Rationale for Initiation, Continuation and Discontinuation (RICaD)

Apixaban ▼ (Eliquis)

Treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (NICE TA341)

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

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

Rationale for Choice

Relevant Diagnosis:	Treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism ☐
Agreed Indication(s) for inclusion in the BSSE APC Formulary:	NICE TA341 states that Apixaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults
Reason why apixaban has been chosen in preference to drugs without Formulary restrictions:	Specialists please type text below and check boxes: I can confirm that an informed discussion about the benefits and risks of apixaban compared with warfarin has taken place with the patient. A copy of the checklist is enclosed ☐ Commissioned in DVT pathway in locality ☐ Allergic reaction/intolerance of coumarins (warfarin, phenindione, sinthrome) ☐ Patients with important and unavoidable drug interactions that favour apixaban over warfarin ☐ Patients in whom monitoring and/or coping with variable dose regimen is difficult but who are able to comply with a fixed dose drug regime. ☐ Previous significant bleed on warfarin in patients at high risk for stroke, if bleed was associated with poor INR control in a patient who is believed to be adherent with prescribed medication. ☐ Poor INR control (e.g. more than 2 INRs >8.0 or more than 3 INRs >5.0 in 6 months) ☐ Poor Time to Therapeutic Range List TTR value: …… ☐ Patients who, following informed discussion of risks and benefits of apixaban and warfarin, request apixaban as their preferred choice in terms of a favourable lifestyle in comparison to warfarin
Special precautions	**Contraindications** • Hypersensitivity to the active substance or to any of the excipients listed. • Active clinically significant bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. • Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, 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 **Cautions** <u>Haemorrhage risk</u> As with other anticoagulants, patients taking apixaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. apixaban administration should be discontinued if

	severe haemorrhage occurs Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery. Interaction with other medicinal products affecting haemostasis Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated. The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid. Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with apixaban In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with apixaban. In a clinical trial of high-risk post acute coronary syndrome patients, characterized by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year) . Use of thrombolytic agents for the treatment of acute ischaemic stroke There is very limited experience with the use of thrombolytic agents for the treatment of acute ischaemic stroke in patients administered apixaban. Patients with prosthetic heart valves Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of apixaban is not recommended in this setting. Surgery and invasive procedures Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established. Temporary discontinuation Discontinuing anticoagulants, including apixaban, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible. Patients with active cancer Efficacy and safety of apixaban in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established. Renal impairment Limited clinical data indicate that apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15-29 mL/min) which may lead to an increased bleeding risk. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min). For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromoles/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. Elderly patients Increasing age may increase haemorrhagic risk. Also, the co-administration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk. Body weight Low body weight (< 60 kg) may increase haemorrhagic risk. Hepatic impairment Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore apixaban should be used cautiously in this population. Prior to initiating apixaban, liver function testing should be performed. Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of

both CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir). These medicinal products may increase apixaban exposure by 2-fold, or greater in the presence of additional factors that increase apixaban exposure (e.g. severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with co-administration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply:

- for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE, apixaban should be used with caution;
- for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

Laboratory parameters

Clotting tests (e.g. PT, INR, and aPTT) are affected as expected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability.

Drug Interaction (significant interaction as outlined in BNF, please see BNF and SPC for more detail)

Apixaban has the following interaction information:

Anticoagulants	increased risk of haemorrhage when apixaban given with other anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
Carbamazepine	plasma concentration of apixaban possibly reduced bycarbamazepine —manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism
Fosphenytoin	plasma concentration of apixaban possibly reduced byfosphenytoin
Ketoconazole	plasma concentration of apixaban increased byketoconazole —manufacturer of apixaban advises avoid concomitant use
Phenobarbital	plasma concentration of apixaban possibly reduced byphenobarbital
Phenytoin	plasma concentration of apixaban possibly reduced byphenytoin
Primidone	plasma concentration of apixaban possibly reduced byprimidone
Rifampicin	plasma concentration of apixaban possibly reduced byrifampicin —manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism
St John's Wort	plasma concentration of apixaban possibly reduced by St John's wort —manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism

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

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

Rationale for Choice cont……

Pre-treatment test results	Specialists please complete the information in table below: Date of test | eGFR | LFT | • Note: In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. See full SPC for prescribing information. • The patient has been informed of the need for annual (or more frequent if clinically appropriate) renal function tests in order to assess suitability for ongoing treatment. ☐ • Prior to initiating apixaban, liver function testing should be performed.

Guidance on initiation (to be completed by the specialist)

Initiation dose:	*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)* The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation). The recommended dose of apixaban for prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in Table 1 below Table 1: **Please tick as appropriate** | Dosing schedule | Maximum daily dose Treatment of DVT or PE ☐ | 10 mg twice daily for the first 7 days | 20 mg | followed by 5 mg twice daily | 10 mg Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE ☐ | 2.5 mg twice daily | 5 mg The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. **Recommendation:-** GP to add an end/review date on the directions and patients notes
Specialist recommendations	Specialist to complete
Additional info:	There is no known antidote to apixaban Tablets should be swallowed with water, with or without food. A liquid formulation is not available Apixaban ▼ is a black triangle drug. All suspected adverse effects should be reported to the CHM www.yellowcard.gov.uk
Monitoring:	Deterioration of renal function can significantly increase plasma concentration. Renal function should be assessed in all patients before starting apixaban and at least once a year or more frequently as needed in clinical situations when it is suspected that the renal function could decline or deteriorate. Liver function test

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

<table>
<tr><th colspan="2">Assessment of Efficacy</th></tr>
<tr><td>Frequency</td><td>Maximum 6 months after initiation then at least annually</td></tr>
<tr><td>Location</td><td>GP practice</td></tr>
<tr><td>Method</td><td>Renal function test
Discussion with patient regarding compliance and any factors that may affect compliance (i.e. need for monitored dose system or swallowing difficulties)
Reassess bleeding risk, including risk of falls, and use of medication associated with gastro-intestinal bleeding
Review hepatic function</td></tr>
<tr><td>Continuation Criteria</td><td>Appropriate renal & hepatic function and compliance confirmed</td></tr>
<tr><td>Review</td><td>At least annually.</td></tr>
<tr><td>Discontinuation Criteria</td><td>• Renal function – CrCl < 15 mL/min – discontinue.
• CrCl 15-29 mL/min – seek specialist advice.
• Recommended course completed.
• Poor compliance
• Unacceptable bleeding risk
• Severe hepatic impairment
• Use with interacting medication</td></tr>
<tr><td>Follow up action</td><td>Specialist to complete</td></tr>
<tr><td>Shared Care read code</td><td>In the patients notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement/RICaD

<table>
<tr><th>GP Prescribing System</th><th>Read Code</th><th>Description</th></tr>
<tr><td>EMIS and Vision</td><td>8BM5.00</td><td>Shared care prescribing</td></tr>
<tr><td>SystmOne</td><td>XaB58</td><td>Shared care</td></tr>
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