Croydon Health Services NHS
NHS Trust

# GUIDELINES FOR THE USE OF DIRECT ORAL ANTICOAGULANTS (DOACs) IN ADULTS WITH ACUTE DVT & PE AND PREVENTION OF RECURRENT VTE

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| Version: | 3 |
| Ratified by:<br>***(NB: All Procedural Documents which include details of drugs or their management must be approved by the Medicines Management Committee)*** | Risk Assurance and Policy Group |
| Date ratified: | 10 April 2017 |
| Approving Committee/Group (Date) | Thrombosis Committee (15/03/2017)<br>Medicine Management Committee (20/03/2017) |
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| Date issued: | April 2017 |
| Review due date: | April 2020 |
| Target audience: | Trust- Wide |
| Superseded documents | Version 2.1 |
| Related CQC Domain<br>***(Please tick)*** | ☑ Safe ☑ Effective ☑ Caring<br>☐ Responsive ☐ Well-Led |
| Relevant Standards(e.g. HSE, Health and Social Care Act) | N/A |
| Acknowledgements | Dr Carol Buttriss, Specialist Doctor in Haematology |
| Key Words | VTE, deep vein thrombosis, pulmonary embolism, rivaroxaban,apixaban, edoxaban, dabigatran,DOAC, anticoagulation |

# EXECUTIVE SUMMARY

These guidelines are intended to provide guidance to Croydon Health Service's staff on the clinical use of direct oral anticoagulants (DOACs) for the treatment of acute DVT or PE and the secondary prevention of recurrent VTE.

Rivaroxaban is the first line treatment option for the management of VTE due to its simple dosing regime and ease of follow up; the remaining DOACs are available as treatment options in cases where rivaroxaban is unsuitable.

The document summarises the procedure for using DOACs in the management of DVT or PE, covering the initiation, referral and transfer of care for such patients. It includes monographs with prescribing information for all DOACs as well as sections focusing on

- Interpretation of clotting parameters in patients on DOACs
- Switching between all forms of anticoagulants (oral or parenteral)
- Managing DOACs in patients requiring invasive procedures or surgery
- Bleeding while on DOAC therapy

# CONTENTS

# 1 INTRODUCTION

Dabigatran, Rivaroxaban, Edoxaban and Apixaban are direct oral anticoagulants (DOACs). They have been licensed in the UK and reviewed by NICE as an option for the treatment of acute deep vein thrombosis or pulmonary embolism, and the prevention of recurrent venous thromboembolism.

These direct oral anticoagulants are different from warfarin as they are not vitamin K antagonists and do not require regular INR monitoring. Dabigatran is a direct thrombin inhibitor; rivaroxaban, edoxaban and apixaban, are all direct factor Xa inhibitors.

# 2 PURPOSE

This guideline is intended to provide guidance to Croydon Health services doctors, pharmacists, nurses and other health care professionals across primary and secondary care on the clinical use of DOACs in the management of venous thromboembolism.

***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.***

# 3 DEFINITIONS

**DVT-** Deep Vein thrombosis.
**PE-** Pulmonary Embolism
**LMWH-** Low molecular weight heparin
**UFH-** Unfractionated heparin
**VKA-** Vitamin K antagonist
**eGFR-** Estimated Glomerular Filtration Rate
**CrCl-** Creatinine Clearance
**FBC**- Full Blood Count
**U&E**- Urea & Electrolytes
**LFT** – Liver Function Tests
**INR-** International Normalised Ratio
**APTT-** activated partial thromboplastin time
**PT –** prothromin time
**TT –** thrombin time
**FFP-** Fresh Frozen Plasma
**PCC-** Prothrombin Complex Concentrate
**APPC-** Activated prothrombin complex concentrate
**rFVIIa-** Recombinant FVIIa

# 4 ACCOUNTABILITIES AND RESPONSIBILITIES

**The Thrombosis Committee** is responsible for reviewing, updating and auditing adherence to the guidelines, promoting awareness to the medical/ surgical teams as well as devising and implementing action plans to improve performance. They are also responsible for providing education and training to members of staff.

**The lead directorate pharmacist** is responsible for co-ordinating the review of the guidelines, promoting awareness amongst prescribers, pharmacists and nursing staff, designing and implementing initiatives to support and audit adherence as well as reporting audit results to relevant teams.

**Prescribers** are responsible for adhering to the guidelines when caring for patients with acute DVT/ PE or recurrent VTE.

**Nursing staff and HCAs** are responsible for adhering to the guidelines and the timely administration of prescribed medications.

**Trust pharmacists** are responsible for alerting prescribers of the guidelines, encouraging adherence and reporting non-adherence to the directorate pharmacist**.**

## 5 INITIATION & CHOICE OF DOAC

DOACs are indicated for the treatment of DVT & PE and prevention of recurrent VTE. They are **not** licensed for the treatment of cancer related DVT; patients with suspected or known cancer should be discussed with a Haematologist.

Rivaroxaban is the first line option for the treatment of acute VTE (DVT & PE) and for patients requiring long-term secondary prevention of VTE due to its simple dosing regime and convenient timeframe to arrange follow up. If rivaroxaban is deemed unsuitable as a treatment option, the remaining DOACs (apixaban, edoxaban and dabigatran) are available as second line treatment options in consultation with the Anticoagulation Service.

The first three months supply of DOAC therapy will be provided by Croydon University Hospital. For patients requiring longer than 3 months therapy, a transfer of care document requesting their GP to take over prescribing responsibility will be sent.
In line with NICE guidance, prescribers will start treatment with a DOAC after an informed discussion with the patient about the risks and benefits of DOAC compared to warfarin.

Prior to commencing a DOAC, all patients **MUST** have baseline investigations including:
a. **FBC**
b. **U&E**
c. **LFT**
d. **Clotting screen (PT & APTT)**

Creatinine clearance must always be calculated using the Cockcroft-Gault Method (available through many online calculators):

$$\text{CrCl } \textbf{male} \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{Weight (kg)} \times 1.23}{\text{serum creatinine(micromole/L)}}$$

$$\text{CrCl } \textbf{female} \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{Weight (kg)} \times 1.04}{\text{serum creatinine(micromole/L)}}$$

### 5.1 Rivaroxaban

Rivaroxaban▼(Xarelto®) is a 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 rivaroxaban as an option for the acute management and secondary prevention of VTE.

Initiation of rivaroxaban should be undertaken by clinicians with expertise in managing anticoagulation. The initiating clinician / organisation is responsible for ensuring patient follow up and providing rivaroxaban 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 therapy may be considered for transfer back to the patient's own GP, provided the agreed transfer of care guidance is followed. If rivaroxaban is prescribed for unlicensed indications outside the scope of local guidance, prescribing responsibility will remain with the initiating clinician.

| Contraindications | Cautions |
|---|---|
| - Hypersensitivity to the active substance or to any of the excipients<br>- Clinically significant active bleeding<br>- Any lesion or condition considered a significant risk factor for major bleeding. e.g. co-morbidities such as active ulcerative gastrointestinal disease, congenital or acquired bleeding disorders<br>- Rare hereditary conditions such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption as **Xarelto** contains lactose<br>- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk<br>- Pregnancy and breast feeding<br>- Patients with severe renal impairment (CrCL< 15 ml/min; CKD stage 5)<br>- Prosthetic heart valves requiring anticoagulant treatment<br>- For contra-indications for use with other medicines, see overleaf | - Patients with an increased bleeding risk such due to:<br>o Congenital or acquired bleeding disorders<br>o Uncontrolled severe hypertension,<br>o Other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease), vascular retinopathy, bronchiectasis or history of pulmonary bleeding<br>- Active cancer<br>- Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy<br>- Liver enzymes are elevated > twice the upper limit of normal<br>- Moderate (CrCl 30-49ml/min) or severe (CrCl 15-29 ml/min) renal impairment<br>- For cautions for use with other medication, see overleaf |

**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.**

**Dosing**
**The recommended dose of rivaroxaban for management of acute DVT or PE is 15mg twice daily for three weeks, then 20mg once daily thereafter**. (In the maintenance phase, the initiating clinician may recommend a reduced dose of 15mg daily in patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment if their risk of bleeding is considered high
- The dose should be taken with food, at the same time each day
- No dose adjustment is required in the elderly

*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 rivaroxaban. However, clinical surveillance is recommended throughout the treatment period in line with good anticoagulation practice.

- All patients prescribed rivaroxaban should be reviewed **at least annually** to assess benefits and risks of on-going therapy, weighing the risk for thrombotic events against bleeding risk.
- 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 renal function and bleeding risk (see dosage section above).

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

- As with any other form of anticoagulation, there is an associated bleeding risk during treatment with rivaroxaban, 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 severe bleeding should seek urgent medical advice.

- Other common side effects include: dyspepsia, diarrhoea, nausea, vomiting, hypotension, oedema, tachycardia, thrombocytopenia, syncope, dizziness and headache

## Rivaroxaban *is a black triangle drug - any adverse effect must be reported to the MHRA using the* yellow card system *and via the local incident reporting system*

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

| Drug / Drug class | Recommendation |
|---|---|
| Concomitant administration of CYP3A4 inducers - such as rifampicin, St. John`s wort, phenobarbital, carbamazepine or phenytoin | Will result in decreased rivaroxaban plasma concentrations, and the SPC recommends should be co-administered with caution. The co-administration of rivaroxaban with any of these agents should only be considered under specialist haematology supervision. |
| 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 |
| 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 |
| 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 |
| Systemic ketoconazole, voriconazole, itraconazole or posaconazole | Concomitant use not recommended due to increased plasma rivaroxaban levels |
| Clarithromycin, erythromycin , fluconazole | Concomitant use of clarithromycin, eryhtroycin or fluconazole will increase rivaroxaban levels. This is not clinically significant in normal renal function, but may be significant in patients with renal impairment. In these patients alternative antibiotic therapy is preferred. Avoid use in CKD stage 4/5. |
| HIV Protease inhibitors e.g. ritonavir, indinavir | Not recommended for concomitant treatment with rivaroxaban |
| Dronedarone | Not recommended for concomitant treatment with rivaroxaban |
| 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 |
| Any other medicinal products affecting haemostasis | May increase the risk of bleeding when used concomitantly, close monitoring required |

**Roles and responsibilities**

| Initiating clinician / organisation | Patient's own GP |
|---|---|
| - To initiate rivaroxaban in line with NICE and local guidance<br>- To supply rivaroxaban for the first 3 months of treatment<br>- To provide counselling to improve adherence and deal with any early adverse effects<br>- If treatment is required for longer than three months; to transfer care to the GP in line with local transfer of care guidance<br>- If treatment is required for longer than three months; to give the GP clear guidance about intended duration of treatment or further follow-up required<br>- For patients requiring long-term treatment; | - To ensure use of rivaroxaban is in line with NICE / local guidance<br>- To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation)<br>- 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<br>- To emphasise the importance of adherence to rivaroxaban therapy and address any patient concerns<br>- To ensure monitoring of renal and hepatic function is undertaken as directed by the initiating clinician and at least annually. 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<br>- To monitor on-going risk of bleed and if appropriate, seek |

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| to arrange a follow-up at 12 months to review ongoing need for therapy | specialist advice |

**Additional information**

1. Patients taking rivaroxaban should be encouraged to carry an anticoagulation card (available from initiating clinician / anticoagulation clinics) at all times or to wear a medic-alert bracelet.
2. There is no specific reversal agent should a patient experience a bleed on rivaroxaban. In the event of a significant bleed, the patient should be referred to accident and emergency for supportive measures.
3. Other healthcare professionals should be made aware that rivaroxaban 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:
 If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
 If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.
5. If a patient has been assessed as being appropriate for a multi-compartment compliance aid (MCA), often known as a dosette box, consideration can be given to including rivaroxaban tablets as they do not have special storage requirements.

## 5.2 Apixaban

Apixaban (Eliquis®) is a 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 apixaban as an option for the acute management and secondary prevention of VTE.

Initiation of apixaban should be undertaken by clinicians with expertise in managing anticoagulation. The initiating clinician / organisation is responsible for ensuring patient follow up and providing apixaban 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 therapy may be considered for transfer back to the patient's own GP, provided the agreed transfer of care guidance is followed. If apixaban is prescribed for unlicensed indications outside the scope of local guidance, prescribing responsibility will remain with the initiating clinician.

| Contraindications | Cautions |
|---|---|
| - Hypersensitivity to the active substance or to any of the excipients<br>- Clinically significant active bleeding<br>- Any lesion or condition considered a significant risk factor for major bleeding. e.g. co-morbidities such as active ulcerative gastrointestinal disease, congenital or acquired bleeding disorders<br>- Rare hereditary conditions such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption as **Eliquis** contains lactose<br>- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk<br>- Pregnancy and breast feeding<br>- Patients with severe renal impairment (CrCL< 15 ml/min; CKD stage 5)<br>- Prosthetic heart valves requiring anticoagulant treatment<br>- 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<br>- Low body weight < 60kg<br>- Active cancer<br>- Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy<br>- Uncontrolled severe hypertension<br>- Mild or moderate hepatic impairment (Child Pugh A or B)<br>- Patients with elevated liver enzymes (alanine transaminase (ALT) / aspartate aminotransferase (AST)) > twice the upper limit of normal (ULN) or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore, to be used with caution<br>- Severe renal impairment (CrCl 15-29ml/min*)<br>- For cautions for use with other medication see overleaf |

**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.**

**Dosing**

- **The recommended dose of apixaban for management of acute DVT or PE is 10mg TWICE daily for the first 7 days, then 5mg TWICE daily thereafter**. For patients with severe renal impairment (CrCl 15– 29 ml/min), apixaban 5mg twice daily should be used with caution.
- **The recommended dose of apixaban for secondary prevention of recurrent DVT and/or PE is 2.5mg TWICE daily.** This should be initiated following completion of 6 months of acute treatment either with apixaban 5mg TWICE daily or alternative anticoagulant.

*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 apixaban. However, clinical surveillance is recommended throughout the treatment period in line with good anticoagulation practice.

- All patients prescribed apixaban should be reviewed **at least annually** to assess benefits and risks of on-going therapy, weighing the risk for thrombotic events against bleeding risk.
- 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 length of treatment completed (see dosage section above).

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

- As with any other forms of anticoagulation, there is a risk of bleeding during treatment with apixaban, 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 severe bleeding should seek urgent medical advice.
- Other side effects include itching and allergic reactions.

**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 where switching therapy to or from apixaban or when UFH is given at doses necessary to maintain a patent catheter |
| 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 |
| HIV Protease inhibitors e.g. ritonavir, indinavir | Not recommended for concomitant treatment with apixaban |
| Strong CYP3A4 or P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) | Concomitant use will result in decreased apixaban plasma concentrations. No dose adjustment to apixaban is required, however it should be used with caution. The co-administration of apixaban with any of these agents should only be considered under specialist haematology supervision |
| 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 |
| 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 |
| Any other medicinal products affecting haemostasis | May increase the risk of bleeding when used concomitantly, close monitoring required |
| Systemic ketoconazole, voriconazole, itraconazole or posaconazole | Concomitant use not recommended due to increased plasma apixaban levels |

**Roles and responsibilities**

| Initiating clinician / organisation | Patient's own GP |
|---|---|
| - To initiate apixaban in line with NICE and local guidance<br>- To supply apixaban for the first 3 months of treatment<br>- To provide counselling to improve adherence and deal with any early adverse effects<br>- If treatment is required for longer than three months; to transfer care to the GP in line with local transfer of care guidance<br>- If treatment is required for longer than three months; to give the GP clear guidance about intended duration of treatment or further follow-up required<br>- For patients requiring long-term treatment; to arrange a follow-up at 12 months to review ongoing need for therapy | - To ensure use of apixaban is in line with NICE / local guidance<br>- To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation)<br>- 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<br>- To emphasise the importance of adherence to apixaban therapy and address any patient concerns<br>- To ensure monitoring of renal and hepatic function is undertaken as directed by the initiating clinician and at least annually. 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<br>- To monitor on-going risk of bleed and if appropriate, seek specialist advice |

**Additional information**

1. Patients taking apixaban should be encouraged to carry an anticoagulation card (available from initiating clinician / anticoagulation clinics) at all times or to wear a medic-alert bracelet.
2. There is no specific reversal agent should a patient experience a bleed on apixaban. In the event of a significant bleed, the patient should be referred to accident and emergency for supportive measures.
3. Other healthcare professionals should be made aware that apixaban 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: If a dose is missed, it should be taken immediately and then continue to take twice daily as before.
5. If a patient has been assessed as being appropriate for a multi-compartment compliance aid (MCA), often known as a dosette box, consideration can be given to including apixaban tablets as they do not have any special storage requirements.

## 5.3 Edoxaban

Edoxaban▼ (Lixiana®) is a 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 edoxaban as an option for the acute management and secondary prevention of VTE.

Initiation of edoxaban should be undertaken by clinicians with expertise in managing anticoagulation. The initiating clinician / organisation is responsible for ensuring patient follow up and providing edoxaban 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 therapy may be considered for transfer back to the patient's own GP, provided the agreed transfer of care guidance is followed. If edoxaban is prescribed for unlicensed indications outside the scope of local guidance, prescribing responsibility will remain with the initiating clinician.

| Contraindications | Cautions |
|---|---|
| - Hypersensitivity to the active substance or to any of the excipients<br>- Clinically significant active bleeding<br>- Any lesion or condition considered a significant risk factor for major bleeding. e.g. co-morbidities such as active ulcerative gastrointestinal disease, congenital or acquired bleeding disorders<br>- Uncontrolled severe hypertension<br>- Hepatic disease associated with coagulopathy and | - Patients with conditions which carry a haemorrhagic risk e.g. bacterial endocarditis, thrombocytopenia, congenital or acquired coagulation disorders<br>- Active cancer<br>- Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy<br>- Low body weight < 60kg<br>- Mild or moderate hepatic impairment (Child Pugh A or B) or elevated liver enzymes (alanine transaminase |

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|---|---|
| clinically relevant bleeding risk<br>- Pregnancy and breast feeding<br>- Patients with severe renal impairment (CrCL< 15 ml/min; CKD stage 5)<br>- Prosthetic heart valves requiring anticoagulant treatment or mitral stenosis<br>- For contra-indications for use with other medicines see overleaf | (ALT) / aspartate aminotransferase (AST)) > twice the upper limit of normal (ULN) or total bilirubin ≥ 1.5 x ULN (these patients were excluded in clinical trials)<br>- Moderate to severe renal impairment (CrCl 15-49ml/min*)<br>- For cautions for use with other medication see overleaf |

**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.**

**Dosing**

**The recommended dose of edoxaban is 60mg ONCE 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). *For dosing of parenteral anticoagulants refer to **LMWH guidance** or **UFH infusion in adults guideline** available on the Trust intranet.*

- Reduce dose to 30mg ONCE daily with or without food in patients with one of the following characteristics:
  - Low body weight ≤ 60kg
  - Moderate to severe renal impairment (CrCl 15-49 ml/min), or
  - Concomitant treatment with ciclosporin, dronedarone, erythromycin, ketoconazole.

- Treatment must only be started when parenteral anticoagulation therapy (LMWH / UFH) is discontinued. Edoxaban must not be administered concomitantly with any additional anticoagulation.
  - For patients on LMWH – the first dose of edoxaban must be given when the next dose of LMWH is due.
  - For patients on continuous infusions of UFH – stop the heparin infusion and give the first dose of edoxaban 4 hours later.

*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 edoxaban. However, clinical surveillance is recommended throughout the treatment period in line with good anticoagulation practice.

- All patients prescribed edoxaban should be reviewed **at least annually** to assess benefits and risks of on-going therapy, weighing the risk for thrombotic events against bleeding risk.
- 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 bodyweight, renal function and concomitant medicines (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 edoxaban, 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.
- Other common side effects include: nausea, rash, pruritus, abnormal liver function tests (raised bilirubin and gamma-glutamyl transferase (GGT)).

**- Edoxaban *is a black triangle drug - any adverse effect must be reported to the MHRA using the* yellow card system *and via the local incident reporting system***

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

| Drug / Drug class | Recommendation |
|---|---|
| Concomitant administration of CYP3A4 inducers - such as rifampicin, St. John`s wort, phenobarbital, carbamazepine or | Will result in decreased edoxaban plasma concentrations. No dose adjustment is required but the SPC recommends should be co-administered with caution. The co-administration of edoxaban with |

| | |
|---|---|
| phenytoin | any of these agents should only be considered under specialist haematology supervision. |
| 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 |
| 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 |
| 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 |
| Systemic ketoconazole, ciclosporin, dronedarone or erythromycin | Concomitant administration increases plasma edoxaban level. Maximum edoxaban dose of 30mg once daily when prescribed concurrently |
| Amiodarone, quinidine, verapamil | No dose adjustment necessary |
| HIV Protease inhibitors e.g. ritonavir, indinavir | Not recommended for concomitant treatment |
| 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 |
| Any other medicinal products affecting haemostasis | May increase the risk of bleeding when used concomitantly, close monitoring required |

**Roles and responsibilities**

| Initiating clinician / organisation | Patient's own GP |
|---|---|
| - To initiate edoxaban in line with NICE and local guidance<br>- To supply edoxaban for the first 3 months of treatment<br>- To provide counselling to improve adherence and deal with any early adverse effects<br>- If treatment is required for longer than three months; to transfer care to the GP in line with local transfer of care guidance<br>- If treatment is required for longer than three months; to give the GP clear guidance about intended duration of treatment or further follow-up required<br>- For patients requiring long-term treatment; to arrange a follow-up at 12 months to review ongoing need for therapy | - To ensure use of edoxaban is in line with NICE / local guidance<br>- To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation)<br>- 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<br>- To emphasise the importance of adherence to edoxaban therapy and address any patient concerns<br>- To ensure monitoring of renal and hepatic function is undertaken as directed by the initiating clinician and at least annually. 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<br>- To monitor on-going risk of bleed and if appropriate, seek specialist advice |

**Additional information**

Patients taking edoxaban should be encouraged to carry an anticoagulation card (available from initiating clinician / anticoagulation clinics) at all times or to wear a medic-alert bracelet.
2. There is no specific reversal agent should a patient experience a bleed on edoxaban. In the event of a significant bleed, the patient should be referred to accident and emergency for supportive measures.
3. Other healthcare professionals should be made aware that edoxaban 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: If a dose of edoxaban is missed, the dose should be taken immediately and then be continued the following day with the once-daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.
5. If a patient has been assessed as being appropriate for a multi-compartment compliance aid (MCA), often known as a dosette box, consideration can be given to including edoxaban tablets as they do not have any special storage requirements.

## 5.4 Dabigatran

Dabigatran etexilate (Pradaxa®) is a 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.

Initiation of dabigatran should be undertaken by clinicians with expertise in managing anticoagulation. The initiating clinician / organisation is responsible for ensuring patient follow up and providing 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 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 indications outside the scope of local guidance, prescribing responsibility will remain with the initiating clinician.

| Contra-indications | Cautions |
|---|---|
| - Hypersensitivity to the active substance or to any of the excipients<br>- Patients with severe renal impairment (CrCL < 30 ml/min)<br>- Active clinically significant bleeding<br>- Any lesion or condition considered a significant risk factor for major bleeding. e.g. co-morbidities such as active ulcerative gastrointestinal disease, congenital or acquired bleeding disorders<br>- Hepatic impairment or liver disease expected to have any impact on survival<br>- Pregnancy and breast-feeding<br>- Prosthetic heart valves requiring anticoagulant treatment<br>- For contraindications 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<br>- Active cancer<br>- Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy<br>- Uncontrolled severe hypertension<br>- Low body weight ≤ 50kg – close clinical surveillance is recommended<br>- Liver enzymes > twice the upper limit of normal – patients were excluded from trials therefore use is not recommended for this subpopulation of patients<br>- Moderate renal impairment (CrCL 30 – 49 ml/min*)<br>- For cautions for use with other medication see overleaf |

**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.**

**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). *For dosing of parenteral anticoagulants refer to **LMWH guidance** or **UFH infusion in adults guideline** available on the Trust intranet.*

- 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)
- Treatment must only be started when parenteral anticoagulation therapy (LMWH / 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 |
|---|---|
| Concomitant administration of P-gp inducers - such as rifampicin, St. John`s wort, carbamazepine or phenytoin | Will result in decreased dabigatran plasma concentrations, and therefore should be avoided |
| 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 |
| 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 |
| NSAIDS | Increased risk of bleeding if used long-term. Avoid where possible, but if used, close monitoring required |
| Systemic ketoconazole, ciclosporin, itraconazole and tacrolimus | Concomitant use is contra-indicated due to increased plasma dabigatran levels |
| Dronedarone | Concomitant treatment with dronedarone is contraindicated. |
| Amiodarone, posaconazole and quinidine | May increase plasma dabigatran levels; close surveillance recommended, especially in mild to moderate renal impairment; use with caution |
| Clarithromycin | May increase plasma dabigatran levels especially where there is moderate to severe renal impairment – use with caution |
| Protease inhibitors including ritonavir and its combinations with other protease inhibitors | Not recommended for concomitant treatment with dabigatran |
| SSRIs and SNRIs | Increased bleeding risk with dabigatran, close monitoring |

| | |
|---|---|
| | required |
| 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<br>- To supply dabigatran for the first 3 months of treatment<br>- To provide counselling to improve adherence and deal with any early adverse effects<br>- If treatment is required for longer than three months; to transfer care to the GP in line with local transfer of care guidance<br>- If treatment is required for longer than three months; to give the GP clear guidance about intended duration of treatment or further follow-up required<br>- 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 NICE / local guidance<br>- To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation)<br>- 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<br>- To emphasise the importance of adherence to dabigatran therapy and address any patient concerns<br>- To ensure monitoring of renal and hepatic function is undertaken as directed by the initiating clinician and at least annually. 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<br>- To monitor on-going 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.

## 6 DURATION OF THERAPY

• Patients should be referred to the Anticoagulation Service at the point of initiation. This will enable patients to be reviewed in the anticoagulation clinic within the appropriate timeframe for the chosen anticoagulant. At that point, a further prescription can be issued for up to 9 weeks to complete the total supply for 12 weeks (3 months) from CUH.

• When initiating rivaroxaban for DVT or PE, the pharmacy will only supply the 3 weeks of the loading phase; a prescription for the maintenance dose will be provided at the anticoagulation clinic follow up. If one of the other DOACs is prescribed for DVT or PE, pharmacy will provide 3-4 weeks of treatment to ensure an adequate supply until the anticoagulation clinic follow up.

• DOACs will be prescribed for 3-6 months in patients with DVT or PE. Any extension of treatment will be decided by the Anticoagulation Service( as is the case with warfarin/ LMWH)

• For patients requiring more than 3 months treatment with a DOAC, prescribing responsibility will be transferred to their GP using the designated transfer of care form **(Appendix D)**

## 7 MONITORING OF DOACS

Routine monitoring of the anticoagulant effect of dabigatran, rivaroxaban, edoxaban and apixaban is not required to guide therapy. PT, TT, INR and APTT may be prolonged in patients taking these DOACs due to their mechanism of action; however, these tests do not provide an accurate measure for monitoring their anticoagulant effects.

Monitoring may be reasonable in the following circumstances:

- In emergency situations, such as serious bleeding or thrombotic events, need for urgent surgery (check APTT and TT for patients on dabigatran or PT for patients on rivaroxaban, edoxaban and apixaban prior to surgery or other invasive procedures)
- In special clinical situations, such as patients presenting with renal or hepatic insufficiency, in case of potential drug-drug interactions or of suspected overdosing.

Due to the relatively short half lives of all DOACs the timing of blood sampling in relation to ingestion of the drug is of paramount importance to minimise the interference of the DOAC and accurately assess clotting parameters.

- Clotting results obtained within 4 hours of taking a dose of any DOAC are likely to be affected by the peak concentration of DOAC in the blood stream.
- Clotting parameters may be deranged due to a number of co-morbidities (e.g sepsis, hepatitis etc) thus monitoring may be warranted for these reasons. **In such situations, a blood sample should be obtained right before the next dose of the DOAC is due.** (Trough levels: 12 hours post dose for dabigatran or apixaban, 24 hours post dose for rivaroxaban or edoxaban)

## 8 SWITCHING BETWEEN ANTICOAGULATION THERAPIES

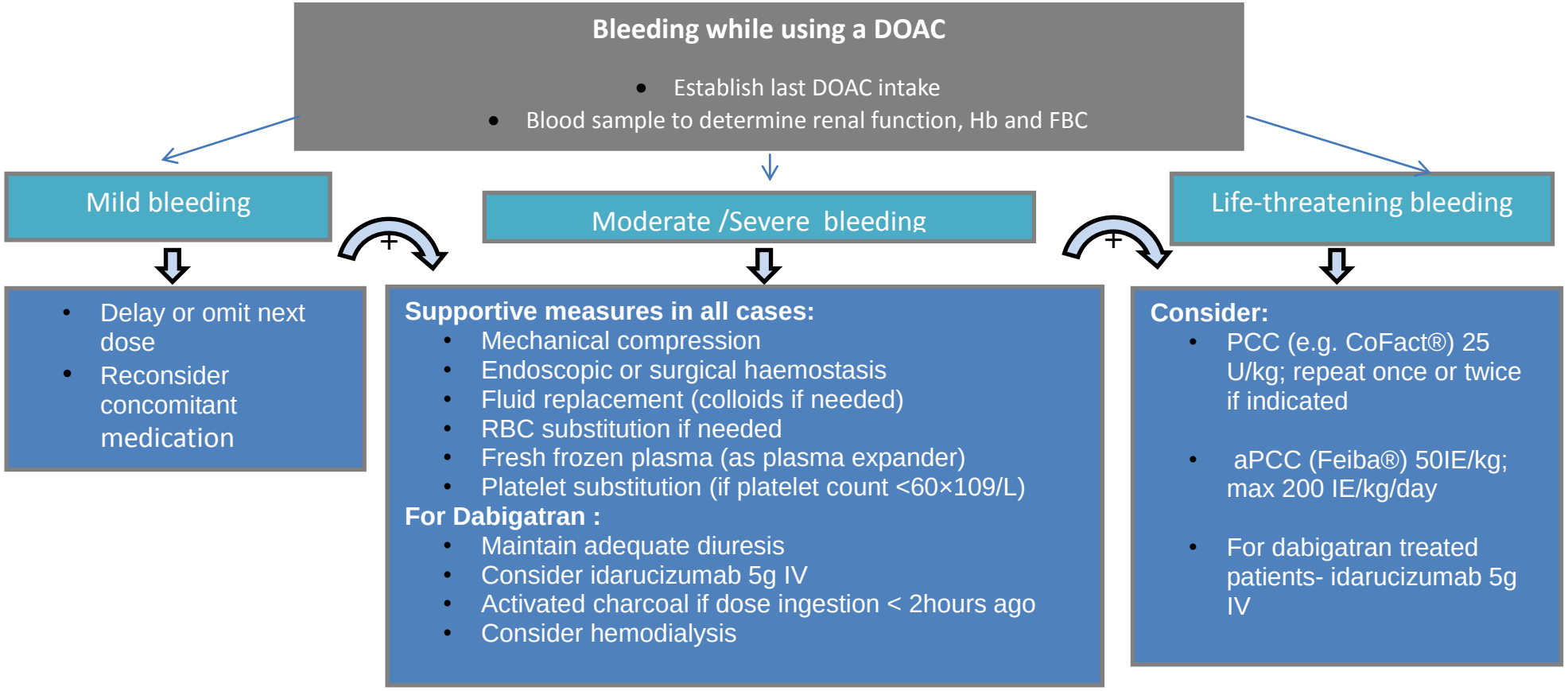
| | **Dabigatran *(Pradaxa®)*** | **Rivaroxaban *(Xarelto®)*** | **Apixaban *(Eliquis®)*** | **Edoxaban *(Lixiana®)*** |
|---|---|---|---|---|
| **Parenteral anticoagulant to DOAC** | Dabigatran should be initiated 0-2 hours prior to the time that the next dose of parenteral therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous UFH) | Rivaroxaban should be initiated 0-2 hours prior to the time that the next dose of parenteral therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous UFH) | Apixaban should be initiated at the time that the next dose of parenteral therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous UFH) | Edoxaban should be initiated at the time that the next dose of parenteral therapy would be due, or 4 hours after discontinuation in case of continuous treatment (e.g. intravenous UFH) |
| **DOAC to parenteral anticoagulant** | Parenteral anticoagulant should be initiated 12 hours after the last dose of dabigatran | Parenteral anticoagulant should be initiated at the time the next rivaroxaban dose would be due. | Parenteral anticoagulant should be initiated at the time the next dose of apixaban would be due | Parenteral anticoagulant should be initiated at the time the next edoxaban dose would be due. |
| **Vitamin K antagonist (VKA eg warfarin) to DOAC** | VKA should be stopped and dabigatran initiated when INR < 2 | VKA should be stopped and rivaroxaban initiated when INR ≤ 3. | VKA should be stopped and apixaban initiated when INR < 2 | Discontinue the VKA and start edoxaban when the INR ≤ 2.5 |
| **DOAC to Vitamin K antagonist (VKA eg warfarin)** | The starting time of VKA should be based on the patients CrCL as follows:<br><br>• CrCL ≥ 50 ml/min, start warfarin 3 days before discontinuing dabigatran<br><br>• CrCL 30 - < 50 ml/min, start warfarin 2 days before discontinuing dabigatran<br><br>*Note: Dabigatran can increase INR. INR will better reflect VKA's effect only after dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.* | VKA should be given concurrently with rivaroxaban until the INR is ≥ 2.0.<br>For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.<br>While patients are on both rivaroxaban and VKA, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban.<br>Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose. | VKA should be given concurrently with apixaban for at least 2 days. After 2 days, check INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and VKA therapy until the INR is ≥ 2.0. | Patients should not take a loading dose of VKA:<br>• For patients currently on a 60 mg dose, reduce the dose to 30 mg daily together with an appropriate VKA dose.<br>• For patients currently on a 30 mg dose, reduce the dose to 15 mg daily together with an appropriate VKA dose.<br><br>Once an INR ≥ 2.0 is achieved, edoxaban should be discontinued. |
| **Switching Between DOACs** | A period of 12 hours should be left after the last dose of dabigatran before initiating another DOAC | A period of 24 hours should be left after the last dose of rivaroxaban before initiating another DOAC. | A period of 12 hours should be left after the last dose of apixaban before initiating another DOAC. | A period of 24 hours should be left after the last dose of edoxaban before initiating another DOAC. |

## 9 PERIOPERATIVE MANAGEMENT /SURGICAL INTERVENTIONS

<table>
<tr><td></td><td colspan="3">Dabigatran (Pradaxa®)</td><td colspan="3">Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Edoxaban (Lixiana®)</td></tr>
<tr><td>Surgery & invasive procedures</td><td colspan="6">No important bleeding risk and/or adequate local haemostasis possible (e.g. dental interventions, ophthalmological precedures, endoscopy without surgery, superficial surgery):<br>Perform procedure ≥12 hours after last intake of dabigatran or apixaban/ perform procedure ≥24 hours after last intake of rivaroxaban or edoxaban<br>There is no need for bridging with LMWH/ UFH</td></tr>
<tr><td></td><td>Renal function</td><td>Low risk procedure*</td><td>High risk procedure^</td><td>Renal function</td><td>Low risk procedure*</td><td>High risk procedure^</td></tr>
<tr><td></td><td>CrCL> 80 ml/min</td><td>Stop DOAC ≥ 24 hours prior to procedure</td><td>Stop DOAC ≥ 48 hours prior to procedure</td><td>CrCL> 80 ml/min</td><td>Stop DOAC ≥ 24 hours prior to procedure</td><td>Stop DOAC ≥ 48 hours prior to procedure</td></tr>
<tr><td></td><td>CrCL 50-80 ml/min</td><td>Stop DOAC ≥ 36 hours prior to procedure</td><td>Stop DOAC ≥ 72 hours prior to procedure</td><td>CrCL 50-80 ml/min</td><td>Stop DOAC ≥ 24 hours prior to procedure</td><td>Stop DOAC ≥ 48 hours prior to procedure</td></tr>
<tr><td></td><td>CrCL 30-50 ml/min</td><td>Stop DOAC ≥ 48 hours prior to procedure</td><td>Stop DOAC ≥ 96 hours prior to procedure</td><td>CrCL 30-50 ml/min</td><td>Stop DOAC ≥ 24 hours prior to procedure</td><td>Stop DOAC ≥ 48 hours prior to procedure</td></tr>
<tr><td></td><td>CrCL 15-30 ml/min</td><td>N/A</td><td>N/A</td><td>CrCL 15-30 ml/min</td><td>Stop DOAC ≥ 36 hours prior to procedure</td><td>Stop DOAC ≥ 48 hours prior to procedure</td></tr>
<tr><td></td><td colspan="6"><u>*Low bleeding risk procedures</u>: Endoscopy with biopsy, prostate or bladder biopsy, pacemaker or ICD implantation, non-coronary angiography<br><br><u>^High bleeding risk procedures</u>: Spinal or epidural anaesthesia, lumbar puncture, thoracic or abdominal surgery, major orthopaedic surgery, liver or kidney biopsy, transurethral resection of prostate, extracorporeal shockwave lithotripsy</td></tr>
<tr><td>Post operative phase</td><td colspan="6">• Dabigatran, rivaroxaban, edoxaban and apixaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established.<br>• For procedures with immediate and complete haemostasis, dabigatran, rivaroxaban, edoxaban and apixaban can be resumed 6–8 hours after the intervention; therapeutic anticoagulation by restarting dabigatran, rivaroxaban, edoxaban and apixaban should be deferred for 48 to 72 hours after high risk invasive procedures.</td></tr>
</table>

## 10 MANAGEMENT OF BLEEDING WHILE USING A DOAC

- **Idarucizumab (Praxbind®) is available as a specific antidote for reversal of dabigatran only**
- **Seek urgent advice from Haematology**
- **Coagulation tests may help to determine bleeding risk: APTT & TT will be prolonged for dabigatran/ PT will be prolonged for rivaroxaban/ APTT & PT will be prolonged for edoxaban/ APTT, TT &PT likely to be normal for apixaban and does not mean there is no drug present**




Adapted from the European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation (updated in August 2015)

## 11 TRAINING

At induction junior doctors will receive robust training on prescribing all oral anticoagulants and will be made aware that these guidelines are available.
Pharmacists and nursing staff will receive training during induction, clinical governance meetings and other routine training sessions.
The guidelines will be disseminated to all wards and departments of the trust. The guidelines will be accessible to all staff on the trust intranet

### 11.1 Equality Impact Assessment

The Equality Impact Assessment for this policy is attached in Appendix A.

## 12 MONITORING COMPLIANCE

Thrombosis committee monitors compliance in accordance with NPSA guidance alert 18- Action that can make anticoagulant therapy safer. It will be doing through 4monthly auditing

## 13 REFERENCES

1) NICE TA261 (July 2012) Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis an pulmonary embolism
2) NICE TA287(June 2013) Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism.
3) NICE TA341 (June 2015) Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism
4) NICE TA354 (August 2015) Edoxaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism
5) NICE TA327 (December 2014) Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism
6) Associated BNF 72: September 2016-March 2017
7) SPC Pradaxa. Boehringer Ingelheim. March 2016 Accessed at http://www.medicines.org.uk/emc/medicine/20760
8) SPC Xarelto. Bayer. July 2015. Accessed at http://www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/
9) SPC Eliquis. BMS/Pfizer. January 2016. Accessed at http://www.medicines.org.uk/emc/medicine/24988
10) SPC Lixiana. Daiichi Sankyo UK Limited. July 2015. Accessed at http://www.medicines.org.uk/emc/medicine/30506
11) European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation (2013); updated August 2015
12) British Journal of Haematology, 2012, **160**, page 39-40

## 14 ASSOCIATED DOCUMENTATION

None

# 15 VERSION HISTORY TABLE

| Version | Date | Author | Ratified by | Comment/Reason for change |
|---|---|---|---|---|
| 1 | May 2013 | Dr S. Appiah-Cubi &<br>Mr Dimitrios Karagkounis | Policy Committee | |
| 2 | December 2013 | Dr S. Appiah-Cubi &<br>Mr Dimitrios Karagkounis | Policy Committee | Amended to include the following:<br><br>Pharmacy contact details to receive prescription screening check list.<br><br>Referral of patients to haematology |
| 2.1 | July 2014 | Dr S. Appiah-Cubi &<br>Mr Dimitrios Karagkounis | Policy Committee | Updated due to approval for use as first line for VTE |
| 3 | April 2017 | Mr Dimitrios Karagkounis | Risk Assurance and Policy Group | Inclusion of apixaban, edoxaban and dabigatran<br>Introduction of idarucizumab<br>Updated guidance by SWL Medicines Commissioning Group |

## APPENDIX A – EQUALITY IMPACT ASSESSMENT

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval.

| **Policy: GUIDELINES FOR THE USE OF DIRECT ORAL ANTICOAGULANTS (DOAC) IN ADULTS WITH ACUTE DVT & PE AND PREVENTION OF RECURRENT VTE** | | | **Date: November 2016** | |
|---|---|---|---|---|
| **Officer conducting this Analysis : Dimitrios Karagkounis- Lead Pharmacist** | | | | |
| **Protected Characteristic** | **Positive Impact** | **Negative Impact** | **None** | **Reasons for decision** |
| Age | X | | | There is no data on the safety or efficacy of DOACs in children and their use is not licensed in this age group. |
| Disability | | | X | |
| Faith | | | X | |
| Gender | | | X | |
| Race | | | X | |
| Sexual Orientation | | | X | |

## APPENDIX B – CONSULTATION TEMPLATE

| | | |
|---|---|---|
| 1. | Procedural Document's Name: | Guidelines for the use of direct oral anticoagulanta (DOAC) in adults with DVT & PE and prevention of VTE |
| 2. | Procedural Document Author: | Mr Dimitrios Karagkounis |
| 3. | Group/Committee Consulted: | Thrombosis Committee & MMC |
| 4. | Date of Consultation: | December 2016 – March 2017 |
| 5. | Comments Received:<br>**Thrombosis committee**: To reiterate that rivaroxaban remains the first line choice for VTE due to its relatively simple dosing regimen and ease of follow up whilst the other DOACs are available as second line options.<br><br>**Medicines management committee**:<br>To clarify DOACs are not appropriate for children and for adults only<br>To clarify dosing regimen of parenteral anticoagulant prior to initiating dabigatran or edoxaban therapy and refer to Trust guidelines<br>To rationalise the first line choice of DOAC in the document<br>To take to CPC for shared-care approval | |

## APPENDIX C - SCREENING CHECKLIST AND NOTIFICATION OF INITIATION TO GP

Croydon Health Services NHS
NHS Trust

### Direct Oral Anticoagulants (DOACs) for the acute treatment and secondary prevention of Venous Thromboembolism (VTE) - Pulmonary embolism (PE) and deep vein thrombosis (DVT)

### Screening Checklist and Notification of Initiation to GP

- The checklist must be completed and sent to the GP when DOAC therapy is initiated
- Following a 3 month period, if treatment is to continue, care may be transferred to the GP. At this point, a transfer of care document should be completed and sent to the GP
- *Hospital clinicians should be aware that, if a DOAC is prescribed for an unlicensed indication prescribing responsibility will remain with the initiating team*

Important information for GPs:
This is notification that a direct oral anticoagulant agent has been started for your patient
**Please ensure that warfarin or other anticoagulant therapies are stopped**

**Apixaban, dabigatran, edoxaban and rivaroxaban** are options for the treatment of acute VTE and for patients requiring longer-term secondary prevention of VTE

| **Patient Details** | **GP Details** |
|---|---|
| Surname: | Name: |
| Forename: | Address: |
| Address: | Tel: |
| Postcode: | Fax: |
| NHS No: | NHS.net email: |
| DOB: Sex: Male / Female | |

**Date of Diagnosis:** ……..

**Date of DOAC initiation (if different from diagnosis):** ……

**Indication** (Tick as appropriate)

☐ **Confirmed DVT: (indicate type below)**
☐ **Distal (Calf)** ☐ **Proximal (Above knee)**

☐ **Confirmed PE**

☐ **Secondary prevention of VTE (switching to DOAC therapy from an alternative anticoagulant agent):**

**Anticoagulant being stopped ……**

| **Eligibility Criteria** (Refer to the SPC for full details of licensed indications) | **Yes** | **No** |
|---|---|---|
| NICE/ local consensus criteria for apixaban / dabigatran / edoxaban / rivaroxaban use *Note: all four criteria must be met to be within license for use* (Tick yes or no as appropriate) | | |
| 1. Confirmed diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) (acute or recurrent) | | |
| 2. **CrCl ≥30ml/min** (dabigatran) or **CrCl ≥15ml/min** (apixaban, edoxaban, rivaroxaban) (*to calculate creatinine clearance see overleaf) | | |
| 3. **Dabigatran and edoxaban ONLY**: Patient to have received a minimum of 5 days therapy with parental heparin or low molecular weight heparin prior to starting DOAC | | |
| 4. No contraindications to treatment present (refer to prescribing guideline for DOAC) | | |

| **Patient Information** (Tick yes or no as appropriate) | **Yes** | **No** |
|---|---|---|
| 1. Patient is aware of the benefits and risks of DOAC therapy | | |
| 2. Patient has been advised to carry an anticoagulant card or wear a medic-alert bracelet | | |
| 3. Patient has consented to therapy | | |
| 4. Female patients of child-bearing age are aware of the risks of falling pregnant while on DOAC | | |

| | | |
|---|---|---|
| treatment and recommended appropriate contraceptive measures are taken | | |

| **Anticipated duration of therapy** (Tick as appropriate) | **Comments on duration:** |
|---|---|
| ☐ 3 months only ☐ 6 months only<br>☐ Long term | |

| ***Baseline assessment of renal function*** | | |
|---|---|---|
| **Baseline serum creatinine** | Date of test: | Result: |
| **Calculated Creatinine clearance (CrCl) (Cockcroft – Gault)*** | | |

***eGFR should NOT be used to guide dosing decisions. Creatinine clearance must be calculated using the Cockcroft-Gault equation or a Cockcroft-Gault equation calculator**

**TICK THE PRESCRIBED DRUG AND DOSE BELOW:**

| **RIVAROXABAN - Dosing** | **Tick** |
|---|---|
| **Standard dose: 15mg twice daily for three weeks, then 20mg daily thereafter** | |
| **Reduced dose: 15mg twice daily for three weeks, then 15mg daily thereafter**<br>*When to use: Patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment if their risk of bleeding is considered high* | |

| **APIXABAN- Dosing** | **Tick** |
|---|---|
| **Standard dose: 10mg twice daily for 7 days, then 5mg twice daily thereafter**<br>*For patients with severe (CrCl 15–29 ml/min) renal impairment apixaban 5mg twice daily should be used with caution* | |
| **Secondary prevention of recurrent DVT and/or PE following completion of 6 months of acute treatment: 2.5mg twice daily** | |

| **EDOXABAN - Dosing** | **Tick** |
|---|---|
| **Standard dose: 60mg once daily following initial use of parenteral anticoagulant for at least 5 days** | |
| **Reduced dose: 30mg once daily following initial use of parenteral anticoagulant for at least 5 days**<br>*When to use:*<br>• *Patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment*<br>• *Patients with body weight ≤60kg*<br>• *Patients taking concomitant therapy with the following: ciclosporin, dronedarone, erythromycin, or ketoconazole* | |

| **DABIGATRAN- Dosing** | **Tick** |
|---|---|
| **Standard dose: 150mg twice daily following initial use of parenteral anticoagulant for at least 5 days** | |
| **Reduced dose: 110mg twice daily following initial use of parenteral anticoagulant for at least 5 days**<br>*When to use:*<br>• *All patients over 80 years of age*<br>• *Patients taking concomitant verapamil*<br>• *Patients with moderate (CrCl 30–49 ml/min) renal impairment if their bleeding risk is considered high*<br>• *Patients aged 75-80 years if their bleeding risk is considered high*<br>• *Patients with gastritis if their bleeding risk is considered high* | |

**Cautions**

- Concurrent antiplatelet therapies (aspirin, clopidogrel, prasugrel, ticagrelor), NSAIDs will increase bleeding risk – check patient's medication list and review if necessary. Seek specialist advice if on dual antiplatelet therapy.
- For patients identified as at risk of upper GI bleeding the co-prescription of a low cost PPI may be considered

| **ANTIPLATELET THERAPY** | | |
|---|---|---|
| Is the patient receiving concomitant antiplatelet therapy? ☐ Yes ☐ No | | |
| Antiplatelet(s) in use: | Indication: | |
| Should antiplatelet therapy be withheld whilst patient on anticoagulation? ☐ Yes ☐ No<br><br>Comments (including plan for antithrombotic therapy): | | |
| **AUTHORISATION (practitioner undertaking assessment)** | | |
| **Signature:**<br><br>**Position:**<br><br>**Contact number:** | **Print name:**<br><br>**Organisation:**<br><br>**Date:** | **Anticoagulation service contact details: ext. 5673**<br><br>**Haem SpR via switchboard OOH** |

## APPENDIX D - TRANSFER OF CARE FORM

## Direct Oral Anticoagulants (DOACs) for the acute treatment and secondary prevention of venous thromboembolism (VTE)

### Transfer of Prescribing Responsibility

Croydon Health Services NHS
NHS Trust

***Patient Details***

**Name:**..... …. **DOB: ……/……../……**

**Hospital Number: ……** **Address:……**

**NHS Number: ……..**

| **GP Practice Details:** | **Consultant Details:** |
|---|---|
| Name: …… | Consultant Name:..... |
| Address: …… | Clinic Name:…… |
| Tel no: …… | Address: …… |
| Fax no: …… | Tel no: ……..…… |
| NHS.net e-mail: …… | Fax no:: …… NHS.net email:: …… |

Dear Dr……

**The patient is on a DOAC for:** treatment of DVT / treatment of PE / secondary prevention of VTE (delete as appropriate)

***Details of treatment plan***

| DOAC initiated | Tick selected | Date initiated | Dose on transfer | Intended duration of treatment | Date of next review |
|---|---|---|---|---|---|
| Rivaroxaban | | | | | |
| Apixaban | | | | | |
| Edoxaban | | | | | |
| Dabigatran | | | | | |

I have now supplied the first three months of therapy for this patient and am writing to transfer the prescribing responsibility for this patient's on-going treatment from ….. /…../……
This transfer of care document should be reviewed in conjunction with the screening checklist and notification sent previously by the initiating clinician. If this has not been received contact the consultant named above for details.
All patients receiving DOAC therapy for VTE for duration over one year should be reviewed at least annually throughout the treatment period by the anticoagulation clinic, in line with local guidelines.

***Monitoring***

| Test | | Result | Date of test | Please repeat test in: |
|---|---|---|---|---|
| Serum Creatinine | | | | ……..……..months |
| Calculated Creatinine clearance | | | | |
| Haemoglobin | | | | 12 months |
| Liver Function Tests | ALT | | | 12 months |
| | ALP | | | |
| | bilirubin | | | |

***Antiplatelet therapy***

Is the patient receiving concomitant antiplatelet therapy? Yes No

Antiplatelet(s) in use: Indication:

Should antiplatelet therapy be withheld whilst patient on anticoagulation? Yes No
*Comments:*

- I confirm that I have prescribed in accordance with the local VTE guidelines
- I confirm that the patient has been made aware of the benefits and risks of DOAC therapy, including risks of both major and minor bleeding, and that they know how to seek medical help should bleeding occur.
- I confirm that I have provided an anticoagulation card and/or medic-alert bracelet at initiation
- I confirm the patient has consented to treatment
- For female patients of child-bearing age: I have explained the risks of falling pregnant whilst on this treatment and recommended appropriate contraceptive measures are taken.

**Signed:…… Name of Clinician:…… Date: …….**