SHARED CARE GUIDELINE FOR DABIGATRAN ETEXILATE FOR THE TREATMENT AND SECONDARY PREVENTION OF DEEP VEIN THROMBOSIS AND/OR PULMONARY EMBOLISM

INDICATION

Dabigatran etexilate mesilate (dabigatran) is a treatment option in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

NICE Technology Appraisal (TA) 327 recommends:
Dabigatran (also known as Pradaxa) is recommended as a possible treatment for adults with deep vein thrombosis or pulmonary embolism.

Dorset Clinical Commissioning Programme recommends:

Patients who do not have cancer:
Dabigatran is a first line treatment option, alongside other existing options e.g. rivaroxaban and warfarin (combined initially with a low molecular weight heparin (LMWH))

The decision as to which option is selected should, where possible, be made jointly between the patient and healthcare team. Further information to support prescribers can be found in the Greater Manchester CSU Decision Support document (link) and the commissioning statement associated with this shared care guideline (link).

Dabigatran may also be considered for patients unable to tolerate warfarin i.e. true allergy or significant adverse reaction and as an alternative treatment option with poor INR control (suggested time in therapeutic range <65%) and in the absence of any reversible cause, consider treatment with dabigatran, but, only if non-compliance with warfarin treatment is excluded.

Patients who have active cancer:
In the absence of specific evidence around the use of dabigatran to treat VTE in patients with cancer, LMWH is recommended as the first line option. The use of a LMWH is subject to a shared care guideline. Link

Limitations of this guidance:
Dabigatran is also licensed for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery and for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, these indications fall outside of the remit of this guideline.

Traffic Light Categorisation
Dabigatran is categorised as amber; in the case of its use in VTE (treatment and long term secondary prevention) it is recommended that treatment is initiated (to include the minimum 5 day period of LMWH) in a specialist setting (which may be primary, intermediate or secondary care based) and by clinicians with experience in the management of anticoagulation.

For full prescribing information on dabigatran see the SPC (110mg and 150mg doses). Link

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AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of dabigatran can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Specialist Responsibilities	
1	To initiate, supply and manage treatment of the DVT or PE with a minimum of 5 days LMWH prior to commencing dabigatran
2	To initiate and stabilize the patient on treatment with dabigatran, supplying at least a one month course
3	To ask the GP whether he or she is willing to participate in shared care. Requests to GPs should be made in writing and must include appropriate information to allow an informed decision to be made. This should include: • Confirmation of diagnosis and test results • Name, dose and expected duration of treatment • Advice, where applicable on dose alterations • Clarification that the GP will only be asked to continue prescribing following treatment stabilisation i.e. post LMWH doses and initial 1 month supply of dabigatran
4	Where a patient has presented with an unprovoked PE due to a temporary risk factor, that the patient will be reviewed at 3 months within the specialist service and the decision around treatment discontinuation or longer term therapy will be clearly communicated to the patient and the patient's GP to include, the expected length of treatment.
5	To communicate promptly with the GP when treatment is changed (to include both dosage change and change to treatment choice), stopped or adjusted and to communicate changes in response to treatment or the condition itself.
6	Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition and to be available to supply advice if a patient's condition changes including provision of telephone numbers for urgent matters.
8	To ensure the patient has sufficient supply of medication until such time as is appropriate for the GP to assume prescribing responsibility. This may include times to cover initial transfer of responsibility and/or review appointment(s) within the specialist service.
9	To ensure the patient / carer has given informed consent to their treatment.
10	To provide the patient, carers / parents with comprehensive advice and information about the expected side effects and their management.

Specialist Responsibilities	
11	Report adverse events via the Yellow card scheme to the MHRA.

General Practitioner Responsibilities	
1	Initially, to refer the patient for specialist advice.
2	To contact the referring clinician without delay if they do not wish to enter into a shared care agreement.
3	Where appropriate to continue prescriptions of dabigatran, (usually after a minimum of 1 month) for a total of three months treatment. Ensure prescriptions remain on an acute prescription and end date is included. Where subsequent investigations have established that the patient requires longer term therapy ensure length of treatment required is clear.
4	To undertake any necessary monitoring of the patient.
5	To monitor side effects of treatment and seek urgent advice from the consultant as necessary.
6	To review the patient at three monthly intervals and stop therapy after three months of treatment for a first provoked VTE or maintain longer term therapy, e.g. where a patient is unable to tolerate warfarin, has poor INR control or a longer term risk factor has been identified.
7	To monitor concordance with treatment.
8	To liaise with the consultant regarding any complications of treatment.
9	To check for possible drug interactions when newly prescribing or stopping concurrent medication.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate consultant and GP appointments.
3	Share any concerns in relation to treatment with dabigatran.
4	Use written and other information on the medication.
5	Seek help urgently if suffering suspected side effects, or otherwise unwell.

SUPPORTING INFORMATION

Dosage and Administration

The recommended treatment dose of dabigatran is 150mg twice daily following parenteral anti-coagulant for at least 5 days.

The following groups are recommended a dose of 110mg twice daily:

- Patients aged 80 years or above (increased bleeding risk)
- Patients who receive concomitant verapamil (increases plasma levels of dabigatran)

It is suggested that the following groups have thromboembolic risks and risks of bleeding are assessed on an individual basis and the dosage of dabigatran adjusted accordingly:

- Patients between 75-80 years
- Patients with moderate renal impairment

- Patients with gastritis, esophagitis or GI reflux
- Other patients at increased risk of bleeding

Peri-operative dosing:

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50-< 80	~ 15	2-3 days before	1-2 days before
≥ 30-< 50	~ 18	4 days before	2-3 days before (> 48 hours)

- 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

- 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

Monitoring

Renal function should be assessed prior to initiation and more frequently where it could decline during treatment e.g. dehydration, hypovolaemia.

For patients over 75 and patients with mild or moderate renal impairment (30 - 80ml/min) renal function should be monitored at least once a year in patients treated with dabigatran and more frequently where it could decline e.g. dehydration, hypovolaemia.

Renal function should be calculated using the Cockgroft-Gault method as per dabigatran SPC.

No other routine monitoring is normally required 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 Pradaxa 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. The table below shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding:

Test (trough value)	Indication
	SPAF and DVT/PE
dTT [ng/mL]	> 200
ECT [x-fold upper limit of normal]	> 3
aPTT [x-fold upper limit of normal]	> 2

INR	Should not be performed

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- 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 esophageal 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
- Patients with liver enzymes more than twice the normal upper limit (no data in this group)
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole or dronedarone
- Prosthetic heart valves requiring anticoagulant treatment

Cautions

Forgotten doses may be taken up to 6 hours prior to the next scheduled dose, from 6 hours prior to the next scheduled dose on, the missed dose should be omitted.

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.

Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, 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)

Pregnancy and lactation

- Women of childbearing potential should avoid pregnancy during treatment with dabigatran etexilate.

- There are limited amount of data from the use of dabigatran etexilate in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Dabigatran should not be used during pregnancy unless clearly necessary.

- There are no clinical data of the effect of dabigatran on infants during breast-feeding. Breast-feeding should be discontinued during treatment with dabigatran.

Side effects
The most commonly reported side-effect from studies was bleeding which occurred in around 16.5% of patients treated for atrial fibrillation and 14.4% of patients treated for DVT/PE.

Interactions
The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding.

Concomitant P-gp inhibitors
Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation dabigatran and verapamil should be taken at the same time.

No dose adjustment is required for concomitant amiodarone or quinidine use.

Concomitant administration of P-gp inducers
Administration of drugs 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.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs (prices correct January 2015):
Dabigatran (Pradaxa®) 150mg capsules x 60 = £65.90
Dabigatran (Pradaxa®) 110mg capsules x 60 = £65.90

Storage: Dabigatran is sensitive to moisture and should not be dispensed into dosette trays. Bottles of capsules when opened must be used within 4 months.

References:

1. Summary of Product Characteristics for Pradaxa® 150mg capsules accessed via http://www.medicines.org.uk/emc/medicine/24839 24/12/14
2. Summary of Product Characteristics for Pradaxa® 110mg capsules accessed via http://www.medicines.org.uk/emc/medicine/20760 24/12/14

3. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal TA 327 accessed via http://www.nice.org.uk/guidance/ta327 29/12/14