL/min) may require a lower dose.[1] See dosing information (page 3). Older patients and patients with unstable renal function are at risk of undertreating or overtreating with fixed doses of dabigatran.[4] For these patients in particular, carefully consider the risk-benefit of prescribing dabigatran; other anticoagulants may be more suitable.

It is recommended that prescribers do not rely on the laboratory reported eGFR to assess renal function. Calculate CrCl based on lean body weight (or actual body weight if the patient is lean) before prescribing, and every 6-12 months while on treatment.[1,3] Reassess if the patient becomes dehydrated, or is prescribed concomitant medicines that will further compromise renal function (such as diuretics or NSAIDs).

Medsafe recommends careful monitoring of patients aged 80 years and above who are taking dabigatran, particularly those with impaired renal function or low body weight.[5]

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Note: Dabigatran is best avoided in patients with severe liver disease, especially if the prothrombin time is prolonged.[6] Patients with moderate-to-severe hepatic impairment are generally excluded from clinical trials,[1] so there is insufficient evidence to recommend use in these patients.

CONSIDER POTENTIAL INTERACTIONS AND ADVERSE EFFECTS

The well-known dietary and drug interactions associated with warfarin do not appear to be so prevalent with dabigatran,[7] however, there are several important interactions to be aware of. Concomitant administration with **ketoconazole** is contraindicated due to the increased dabigatran plasma concentrations and the increased risk of bleeding.

Amiodarone, verapamil, quinidine and **clarithromycin** are also expected to result in increased dabigatran plasma concentrations.[1] Combinations with **amiodarone** and **verapamil** are best avoided but if they must be given, it is advisable to either reduce the dose of dabigatran, or to dose at different times of day and monitor closely for signs of bleeding.[6] Because **amiodarone** has a very long half-life, the interaction may still be apparent for several weeks after amiodarone has been discontinued.[6]

Particular care is needed in patients with renal impairment who are also taking the medications listed above, because of the high dependence of dabigatran on renal elimination.[3]

Rifampicin reduces the exposure of dabigatran and will compromise its efficacy, so is best avoided. Interactions with **St John's Wort, phenytoin** and **carbamazepine** are yet to be studied in detail, but are also expected to reduce the efficacy of dabigatran, and should be avoided if at all possible.[6]

Concomitant treatment with **clopidogrel**, **ticagrelor**, **aspirin** or **dipyridamole** will increase the risk of bleeding with dabigatran, and caution is advised when using **NSAIDs**.[1,3] Concurrent use of **SSRIs** or **SNRIs** could also increase the risk of bleeding.[6] Because routine monitoring of dabigatran is not required, the extent of individual interactions may only become apparent after patients present with bleeding or an embolic event. Please ensure the patient is aware of this and reports any unexplained bruising or bleeding immediately, especially gastrointestinal bleeds.[4]

COMMUNICATE APPROPRIATE ADMINISTRATION AND GOOD COMPLIANCE

It is important that patients are informed about the appropriate administration of dabigatran to minimise the risk of oesophageal ulcer.

Advise all patients to swallow the capsules whole with a large glass of water, and preferably with food.[7] If possible, patients should remain upright after swallowing the capsules. Dabigatran must not be crushed or chewed, and the capsule should not be opened and sprinkled onto food.[1] Because of the risk of oesophageal ulceration, dabigatran is not suitable for patients who have oesophagitis or difficulty swallowing.[7]

Ask patients about dyspepsia or 'heart burn' at each visit and inform patients about appropriate administration.

Good compliance with dabigatran is vital because there is a rapid loss of effect if doses are missed.[6] Make sure the patient is aware of this, and consider other options if there are any concerns about compliance.

Dabigatran must be kept in the original pack due to a rapid loss of chemical stability once the packaging is opened.[1] Dabigatran is not suitable for re-packing into compliance aids like Webster® or Medico® packs.

Atrial fibrillation (AF)

Patients with AF require ongoing anticoagulation to reduce the risk of blood clots. These can potentially lead to stroke and systemic embolism. Dabigatran may be a useful alternative for patients with AF who are not managing the monitoring requirements for warfarin, or are not well controlled.[3] Patients who are currently prescribed aspirin instead of warfarin because of concerns about interactions or managing regular testing, may benefit from dabigatran instead of aspirin. Ensure that the patient understands that compliance with **twice daily** dosing is very important to ensure efficacy.[6]

Be aware that the risk of a major bleed associated with dabigatran is similar to warfarin[3,8,9] and much higher than aspirin alone. If there are uncertainties about dabigatran, do not change from warfarin without specialist advice. For patients who are well controlled with warfarin, there is little reason to switch between anticoagulant treatments.[4]

Venous thromboembolism (VTE)

Dabigatran is indicated for the treatment and prevention of VTE under certain circumstances (see dosing information on page 3). Note that the dose and frequency of administration varies depending on the indication. For some indications, there is limited data available for patients with multiple risk factors for bleeding; dabigatran should only be prescribed if the expected benefit outweighs the bleeding risks.[1]

Dabigatran may be considered for patients who need short-term prophylaxis of VTE after major orthopaedic surgery.[1] For this indication, dosing is **once daily**, and the dose should be reduced if renal function is compromised. The duration of treatment varies depending on the type of surgery.

For patients at risk of recurrent VTE and related death, treatment with dabigatran is **twice daily** and potentially life-long depending on the individual patient risk.[1]

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For the treatment of VTE, and the prevention of related death, dabigatran should be started after the patient has received at least 5 days of parenteral anticoagulant therapy.[1] Dabigatran may then be given as a **twice daily** dose for up to 6 months.

DOSING INFORMATION

ATRIAL FIBRILLATION[3] (Prevention of stroke, systemic embolism and reduction of vascular mortality)

Age	Dose
18-79y	150mg twice daily
75-80y (if low thromboembolic risk and high bleeding risk)	110mg twice daily
80y and older	110mg twice daily
Renal impairment Moderate (CrCl 30-50mL/min)	110mg twice daily
Severe (CrCl <30mL/min)	do not prescribe
PREVENTION OF VTE following major orthopaedic surgery	
Knee replacement surgery: 1-4 hours following surgery	110mg
Days 2-10 postoperatively	220mg once daily
Hip replacement surgery: 1-4 hours following surgery	110mg
Days 2-28 or 2-35 postoperatively	220mg once daily
Renal impairment: Moderate (CrCl 30-50mL/min)	150mg once daily
Severe (CrCl <30mL/min)	do not prescribe
PREVENTION OF RECURRENT VTE	
Ongoing treatment depending on individual risk	150mg twice daily
Renal impairment: Severe (CrCl <30mL/min)	do not prescribe
TREATMENT OF VTE	
Following parenteral anticoagulant for at least 5 days	150mg twice daily (up to 6months)
Renal impairment Severe (CrCl <30mL/min)	do not prescribe

Note: The majority of dosing data is for patients weighing between 50 and 100kg.[3] There is currently no information about safe dosing for patients under 18 years, or during pregnancy or lactation.[3] Enoxaparin should still be used for VTE in pregnancy, and warfarin remains the treatment of choice when breastfeeding.

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