Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS043
Apixaban (Eliquis®) for Stroke prevention in Atrial Fibrillation	August 2018

VERDICT

Apixaban, within its licensed indications and in line with NICE TA275 is recommended as an option for the prevention of stroke in non-valvular AF and should be initiated by a specialist, tailored to the clinical situation of the patient. Follow on prescribers should receive a checklist from the initiating specialist indicating that the patient is suitable for apixaban therapy and has received appropriate guidance form the specialist. If the checklist is not made available, follow on prescribing in primary care should not commence until the specialist has been contacted and a checklist obtained.

For Primary Care Prescribers: The committee recognises the beneficial effect of anticoagulant therapy once a diagnosis of AF has been made in primary care. In this instance, apixaban may be initiated by a primary care prescriber where they have attended a suitable training course and can demonstrate expertise in managing anticoagulant therapy. The committee also advise that the specialist initiated drug checklist is also completed by the primary care prescriber.

Specialist Drugs Status: Specialist Advised (SA)

SUMMARY NOTES[1]

Indication: Prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation (NVAF) , with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)

Pharmacological action: Apixaban is a potent, oral, direct and highly selective active site inhibitor of factor Xa. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

Presentation: Eliquis® 2.5 mg and 5 mg film coated tablets

Dose: 5 mg twice daily; 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 micromole/l). Therapy should be continued long term.

Cost comparison - cost per 28 days (updated August 2018)[2]:

Dabigatran	150 mg bd	£47.60	Warfarin 5 mg daily £0.61 (variable depending on INR; costs range widely)
Rivaroxaban	20 mg od	£50.40	
Apixaban	5 mg bd	£53.20	
Edoxaban	30 – 60 mg od	£49.00	

DRUG PROFILE

Clinical effectiveness[3] ARISTOTLE[4], a double blind, double dummy phase lll trial randomised 18,201 patients with AF (plus one other risk factor for stroke) to receive apixaban 5 mg bd or dose adjusted warfarin with a target INR of 2.0 to 3.0. A dose of 2.5 mg BD was given to patients older than 80 years, weight <60kg or serum creatinine ≥132 micromole/dl. The primary objective was to test for non-inferiority of apixaban for prevention of the composite endpoint of stroke and systemic embolism. Median follow up was 1.8 years. Apixaban was found to be non-inferior to warfarin for the prevention of stroke and systemic embolism in the intention-to-treat (ITT) population. The primary outcome occurred in 212 patients in the apixaban group compared to 265 with warfarin (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.66 to 0.95, p<0.001 for non-inferiority and p=0.01 for superiority). NNT to prevent one stroke or embolism was 304. AVERROES compared apixaban to aspirin in 5599 patients for whom Vitamin K antagonists were unsuitable. Apixaban was superior to aspirin for the prevention of composite outcomes of stroke or systemic embolism, with 51 events recorded (1.6% per year) compared to 113 (3.7% per year) with aspirin (HR 0.45, 95% CI 0.32 to 0.62, p<0.001). The NNT was 48.

Safety[3,4] The primary safety outcome in both trials was major bleeding. In ARISTOTLE major bleeding occurred in 327 patients (2.13% per year) with apixaban and 462 (3.09% per year) with warfarin (HR 0.69, 95% CI 0.60 to 0.80, p<0.001, NNT 105). The difference was more marked in patients with reduced creatinine clearance. Rates of intracranial haemorrhage (0.33% vs. 0.80%, p<0.001, NNT 213) and all bleeding (18.1% vs. 25.8%, p<0.001, NNT 13) were also lower with apixaban. There was no difference in the frequency of gastrointestinal bleeding between groups (0.76% vs. 0.86% per year, p=0.37). The rates of adverse events (81.5% vs. 83.1%) and serious adverse events (35.0% vs. 36.5%) were similar in the apixaban and warfarin groups. Apixaban was associated with a lower risk of death from any cause than warfarin, although the statistical significance of this result was borderline (3.52% vs. 3.94%, HR 0.89, 95% CI 0.80 to 0.998, p=0.047, NNT 239).

DRUG PROFILE cont'd

Adverse effects[1] Common adverse reactions for apixaban were epistaxis (nosebleed), contusion (bruising), haematuria, haematoma, eye haemorrhage and gastrointestinal haemorrhage.

Renal impairment[1] No dosage adjustment is necessary in mild or moderate renal impairment. Patients with exclusive criteria of severe renal impairment (calculated creatinine clearance using Cockcroft-Gault Equation = 15-29ml/min), should receive the lower dose of apixaban 2.5 mg twice daily.

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. Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/l) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily.

Hepatic impairment [1] 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) **Elderly**[1] The co-administration of apixaban with aspirin in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Cautions/Contra-indications[1] 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 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 the circumstances of switching therapy to or from apixaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

CURRENT PLACE IN THERAPY

National Institute for Health and Care Excellence (NICE)[5]
Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure.

The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of INR control.

Scottish Medicines Consortium (SMC)[6]
Accepted for use for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥II).

Apixaban was superior to standard oral anticoagulation at preventing stroke or systemic embolism in one large, double-blind study in patients with atrial fibrillation and at least one risk factor for stroke. It was also associated with a significant reduction in risk of major bleeding.

Midlands Therapeutics Review and Advisory Committee (MTRAC): No current verdict.

Summary - In clinical trials apixaban was found to be both non-inferior (primary endpoint) and superior (key secondary endpoint) to warfarin and superior to aspirin, and was associated with fewer major bleeds than warfarin. Apixaban does not require routine coagulation monitoring, and there is no available antidote. It will compete with the other new oral anticoagulants and is priced accordingly.
There are no data available directly comparing apixaban, dabigatran or rivaroxaban.

References

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2. Drug Tariff August 2018 Available from: http://www.drugtariff.nhsbsa.nhs.uk/#/00616707-DB/DB00616702/Home
3. UKMI NYRDTC NDE No.117 October 2012. Apixaban in atrial fibrillation. Available from http://rdtc.nhs.uk/sites/default/files/publications/nde_122_apixaban.pdf <Accessed 22.08.18>
4. Apixaban versus Warfarin in Patients with Atrial Fibrillation. Granger CB et al. N Engl J Med 2011; 365:981-92. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039 <Accessed 22.08.18>
5. National Institute for Health and Clinical Excellence. TA 275. Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation Feb 2013. Available from https://www.nice.org.uk/guidance/TA275/chapter/1-Guidance <Accessed 22.08.18>
6. Scottish Medicines Consortium. SMC ID 836/13 Available from : http://www.scottishmedicines.org.uk/SMC_Advice/Advice/836_13_apixiban_Eliquis/apixaban_Eliquis <Accessed 22.08.18>