Rationale for Initiation, Continuation and Discontinuation (RICaD)

Dabigatran etexilate ▼ (Pradaxa)

For the prevention of stroke and systemic embolism in atrial fibrillation (NICE TA 249)

This document supports the use and transfer of an agent which is classified as **AMBER**.
It is intended for completion by specialist in order to give Primary Care prescribers a clear indication of the reason for recommending an **AMBER** medication together with suggested criteria for its subsequent continuation or discontinuation. This RICaD should be provided as a supplement to the specialist's clinical letter.

Patient details		**GP details**		**Specialist details**	
Name		**GP name**	**Dr**	**Specialist name**	
PID		**GP address**		**I confirm that this patient is eligible to receive dabigatran under the restrictions listed below**	
DOB				**Signature**	
Patient address				**Date**	
				Contact details	

Rationale for Choice

Relevant Diagnosis:	Non-valvular atrial fibrillation ☐
Agreed Indication(s) for inclusion in the BSSE APC Formulary:	As specified in NICE TAG 249: for patients with non-valvular atrial fibrillation with one or more of the following risk factors. Specialists please check appropriate box • Previous stroke, transient ischaemic attack or systemic embolism ☐ • Left ventricular ejection fraction below 40% ☐ • Symptomatic heart failure of New York Heart Association class 2 or above ☐ • Age 75 years or older ☐ • Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension ☐
Reason why dabigatran has been chosen in preference to drugs without Formulary restrictions:	Specialists please check appropriate boxes and complete relevant information: I can confirm that an informed discussion about the benefits and risks of dabigatran compared with warfarin has taken place with the patient. A copy of the checklist is enclosed ☐ Allergic reaction/intolerance of coumarins (warfarin, phenindione, sinthrome) ☐ Patients with important and unavoidable drug interactions that favour dabigatran over warfarin ☐ Patients in whom monitoring and/or coping with variable dose regimen is difficult but who are able to comply with a fixed dose drug regime. ☐ Previous significant bleed on warfarin in patients at high risk for stroke, if bleed was associated with poor INR control in a patient who is believed to be adherent with prescribed medication. ☐ Poor INR control (e.g. more than 2 INRs >8.0 or more than 3 INRs >5.0 in 6 months) ☐ Poor Time to Therapeutic Range List TTR value: …… ☐ Patients who, following informed discussion of risks and benefits of dabigatran and warfarin, request dabigatran as their preferred choice in terms of a favourable lifestyle in comparison to warfarin

Rationale for Choice cont….

Special precautions	**Contraindications** • Hypersensitivity to the active substance or to any of the excipients listed. • Patients with severe renal impairment (CrCL < 30 mL/min). • Active clinically significant bleeding. • 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. • 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. • Hepatic impairment or liver disease expected to have any impact on survival. • Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole and dronedarone. • Prosthetic heart valves requiring anticoagulant treatment. **Cautions** <u>Hepatic impairment</u> • Patients with elevated liver enzymes > 2 ULN were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of dabigatran is not recommended in this population. <u>Haemorrhagic risk</u> • Dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding and in situations with concomitant use of drugs affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy with dabigatran etexilate. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. • Factors, such as decreased renal function (30-50 mL/min CrCL), age ≥ 75 years, low body weight < 50 kg, or mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels. • The concomitant use of ticagrelor increases the exposure to dabigatran etexilate and may show pharmacodynamic interaction, which may result in an increased risk of bleeding. • In a study of prevention of stroke and SEE in adult patients with NVAF, dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding which was statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of oesophagitis, gastritis or gastroesophageal reflux increase the risk of GI bleeding. In these atrial fibrillation patients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered. The administration of a PPI can be considered to prevent GI bleeding. • Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs). • Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined • The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks. • Dabigatran etexilate does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on dabigatran and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution • Patients who develop acute renal failure must discontinue dabigatran • Limited data is available in patients < 50 kg. • When severe bleedings occur treatment must be discontinued and the source of bleeding investigated. • Medicinal products that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with dabigatran <u>Use of fibrinolytic medicinal products for the treatment of acute ischaemic stroke</u> • The use of fibrinolytic medicinal products for the treatment of acute ischaemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range. <u>Interaction with P-gp inducers</u>

	• Concomitant administration of P-gp inducers (such as rifampicin, St. John`s wort (*Hypericum perforatum*), carbamazepine, or phenytoin) is expected to result in decreased dabigatran plasma concentrations, and should be avoided. Surgery and interventions • Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate. • Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures. In such cases a coagulation test may help to determine whether haemostasis is still impaired. • If an acute intervention is required, dabigatran etexilate should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention. *Spinal anaesthesia/epidural anaesthesia/lumbar puncture* • Procedures such as spinal anaesthesia may require complete haemostatic function. • The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma. *Postoperative phase* • Dabigatran etexilate should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established. • Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (CrCL 30-50 mL/min), should be treated with caution Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events • There are limited efficacy and safety data for dabigatran etexilate available in these patients and therefore they should be treated with caution. Hip fracture surgery • There is no data on the use of dabigatran etexilate in patients undergoing hip fracture surgery. Therefore treatment is not recommended. Myocardial Infarction (SPAF) • In the phase III study RE-LY the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.
Drug Interaction (significant interaction as outlined in BNF, please see BNF and SPC for more detail)	**Dabigatran** has the following interaction information:

Amiodarone	plasma concentration of dabigatran increased by amiodarone **Note:** Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped
Anticoagulants	increased risk of haemorrhage when dabigatran given with other anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
Antidepressants, SSRI	possible increased risk of bleeding when dabigatran given with SSRIs
Antidepressants, SSRI (related)	possible increased risk of bleeding when dabigatran given with SSRI-related antidepressants

Ciclosporin	plasma concentration of dabigatran possibly increased by ciclosporin —manufacturer of dabigatran advises avoid concomitant use
Dronedarone	plasma concentration of dabigatran increased by dronedarone —avoid concomitant use
Ketoconazole	plasma concentration of dabigatran increased by ketoconazole —avoid concomitant use
NSAIDs	possible increased risk of bleeding when dabigatran given with NSAIDs **Note:** Interactions do not generally apply to topical NSAIDs
Rifampicin	plasma concentration of dabigatran reduced by rifampicin —manufacturer of dabigatran advises avoid concomitant use
Sulfinpyrazone	possible increased risk of bleeding when dabigatran given with sulfinpyrazone
Tacrolimus	plasma concentration of dabigatran possibly increased by tacrolimus —manufacturer of dabigatran advises avoid concomitant use **Note:** Interactions do not generally apply to tacrolimus used topically; risk of facial flushing and skin irritation with topical tacrolimus on consumption of alcohol
Ticagrelor	plasma concentration of dabigatran increased by ticagrelor
Verapamil	plasma concentration of dabigatran possibly increased by verapamil

Dabigatran belongs to **Anticoagulants** and will have the following interactions:

Apixaban	increased risk of haemorrhage when other anticoagulants given with apixaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
Dabigatran	increased risk of haemorrhage when other anticoagulants given with dabigatran (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
Diclofenac	increased risk of haemorrhage when anticoagulants given with *intravenous* diclofenac (avoid concomitant use, including low-dose heparins)
Ketorolac	increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant use, including low-dose heparins)
Rivaroxaban	increased risk of haemorrhage when other anticoagulants given with rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Pre-treatment test results

Specialists please complete the information in table below:

Date of test	
eGFR	

- Note: Dabigatran is not licensed in CrCl <30ml/min. Caution and dose adjustment maybe advised in CrCl 30-50ml/min. See full SPC for prescribing information.
- The patient has been informed of the need for annual (or more frequent if clinically appropriate) renal function tests in order to assess suitability for ongoing treatment. ☐

Guidance on initiation (to be completed by the specialist)

Initiation dose:	Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors (SPAF) 150 mg bd ☐ 110 mg bd ☐ For a full list of interactions etc please refer to the SPC.
Additional info:	• There is no known antidote to dabigatran. • Dabigatran may not be transferred to "monitored dose systems" • Capsules must be swallowed whole. A liquid formulation is not available • Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. • A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high. • Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population. • As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with dabigatran to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). • Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin and ticagrelor) is expected to result in increased dabigatran plasma concentrations. • Dabigatran ▼ is a black triangle drug. All suspected adverse effects should be reported to the CHM www.yellowcard.gov.uk
Monitoring:	• Deterioration of renal function can significantly increase plasma concentration. • Renal function should be assessed in all patients before starting dabigatran and at least once a year or more frequently as needed in clinical situations when it is suspected that the renal function could decline or deteriorate.

Suggested Criteria for Continuation or Discontinuation (to be completed by the specialist)

Assessment of Efficacy	
Frequency	At routine appointments but at least annually
Location	GP practice
Method	• Renal function test • Discussion with patient regarding compliance and any factors that may affect compliance (i.e. need for monitored dose system or swallowing difficulties) • Reassess bleeding risk, including risk of falls, and use of medication associated with gastro-intestinal bleeding • Review hepatic function
Continuation Criteria	Appropriate renal and hepatic function and compliance confirmed
Review	At least annually.
Discontinuation Criteria	• Renal function – CrCl <30 ml/min – discontinue • CrCl 50-30 ml/min – reconsider use and dose **Please note** BNF states that, in practice, eGFR may be used in place of creatinine clearance, except for patients at extremes of weight (BMI <18.5kg/m2 or >30 kg/m^2) where CrCl should be used to adjust dose. Specialist advice should be sought. • Poor compliance • Unacceptable bleeding risk • Severe hepatic impairment • Use with interacting medication
Follow up action	Specialist to complete
Shared Care read code	In the patients notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement.

GP Prescribing System	Read Code	Description
EMIS and Vision	8BM5.00	Shared care prescribing
SystmOne	XaB58	Shared care