NHS
South London
Cardiovascular and Stroke Network

Guidance on the use of apixaban for stroke prevention in atrial fibrillation (AF)

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.

Apixaban is a novel oral anticoagulant recently licensed for use for stroke prevention in atrial fibrillation (SPAF). NICE has approved the use of apixaban as an option for SPAF, in patients with additional stroke risk factors.

In south London, apixaban should be considered, in line with its licensed indications, as an alternative to warfarin for SPAF in patients with $CHADS_2 \geq 1$ who:

- **have a warfarin allergy, warfarin specific-contraindication or are unable to tolerate warfarin therapy due to severe adverse effects[1]**
- **are unable to comply with the specific monitoring requirements of warfarin[2]**
- **are unable to achieve a satisfactory INR after an adequate trial of warfarin (usually at least 3 months) despite compliance with drug therapy. Patients at particular risk are those that remain sub-therapeutic (INR persistently <2), those where the INR regularly fluctuates above 4 and those requiring dosages at the extreme ends of the dose range.**

Patients currently stable on warfarin therapy should not usually be considered for a switch to apixaban.

Initiation of apixaban should only be undertaken by clinicians with expertise in initiating anticoagulant therapy for SPAF.

The initiating clinician is responsible for ensuring patient follow up and providing medicine supplies 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 patients own GP

Following the initial 3 month period, patients may be considered for transfer back to the patient's own GP, provided the patient meets the criteria for use of apixaban (as above), the GP agrees to take over prescribing responsibility and SLCSN transfer of care guidance is followed. If apixaban is prescribed for patients / indications that do not meet the criteria above, prescribing responsibility will remain with the initiating clinician / organisation.

Contraindications	Cautions
• Hypersensitivity to the active substance or to any of the excipients • Clinically significant active bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms, recent brain or spinal injury or surgery recent 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 (see overleaf for more information) • Patients with severe renal impairment (CrCL< 15ml/min / eGFR<15ml/min; CKD stage 5) • Contains lactose therefore avoid in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. • Pregnancy and breast feeding	• As there is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, apixaban is not recommended in these patients • Limited clinical data in patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that apixaban plasma concentrations are increased in this patient population, therefore, apixaban alone or in combination with aspirin is to be used with caution in these patients because of a potentially higher bleeding risk • Use cautiously in patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN • Use not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (see overleaf for more information) • Use cautiously with strong CYP3A4 and P-gp inducers (see overleaf for more information) • Concomitant use of apixaban with antiplatelet agents, NSAIDs or aspirin increases the risk of bleeding. This risk is greater in the elderly or those with moderate to severe renal impairment (CKD 4)

Dosing and initiation

The recommended dose of apixaban is 5mg twice daily to be taken with water, with or after food.

- Check liver function prior to administration (see contraindications and cautions above)
- The apixaban dose should be reduced to 2.5mg twice daily in patients with at least two of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥130micromol/L. The dose should also be reduced to 2.5mg twice daily in patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min, eGFR <30ml/min; CKD stage 4).
- For patients at risk of ulcerative gastrointestinal (GI) disease, the co-prescription of a low cost PPI may be considered to reduce the risk of GI bleed.
- Once initiated, apixaban therapy should be continued long term.

[1] Such as intolerable rash, significant alopecia, skin necrosis

[2] Inability to comply with warfarin monitoring may be due to lack of understanding of the monitoring process or inability to access any local monitoring service (this should be discussed with the patient's own GP, before a NOAC is initiated).

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

Bleeding occurs commonly during treatment with apixaban, patients should be monitored for signs of bleeding or anaemia. The overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study, with major bleeding rates reported overall as 2.13% per annum, including 0.33% intracranial bleeding and 0.76% GI bleeding. 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 adverse reactions for apixaban were epistaxis, contusion, haematuria, haematoma, eye haemorrhage and gastrointestinal haemorrhage.

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
NSAIDs or aspirin	Use with caution - will increase risk of bleeding
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).	Concomitant use not recommended - may increase apixaban exposure especially in the presence of additional factors that increase apixaban exposure (e.g. severe renal impairment, CKD stage 4)
Strong CYP3A4 and P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)	Use with caution – in clinical trials 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.
Thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g. clopidogrel, prasugrel), ticagrelor, dipyridamole, dextran and sulfinpyrazone.	Agents associated with serious bleeding are not recommended for concomitant use with apixaban, except with specialist advice

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate apixaban, in line with SLCSN position statement • To supply apixaban for the first 3 months of treatment • To provide counselling to improve adherence and deal with any early adverse effects • To ensure the patients GP and current anticoagulant service is informed about the cessation of warfarin therapy (if previously treated with warfarin) • To seek agreement from the patient's own GP at 3 months to take over prescribing of apixaban. Ensure GPs are given sufficient information and time to consider and respond to the request (at least two weeks) • To transfer care to the GP in line with SLCSN transfer of care guidance	• To ensure use of apixaban is line with the SLCSN position statement • To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation and in line with the transfer of care guidance) • To emphasise the importance of adherence to apixaban therapy and address any patient concerns • To ensure renal monitoring is undertaken at least annually throughout therapy and review treatment in line with contra-indications and cautions should renal function decline (see overleaf). 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
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 A & E for supportive measures
3. Other healthcare professionals should be made aware that apixaban is prescribed for any patients undergoing invasive treatments, including elective surgery and dental treatment
4. If a dose is missed the patient should take apixaban immediately and continue with twice daily dosing as before. 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[3].

References

- NICE TA275 Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation with one or more risk factor for stroke or systemic embolism. February 2013. Accessed 1st March 2013 at: http://guidance.nice.org.uk/TA275
- SPC Eliquis. BMS/Pfizer. 12 February 2013. Accessed 1st March 2013 at http://www.medicines.org.uk/emc/medicine/24988
- Granger CB, Alexander JH, McMurray JJV et al. 2011. Apixaban versus warfarin in Patients with Atrial fibrillation. N Engl J Med 2011;365:981-92 accessed 1st March 2013 at http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039

[3] **Please note BMS/Pfizer are unable to recommend apixaban is included in a MCA as stability has not been analysed by the company**