

Prescribing Criteria for Dabigatran (Pradaxa®) in Stroke Prevention in (non-valvular) AF

Dabigatran is licensed for prevention of stroke and systemic embolism in ADULT patients with non-valvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke or transient ischemic attack
- Age ≥ 75 years
- Diabetes mellitus, heart failure (NYHA Class \geq II) or hypertension

Dabigatran has been approved as a GREEN drug across Wiltshire.

However, any potential use of Dabigatran outside of NICE and/or license should be discussed with the CCG Medicines Management Team

NICE TA249 (published March 2012) allows Dabigatran to be used as an option in stroke prevention in AF as per the license above. **The CHADS2-VASc score can be used to assess a patient's stroke risk.**

Please use the following checklists in order to prescribe Dabigatran appropriately and safely.

***NOTE: These lists are not exhaustive and professional judgment should be used on an individual patient basis.**

1. Does the patient have any of the following contra-indications (from Summary of Product Characteristics (SPC))? **(tick any that apply)*

<input type="checkbox"/>	Severe renal impairment (CrCL < 30 ml/min)
<input type="checkbox"/>	Patients with prosthetic heart valves requiring anticoagulant treatment
<input type="checkbox"/>	Active clinically significant bleeding
<input type="checkbox"/>	Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
<input type="checkbox"/>	Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
<input type="checkbox"/>	Hepatic impairment or liver disease expected to have any impact on survival.
<input type="checkbox"/>	Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole and dronedarone.
<input type="checkbox"/>	Hypersensitivity to dabigatran or to any of the excipients

If any of the above contra-indications apply to your patient do not prescribe Dabigatran and seek advice.

2. Patient groups where specialist advice should be sought before prescribing **(tick any that apply)*

<input type="checkbox"/>	Previous history of intracranial haemorrhage – <i>some AF patients especially those considered at high risk of stroke may benefit from anti-thrombotic therapy</i>
<input type="checkbox"/>	Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated
<input type="checkbox"/>	Women of child-bearing potential should avoid pregnancy during treatment with Dabigatran.
<input type="checkbox"/>	Patient with recent history of recurrent falls who are at higher bleeding risk.

3. Assess your patient's bleeding risk. - The following risk factors can increase the risk of bleeding: (the HAS-BLED score can be used to assess the bleeding risk of the patient – see reverse of 'Choosing the most suitable oral anticoagulant' document for further information)

<input type="checkbox"/>	Previous history bleed or predisposition to bleeding (e.g. diverticulitis)	<input type="checkbox"/>	Brain spinal or ophthalmic surgery
		<input type="checkbox"/>	Chronic alcohol abuse- especially if associated with binge drinking.
<input type="checkbox"/>	Congenital or acquired coagulation disorders	<input type="checkbox"/>	Uncontrolled hypertension
<input type="checkbox"/>	Recent biopsy or major trauma	<input type="checkbox"/>	Bacterial Endocarditis
<input type="checkbox"/>	Moderate renal impairment CrCl 30-50ml/min (see dosing in renal impairment info on page 2)	<input type="checkbox"/>	Acute hepatic impairment (e.g. bilirubin > 2xULN + LFTS > 3x ULN), chronic liver disease (e.g.cirrhosis)
<input type="checkbox"/>	Low platelet count < 80 x 10 ⁹ /L, thrombocytopenia, functional platelet defects or anaemia of undiagnosed cause	<input type="checkbox"/>	On concomitant drugs associated with an increased bleeding risk e.g. SSRIs, SNRIs, oral steroids, NSAIDs, clopidogrel, methotrexate or other immune-suppressant agents or P-gp inhibitors which increase plasma levels of Dabigatran.
<input type="checkbox"/>	Low body weight (<50kg)	<input type="checkbox"/>	

Patients at high risk of bleeding should be considered for the lower daily dose (110mg bd). It would also be worth considering co-prescription of a PPI to add gastroprotection.

What dose to prescribe

Patient Group	Dosing
Standard adult dosing	150mg twice a day, continued in long term
Patients aged between 75 – 80 years	150mg twice a day. <i>However 110mg twice a day could be considered at the discretion of the prescriber when the thromboembolic risk is low & bleeding risk is high.</i>
Patients aged 80 years or above	110mg twice a day due to the increased risk of bleeding in this population
Patients with gastritis, oesophagitis, or gastroesophageal reflux	<i>110mg twice a day may be considered due to the elevated risk of major gastrointestinal bleeding in this population</i>
Other patients at high risk of bleeding	<i>Consider using 110mg twice a day</i>

Other Prescribing Considerations

Renal Function - As the renal function declines, the drug clearance is reduced.	
Creatinine Clearance (ml/min)	Recommended dose
Mild renal impairment (Cr Cl 50 to ≤80ml/min)	No dose adjustment
Moderate renal impairment (Cr Cl 30-50ml/min)	150mg BD but if pt has a high bleeding risk, consider 110mg BD.
Severe renal impairment (Cr Cl <30ml/min)	Contra-indicated
Do baseline urea & creatinine prior to initiating Dabigatran and at least once a year during continued treatment in those aged >75 years or those with suspected decline in renal function.	

Weight of patient
No dose adjustment is necessary, but close monitoring of any adverse effects is recommended for patients with a body weight of less than 50kg. It may be prudent to check the patient's weight regularly & haemoglobin in this situation. Low weight is associated with increased dabigatran plasma levels which could lead to increased bleeding risk.

Patients being switched from Warfarin
Warfarin should be stopped and then dabigatran started once the INR is below 2.0. So INR monitoring would be needed initially.

Other important considerations:
<ul style="list-style-type: none"> Patients should be told that they should not open the capsule as this can increase the risk of bleeding - the bioavailability may be increased by 75% when the pellets are taken out of the capsule shell. Therefore Dabigatran should NOT be put down an enteral tube (e.g. PEG or NG tube). If this affects your patient, contact medicines management at the CCG for further advice. A bleeding risk that would lead to a contra-indication to warfarin would also contra-indicate dabigatran. Sub-optimal compliance with warfarin may not be improved by switching to dabigatran as many of the causes of non-compliance with warfarin may also result in non-compliance with dabigatran (e.g. alcoholism, chaotic lifestyle, wilful non-compliance). As dabigatran has a short half-life (12-17hrs) missing a dose could be associated with an increased risk of stroke. Ensure that the patient is given an alert card by the pharmacy and that the patient knows to carry it around with them. Dabigatran is not stable in monitored dosage systems (e.g. dossette) as per warfarin. Dabigatran has an antidote, idarucizumab, which can be used in secondary care under the advice of a haematologist.

Drug Interactions (See SPC for full details, this list is not exhaustive)

Interacting Drug	Management
Anti-platelets (e.g. aspirin, clopidogrel)	Concomitant use of antiplatelets, ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin. Depending on the patients overall risk of bleeding, the lower 110mg bd dose of Dabigatran could be considered. Careful monitoring for bleeds and anaemia would be essential. Seek advice.
NSAIDs	NSAIDs increased the risk of bleeding by approximately 50% (chronic use) on both Dabigatran and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended. NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk.
P-gp inhibitors: e.g. Amiodarone, Verapamil, Quinidine, Ketoconazole, Dronedarone, Ticagrelor and Clarithromycin	Combination thought to result in increased Dabigatran plasma concentrations. Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole and Dronedarone is contraindicated. Concomitant treatment with tacrolimus is not recommended. Use with mild to moderate P-gp inhibitors such as amiodarone, quinidine, verapamil or ticagrelor is cautioned. For patients on verapamil, do not exceed 110 mg twice daily.
P-gp inducers: e.g. Rifampicin, St. John's wort, Carbamazepine, or Phenytoin	Expected to result in decreased Dabigatran concentrations and should be avoided.
Protease Inhibitors e.g. Ritonavir	They have not been studied and are therefore not recommended for concomitant treatment with Dabigatran.
SSRIs & SNRIs	Increase the risk of bleeding.