City and Hackney Clinical Commissioning Group
Homerton University Hospital Foundation Trust

DRUG NAME: DABIGATRAN (PRADAXA®)
Transfer of Care document
Indication: Treatment of acute venous thromboembolism and prevention of recurrent venous thromboembolism

INTRODUCTION – Indication and Licensing

Dabigatran is a direct thrombin inhibitor, one of the first of non-vitamin K antagonist oral anticoagulants (NOAC). It is licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE. For patients treated for venous thromboembolism (VTE) dabigatran is an attractive and cost effective treatment option. Initiation would be by secondary care only and in accordance with its licensed indication and NICE guidelines.

Due to its selective inhibition of one clotting factor, the anticoagulation effects are more predictable and as such there is no requirement for regular monitoring, unlike vitamin K antagonists (VKA) such as warfarin. Other potential advantages compared to VKAs include a standard dosing regimen and a lower likelihood of drug interactions. Disadvantages of dabigatran are its higher cost (partially offset by the reduced need for INR monitoring) and limited clinical experience of long-term use. An additional disadvantage is no test for monitoring of patient adherence. There is now a licensed antidote available for dabigatran in case of life threatening bleeding. However, in studies comparing against warfarin, less fatal bleeding was shown in comparison to warfarin in both atrial fibrillation and acute VTE and unlike warfarin has far shorter half-life and is therefore cleared quicker than warfarin, which may explain the less fatal bleeding seen in clinical trials.

PATIENT PATHWAY

Clinical Speciality / Indication	**Prescribing Initiated by**	**Prescribing Continued by** ***(detail when suitable for transfer to occur)***	**Monitored by** ***(detail when suitable for transfer to occur IF APPROPRIATE)***	**Duration of treatment**
Haematology	Secondary care prescriber	Hospital after 4 week of initiation, where a further 4 weeks supply will be issued to patients	GP after 8 weeks	Individualised for each patients. All VTE patients will be seen by haematologist within 6 months of initiation to confirm duration of treatment.

(N.B. a temporary discontinuation for surgical procedures is advised, see below for further details).

Patients are to be initiated in the first instance by a clinician in secondary care. The clinician is responsible for the safe prescribing of dabigatran and ensuring the patient meets the defined criteria for use as outlined above. If dabigatran is suitable 4 weeks supply will be issued alongside the anticoagulation alert card and patient booklet.

The patient will return to anticoagulation clinic after the initial 4 weeks to ensure adequate follow up during the initiation phase providing adherence counselling addressing any patients concerns regarding therapy. If dabigatran is tolerated, then a further 4 weeks of treatment will be supplied by the hospital, after which the GP will continue the supply and monitoring. If the patient has concerns prior to commencing continuation with the GP they should contact the hospital anticoagulant team. The patient will be advised to contact their GP within 8 weeks of initiation. A NOAC initiation letter will also be forwarded to GP confirming transfer of care.

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Duration of treatment will be advised initially by the anticoagulation team. A follow up within 3 to 6 months would then be carried out by a haematologist to assess the patient and extend the duration in treatment, if needed. Long-term treatment should be reviewed at least annually by GP and an assessment made for new contraindications to ongoing anticoagulation with dabigatran (e.g. temporary discontinuation for surgery, marked decline in renal function and increased bleeding risk - see below for further advice on bleeding risk). Where new contraindications are found, treatment is to be reviewed and anticoagulation therapy withdrawn if risks are deemed to outweigh benefits. Ongoing adherence should be reviewed on a regular basis, the duration and method of adherence assessment should be determined by the GP, taking into account individual patient circumstances and factors. The GP is to re-educate the patient each time for the need to stop their dabigatran and seeing any doctor as soon as possible in case of bleeding.

ORAL DOSE AND ADMINISTRATION

Dabigatran hard capsules are available in 2 strengths for this indication: 110mg and 150mg

Usual dose:

	Renal function*			
Dose	**CrCl: ≥ 50 mL/minute**	**CrCl: 30–50 mL/minute**	**CrCl: 15 to 29ml/min**	**CrCl <15ml/min**
	150 mg twice daily	**150mg twice daily ****	**Not recommended**	**Not recommended**

*Cockroft and Gault to be used – see below for formula
**For patients with high risk of bleeding, a dose reduction to 110 mg twice daily should be considered.

Dose alterations:

Dose reduction to **110mg twice daily** in patients with two or more of the following:

- Patients who receive concomitant verapamil
- Age ≥ 80years

For the following groups the daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

• Patients between 75-80 years
• Patients with moderate renal impairment
• Patients with gastritis, esophagitis or gastroesophageal reflux
• Other patients at increased risk of bleeding

For DVT/PE the recommendation for the use of Pradaxa 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

<u>Increased risk of bleed:</u>

- For patients with gastritis, oesophagitis, or gastroesophageal reflux, a dose of 110 mg capsule twice daily should be considered due to the increased risk of major gastro-intestinal bleeding (and where appropriate gastro protection prescribed concomitantly e.g. PPI)

- Individuals at low body weight (<50kg) may be more prone to bleeding and as such monitored closely and dose reduction (110mg twice daily) considered.

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- Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia, more details below). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient.

- A coagulation test (see below) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose 110mg twice daily is recommended.

- If clinically relevant bleeding occurs, treatment should be interrupted and reviewed prior to re-initiation.

Cockroft and Gault formula to calculate CrCl (ml/min)

$$\frac{K \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (µmol/L)}}$$

K = 1.23 in males
K = 1.04 in females

MONITORING STANDARDS FOR MEDICATION AT THE ACUTE NHS TRUST

Parameter	**Renal function (Creatinine clearance - CrCl)** Using Cockroft and Gault equation (see above)
Action Required	CrCl ≥50mls/min; no adjustment required CrCl 30 to 49mls/min; 150mg twice daily, but for patients with risk factors for bleeding, consider dose reduction to 110mg twice daily CrCl <30mls/min; contraindicated, avoid use
Frequency of monitoring	Assess renal function prior to treatment to ensure appropriate starting dose. Then: • Annually (alongside Hb and liver function tests) • 6 monthly o >75years o Frail (defined as ≥3 of the following criteria: unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed/gait apraxia, low physical activity) o If CrCl 30–60ml/min • 3 monthly o If CrCl 15-29ml/min More frequent renal function monitoring maybe needed as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate such as hypovolemia and dehydration.
Further Action	Dose reduction may be required based on initial renal function. If renal function declines rapidly may need to temporarily withhold therapy and review prior to restarting.

Parameter	**Minor bleeding (or those at high risk of bleed on treatment)**
Target level	The activated partial thromboplastin time (aPTT) test is widely available and provides an approximate indication of anticoagulation intensity achieved with dabigatran. In patients who are bleeding or at risk of bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution. If required and following haematology advice, a more sensitive quantitative tests such as calibrated diluted Thrombin Time (dTT) could be

	performed. If the dTT is used, dabigatran concentrations above 200 ng/ml, measured at trough after 150 mg twice daily dosing (10-16 hours after the previous dose), are associated with an increased risk of bleeding and may require a dose reduction to 110mg twice daily – If required, close liaison with haematology will be necessary prior to ordering and interpreting the results of these tests.
Frequency of monitoring	Only if excessive minor bleeding observed or patient at high risk of bleed and on 150mg twice daily, a raised APTT should prompt a dose reduction if clinically indicated
Action	If numerous episodes of minor bleeding are observed or patient at high risk of bleed discuss with haematology.

Parameter	**Adherence**
Target level	100%
Frequency of monitoring	Prior to initiation, likely adherence should be considered and discussed with the patient. Following initiation, adherence should be reinforced at a minimum of annually although this is left at the discretion of the physician.
Action	If adherence likely to be low, consider alternative anticoagulation that can be monitored, i.e. warfarin.

KEY ADVERSE EFFECTS & ACTIONS

Adverse effects	**Symptoms/signs**	**Actions*)***
Minor Bleeding	Self-terminating minor bleeding from scratches, cuts, nosebleeds, gum bleeding etc. may be experienced. If these are frequent or patient / physician concerned - contact local haematology department for advice	The degree of bleeding will dictate action. If minor bleeding is infrequent and self terminates, patient can be reassured. If concerns are raised - liaise with haematology for advice.
Moderate bleeding	Bleeding that does not stop with reasonable intervention should be referred to local A&E, if in doubt contact local haematology department for advice	The degree of bleeding will dictate the action. If bleeding stops spontaneously and patient taking 150mg twice daily, consider omitting a day's dose and reducing to 110mg twice daily. If already on lower dose or concerns are raised - liaise with haematology for advice. For bleeding that does not stop with intervention, send patient to local A&E.
Clinically significant bleeding	Major bleeding in the RELY trial was defined as a reduction in haemoglobin of at least 20g/L or leading to a transfusion of at least 2 units of blood. If bleeding presents as clinically significant send patient to local A&E or call 999	Immediate referral to secondary care, protocol in place to manage major bleeding available via A&Es

Gastrointestinal	Dyspepsia	Consider gastro protection in accordance with local guidance. If no further improvement, consider alternatives or referral to specialist.

This only lists the key important ADRs-For comprehensive information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

Important cautions: Surgery and invasive procedures

Patients on dabigatran who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require temporary discontinuation of dabigatran. If an invasive procedure or surgical intervention is required, dabigatran should be stopped from 1 to 4 days before intervention dependent on renal function and type of procedure. See SPC for details. If surgery cannot be delayed the case should be discussed with haematology for advice on reversal if required.

PREGNANCY AND BREAST FEEDING

The safety of dabigatran has not been established in pregnant or lactating women; as such use in these patients is to be avoided.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

Evidence

Dabigatran has been shown to be as effective as standard anticoagulant therapy comprising of low molecular weight heparin in combination with a vitamin K antagonist (VKA) e.g. warfarin; it has less major bleeding.

Use of dabigatran to reduce the incidence of recurrent VTE has been studied in a large multinational, randomised control trial enrolling at least 2,500 patients with DVT or PE. The primary efficacy endpoint was recurrent symptomatic VTE. The RE-COVER trial demonstrated noninferiority of dabigatran to warfarin with respect to the primary endpoint (2.4% vs 2.1% (P<0.001) dabigatran and warfarin respectively).

TRANSFER OF CARE

This document provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The transfer of care should be explained to the patient. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Consultant/Anticoagulant team

1. Ensure that the patient/carer is an informed recipient of dabigatran.
2. Ensure that patients understand dabigatran treatment and monitoring (e.g. renal function) and follow up that is required (using advocacy if appropriate).

3. Ensure baseline investigations are satisfactory before commencing treatment. Give the patient an anticoagulant alert card patient booklet.
4. Counsel the patient on the risks and benefits of treatment with dabigatran as well as importance of adherence to treatment.
5. Initiate treatment, prescribe and monitor for the first 8 weeks.
6. Send a NOAC initiation letter to the GP.
7. Clear documentation should be made as to reason for dose reduction.
8. Report any abnormal blood results to the GP where appropriate.
9. Evaluation of any reported adverse effects by GP or patient.
10. Advise GP on review, duration or discontinuation of treatment where necessary.
11. Ensure a 3 to 6 months follow up is arranged with haematologist.
12. Ensure that backup advice is available at all times.
13. Inform the patient to make a GP appointment within 8 weeks of initiation for further supplies.

General Practitioner

1. Reinforce the patient understands the nature, effect and potential side effects of dabigatran before prescribing and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the CSM, where appropriate.
5. Help in monitoring the progression of disease.
6. Prescribe and monitor the drug treatment as described and stop the drug at the specified time. Consider managing the drug as an acute prescription as oppose to a repeat.

Clinical Commissioning Group

1. To provide feedback to trusts via Joint Prescribing Group
2. To support GPs to prescribe dabigatran safely and effectively.
3. To support trusts in resolving issues that may arise as a result of transferred care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist.
2. Ensure they have a clear understanding of their treatment (dabigatran).
3. Carry an anticoagulation card with them at all times.
4. Report any changes in disease symptoms to GP and/or specialist.
5. Alert GP and/or specialist of any changes of circumstance which could affect management of disease.
6. Administer dabigatran as prescribed and attend hospital/GP for assessment and monitoring as required.

Costs

Drug Product	**Cost in primary care**
Dabigatran capsules [110mg and 150mg]	£801.80 / year*

Based on BNF February 2016

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RESOURCES AVAILABLE

EHRA practical guide (see references)

Relevant contact details	
Doctor via switchboard Registrar on-call out of hours	Dr Neil Chauhan (clinical lead for anticoagulation) via switchboard Contact on-call haematology registrar out of hours via switchboard
Clinical Nurse Specialist/pharmacist	020 8510 4413 or 020 8510 4114 or via email huh-tr.Antico@nhs.net
Trust Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000 or via email mipharmacy@homerton.nhs.uk
City and Hackney Medicines Management Team	020 3816 3224

References

With thanks to Barts Health NHS Trust,

- Barts Health NHS Trust SCG adapted for local use
- Schulman S. et al. Dabigatran versus warfarin in the Treatment of Acute Venous Thromboembolism. *The New England Journal of Medicine.* December 2009; 361(24): 2342-2352.
- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism, December 2014, NICE technology appraisal guidance [TA327]. Available at: https://www.nice.org.uk/guidance/ta327, accessed 20/12/15.
- Summary of Product Characteristics, Pradaxa 150mg hard capsules, Boehringer Ingelheim Limited, Date of revision of the text 20 Oct 2015, accessed 20/12/15.

SCG template adopted from NELMMN and Barts Health NHS Trust (updated by JPG February 2015)

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