Prescribing DABIGATRAN for the acute treatment and secondary prevention of Venous Thromboembolism (VTE) (Pulmonary Embolism (PE) or Deep Vein Thrombosis (DVT)

Note: Dabigatran is also licensed for the prevention of stroke in patients with non-valvular atrial fibrillation. Guidance for use for this indication can be found at: SEL APC CVD Guidelines

Dabigatran etexilate (Pradaxa®) is a direct oral anticoagulant (DOAC) licensed for the acute treatment of VTE (PE or DVT) and for the secondary prevention of VTE in patients at risk of recurrent events. The National Institute for Health and Care Excellence (NICE) has approved the use of dabigatran as an option for the acute management and secondary prevention of VTE.

In South London, dabigatran may be considered as an option for any patient experiencing a provoked or unprovoked DVT or PE, except those patients in whom there is an underlying malignancy or those who are pregnant or breast-feeding where a low molecular weight heparin (LMWH) is preferred, or patients with renal impairment (creatinine clearance (CrCl) < 30ml/min) in whom dabigatran is contraindicated where warfarin or an alternative direct oral anticoagulant may be used.

- Patients with provoked VTE events (e.g. caused by surgery, trauma, long distance travel, immobility, pregnancy or hormone replacement therapy) usually require 3 – 6 months of dabigatran therapy
- Patients with unprovoked events or where there are on-going risk factors for recurrence may require a longer duration, as advised by the initiating clinician.

Additional resources have been developed to support implementation including:

- Overview summary of VTE treatment
- Screening checklist and Notification of initiation of a DOAC for the treatment of VTE This document **must be completed and sent to the General Practitioner (GP) on initiation**.
- Transfer of prescribing responsibility to primary care for DOACs. This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance to South London guidelines.

Dabigatran for VTE should only be initiated by clinicians with expertise in managing anticoagulant therapy. The initiating clinician / organisation is responsible for ensuring patient follow up and providing a supply of dabigatran for the first three months of treatment. During this time, efforts should be made to reinforce adherence and address any adverse effects.

Transfer of Prescribing Responsibility to Patient's Own GP

Following the initial 3 month period, patients requiring longer term anticoagulant therapy may be considered for transfer back to the patient's own GP, provided the agreed transfer of care guidance is followed. If dabigatran is prescribed for unlicensed / non-approved indications prescribing responsibility will remain with the initiating clinician / orgnisation.

Contraindications (for full details – see BNF or SPC)	**Cautions** (for full details – see BNF or SPC)
• Hypersensitivity to the active ingredient or to any of the excipients • Clinically significant active bleeding • Any lesion or condition considered a significant risk factor for major bleeding e.g. 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 • Prosthetic heart valves requiring anticoagulant treatment • Hepatic impairment or liver disease expected to have any impact on survival • Severe renal impairment (CrCl < 30 ml/min*) • Pregnancy and/ or breast feeding • For contra-indications for use with other medicines see overleaf	• Patients with conditions which carry a haemorrhagic risk e.g. bacterial endocarditis, thrombocytopenia, congenital or acquired coagulation disorders, oesophagitis, gastritis and gastroesophageal reflux disease • Active cancer- efficacy and safety of dabigatran in the treatment and/or prevention of VTE in patients with active cancer have not been established – LMWH preferred • Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy- not recommended since the safety and efficacy of dabigatran have not been established in these clinical situations • Uncontrolled severe hypertension • Low body weight ≤ 50kg – close clinical surveillance is recommended • Liver enzymes > twice the upper limit of normal – patients were excluded from trials therefore use is not recommended for this subpopulation of patients • Moderate renal impairment (30 – 49ml/min*) • For cautions for use with other medication see overleaf

Note: BNF=British National Formulary**; SPC=**Summary of Product Characteristics

***Estimated Glomerular Filtration Rate (eGFR) should NOT be used to guide dosing decisions. Creatinine clearance must be estimated using the Cockcroft-Gault equation calculator or refer to the South London creatinine clearance Information sheet.**

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Approved: June 2016 **Review date: June 2018**

South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTFT/KCH/SLAM/Oxleas NHS Foundation Trusts & Lewisham & Greenwich NHS Trust

Dosing

The recommended dose of dabigatran is 150mg TWICE daily with or without food following initial treatment with a parenteral anticoagulant for at least 5 days (this will be supplied by the initiating organisation).

- Reduce dose to 110mg TWICE daily with or without food in patients with one of the following characteristics:
  - ≥ 80 years of age
  - Concomitant treatment with verapamil
- The reduced dose of 110 mg TWICE daily may also be considered for patients with the following characteristics if the risk of bleeding outweighs the risk of recurrent thrombosis:
  - 75–80 years of age
  - Moderate renal impairment - CrCl 30-49 ml/min
  - At increased risk of bleeding (for example those suffering with gastritis, oesophagitis or gastroesophageal reflux)
- Patients with provoked VTE events (e.g. caused by surgery, trauma, long distance travel, immobility, pregnancy or hormone replacement therapy) usually require 3 - 6 months of dabigatran therapy.
- Patients with unprovoked events or where there are on-going risk factors for recurrence may require a longer duration, as advised by the initiating clinician.
- Treatment must only be started when parenteral anticoagulation therapy (LMWH / unfractionated heparin (UFH)) is discontinued. Dabigatran must not be administered concomitantly with any additional anticoagulation.
  - For patients on LMWH – the first dose of dabigatran must be given when the next dose of LMWH is due.
  - For patients on continuous infusions of UFH – the first dose of dabigatran must be given immediately after discontinuation of the heparin infusion.

For patients identified as at risk of upper GI bleeding the co-prescription of a proton pump inhibitor *(e.g. lansoprazole/omeprazole) may be considered.*

Monitoring

International normalised ratio (INR) monitoring is not required for patients taking dabigatran. However, clinical surveillance is recommended throughout the treatment period in line with good anticoagulation practice.

- All patients prescribed dabigatran should be reviewed **at least annually** to assess benefits and risks of on-going therapy weighing the risk for thrombotic events against the bleeding risks:
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- A baseline renal function test is required and consequent re-testing should take place at least annually (frequency determined by the patient's baseline renal function as guided by the initiating clinician).
- For patients on long-term therapy clinicians will need to monitor patients and make any other dose adjustments necessary based on age, body weight, renal function and concomitant medication (see dosage section above).

Side effects (for full details see the BNF or SPC)

- As with any other form of anticoagulation, there is a risk of bleeding during treatment with dabigatran, and patients should be monitored for signs of bleeding or anaemia. Patients should be advised to seek medical advice if they experience persistent or frequent episodes of bleeding. Patients experiencing major or life threatening bleeding should seek urgent medical attention.
- Dyspepsia is another common adverse effect. If significant dyspepsia occurs affecting the patients' quality of life, consider using an alternative anticoagulant agent or co-prescribing a proton pump inhibitor.
- Other common side effects include: nausea, diarrhoea, abdominal pain.

Drug interactions (for full details on drug interactions – see BNF or SPC)

Drug / Drug class	Recommendation
Other anticoagulant agents (e.g. unfractionated heparin (UFH) or heparin derivatives, low molecular weight heparins, oral anticoagulants)	Concomitant use is contraindicated due to increased risk of bleeding, except when UFH is given at doses necessary to maintain a patent catheter or if switching with other anticoagulants
Use of fibrinolytic agents for the treatment of acute ischaemic stroke	May be considered by hyper-acute stroke units if the clinician can be certain that there is no anticoagulant effect present based on laboratory testing of clotting
Aspirin and other antiplatelet agents	Increased risk of bleeding – use with caution; should be stopped if clinically appropriate (seek advice from cardiologist); if required to continue close monitoring required and gastro-protection is advised
Non-steroidal anti-inflammatory drugs (NSAIDS)	Increased risk of bleeding if used long-term. Avoid where possible; if required use at the lowest dose and for the shortest duration possible; close monitoring required and gastro-protection is advised
Selective serotonin re-uptake inhibitors (SSRIs) and Serotonin–norepinephrine reuptake inhibitors (SNRIs). Or any other medicinal products affecting haemostasis	Increased bleeding risk with dabigatran, close monitoring required

P-glycoprotein inducers - such as St. John`s wort (Hypericum perforatum), rifampicin, phenobarbital, carbamazepine or phenytoin	Concomitant use will result in decreased dabigatran plasma concentrations, and therefore should be avoided
Systemic ketoconazole, ciclosporin, itraconazole, tacrolimus,	Concomitant use is contra-indicated due to increased plasma dabigatran levels
Amiodarone, quinidine, posaconazole	May increase plasma dabigatran levels; close surveillance recommended, especially in mild to moderate renal impairment - Use with caution
Dronedarone	Concomitant treatment with dronedarone is contraindicated
Clarithromycin	May increase plasma dabigatran levels especially where there is moderate to severe renal impairment – use with caution
Protease inhibitors (e.g. lopinavir/ritonavir, indinavir)	Not recommended for concomitant treatment with dabigatran
Verapamil	Increases plasma dabigatran level. **Maximum dabigatran dose of 110mg twice daily when prescribed concurrently**

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate dabigatran in line with NICE and local guidance • To supply dabigatran for the first 3 months of treatment • To provide counselling to improve adherence and address any early adverse effects • If treatment is required for longer than three months; to transfer care to the GP in line with local guidance • If treatment is required for longer than three months; to give clear guidance on the intended duration of treatment and / or further follow-up required • For patients requiring long-term treatment; to arrange a follow-up at 12 months to review ongoing need for therapy	• To ensure use of dabigatran is in line with the NICE and local guidance • To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation and in line with the transfer of care guidance) • To agree to take over prescribing earlier in patients with complex medication supply issues e.g. patients using medication compliance aids (MCA) or housebound patients • To emphasise the importance of adherence to dabigatran therapy and address any patient concerns • To ensure monitoring of renal and hepatic function is undertaken at least annually, and more frequently if indicated. If results fall outside normal range then refer to contraindication, caution and dosing sections in the prescribing guidelines and/or seek specialist advice as appropriate • To monitor ongoing risk of bleed and if appropriate, seek specialist advice

Additional information

1. Patients taking dabigatran should be encouraged to carry an anticoagulation card at all times (available from initiating clinician/ anticoagulation clinics) or wear a medic-alert bracelet.
2. There is now a United Kingdom licensed specific reversal agent available for use to manage patients bleeding whilst on dabigatran and for patients on dabigatran requiring emergency surgery. In the event of a significant bleed, the patient should be referred to accident and emergency for reversal and supportive measures.
3. Other healthcare professionals should be made aware that dabigatran is prescribed for any patients who are to undergo invasive treatments, including elective surgery and dental treatment.
4. Missed dose advice should be discussed at initiation: A missed dose may be taken up to 6 hours prior to the next scheduled dose, then 12 hourly dosing resumed. If within 6 hours of next scheduled dose – the dose should be omitted. No double doses should be taken to make up for missed dose. Should the patient wish to return to their usual time of administration; it is recommended that the time the dose is taken is adjusted by one hour every day until the usual time of administration is achieved.
5. Dabigatran capsules must be swallowed whole. Capsules must NOT be opened or chewed. Opening the capsule will increase the amount of drug reaching systemic circulation, increasing the patient's risk of bleeding.
6. Dabigatran capsules absorb water resulting in loss of stability if removed from their original packaging and exposed to the air. This means that they are unsuitable for inclusion in traditional multi-compartment compliance aids (MCA) or dosette boxes. If a patient has been assessed as being appropriate for a multi-compartment compliance aid (MCA) a special dosette box can be ordered from the manufacturer which allows dabigatran to be included inside it's original packaging. Contact a pharmacist for further information.

References

1. NICE TA327. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Dec 2014. Accessed April 2016 at https://www.nice.org.uk/guidance/ta327/resources/dabigatran-etexilate-for-the-treatment-and-secondary-prevention-of-deep-vein-thrombosis-andor-pulmonary-embolism-82602491948485
2. SPC Pradaxa. Boehringer Ingelheim. March 2016. Accessed April 2016 at http://www.medicines.org.uk/emc/medicine/24839
3. Schulman, S. et al. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. N Engl J Med 2009;361:2342-52