South East London Integrated Medicines Optimisation Committee
Formulary recommendation

Reference	**133**
Intervention:	**Apixaban (Eliquis™) 2.5mg tablets as a second line option where vitamin K antagonist (VKA) therapy is inappropriate in adults undergoing haemodialysis for:** **(i) the prevention of recurrent venous thromboembolism (VTE) or** **(ii) the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF)** (Apixaban is an anticoagulant)
Date of Decision	**June 2022. Updated August 2023 following report on outcome data**
Date of Issue:	**July 2022. Reissued September 2023**
Recommendation:	**Red – suitable for prescribing, supply and administration by the hospital only**
Further Information	• Apixaban (Eliquis™) 2.5mg tablets is accepted for use in SEL in adults undergoing haemodialysis in the following settings: i. the prevention of recurrent VTE **or** ii. the prevention of stroke or systemic embolism (SSE) in adults with AF with one or more risk factor such as prior stroke or transient ischemic attack (TIA), age ≥ 75 years, hypertension, diabetes mellitus and symptomatic heart failure (NYHA Class ≥ II) • Use of apixaban is approved only as a **second line** option, where VKA therapy (e.g. warfarin) is considered inappropriate by a consultant nephrologist or a consultant haematologist. • The following criteria will also apply to the use of apixaban 2.5mg tablets in these settings: - Patients poorly controlled on a VKA as defined by NICE guidance on AF: ▪ Time in therapeutic range (TTR) less than 65% over a 6-month period, excluding the first 6-weeks of VKA therapy ▪ One international normalised ratio (INR) greater than 8 or two INRs greater than 5 in a 6-month period ▪ Two INRs less than 1.5 in a 6-month period - Patients unable to adhere to regular INR monitoring - Patients unable to safely administer warfarin and manage variable dosing, including those requiring multi-compartment aids (MCAs) such as dosette boxes • VKA therapy is not felt to be appropriate due to the high risk of calciphylaxis following a review by Consultant Nephrologist or Consultant Haematologist. The multiple risk factors for calciphylaxis include - female gender, history of diabetes mellitus, greater than 5 years of dialysis, body mass index greater than 35 (i.e. obese) or poor mineral bone control (indicated by increased calcium, phosphate or parathyroid hormone levels) • The use of apixaban in this setting is **off-label** and the recommended dose is **2.5mg twice daily**, informed consent should be gained from the patient before treatment is started**.** Full blood count (FBC) and post-dialysis apixaban anti-Xa level should be monitored every 3-months. Liver function tests (LFTs) should be monitored annually unless more frequent monitoring is indicated. • Patients should be counselled on the appropriate administration, interactions, management of missed doses and monitoring requirements as described in the product information. • **August 2023:** A report summarising outcomes with the use of apixaban in this setting was requested by the Committee after 12 months outlining the total number of patients initiated on treatment by indication, outcomes and safety data. The total number of patients initiated on apixaban in this setting was lower than expected but similar proportions were seen between AF and VTE. The outcomes data presented indicated a small proportion of patients had to switch back to VKA therapy. Whilst there were no significant major bleeding episodes, some patients did experience non-major bleeding however apixaban continued in all cases. Given the small patient numbers, the applicant has confirmed use of apixaban in this setting should remain as hospital only.

Shared Care/ Transfer of care required:	N/A
Cost Impact for agreed patient group	• It is estimated there will be approximately 50 patients across SEL per annum eligible for treatment with apixaban in this setting: - Prevention of recurrent VTE: 25 patients - Prevention of SSE: 25 patients • The total drug costs anticipated for SEL is approximately £34,200 per annum for 50 patients (~ £1,800 per 100,000 population). • A report provided in August 2023 found the actual patient number treated to be lower than expected. Over the course of 2 and a half years (which included use through non-formulary processes pre-formulary approval), 34 patients were treated. This equates to ~ 14 patients per year and not all patients are from SEL.
Usage Monitoring & Impact Assessment	**Acute Trusts:** • Monitor and audit usage of apixaban as outlined in the "For information" section and report back upon request to the Committee.
	SEL Borough Medicines Teams: • Monitor exception reports from GPs if inappropriate prescribing requests are made to primary care.
Evidence reviewed	**References (from evidence review)** 1. Hu A, Niu J, Winkelmayer W. Oral anticoagulation in patients with end-stage kidney disease on dialysis and atrial fibrillation. Seminars in Nephrology 2018 38 (6) p618-628. 2. Devabhaktuni S, Mounsey P. Should oral anticoagulation be used in ESKD patients on hemodialysis with atrial fibrillation? PRO. Kidney 360 2021 2 p1405-1408. 3. NG196 Atrial fibrillation. National Institute for Health and Care Excellence 2021. 4. Lu H, Liao K. Increased risk of deep vein thrombosis in end-stage renal disease patients. BMC Nephrology 2018 (19:204). [online] Available here 5. D, Rabbat C, Clase C. Thromboembolism and anticoagulant management in hemodialysis patients: a practical guide to clinical management. Thrombosis research 2006 118 (3) p385-95. 6. Equilis – FDA label. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202155s032lbl.pdf (accessed 25/05/2022). 7. Chan K, Edelam E, Wenger J et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 2015 131 p972-979. 8. Wang X, Tirucherai G, Marbury T et al. Pharmacokinetics, pharmacodynamics and safety of apixaban in subjects with end-stage renal disease on hemodialysis. The Journal of Clinical Pharmacology 2016 56 (5) p628-636. 9. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation - RENAL-AF. Available online at: https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/29/renal-af (accessed 23/05/2022). 10. Kuno T, Takagi H, Ando T et al. Oral anticoagulation for patients with atrial fibrillation on long term dialysis. Journal of the American College of Cardiology 2020 75 (3) p273-285. 11. Murtaza G, Turagam M, Garg J et al. Safety and Efficacy of Apixaban versus Warfarin in patients with atrial fibrillation or Venous Thromboembolism and End-Stage renal disease on hemodialysis: a systematic review and meta-analysis. Indian Pacing and Electrophysiology Journal 2021 21 p221-226. 12. Siontis K, Zhang X, Eckard A et al. Outcomes Association with apixaban use in end stage kidney disease patients with atrial fibrillation in the United States. Circulation 2018 183 (15) 1519-1529. 13. Wetmore J, Herzog C, Yan H et al. Apixaban versus warfarin for treatment of venous thromboembolism in patients receiving long-term dialysis. Clinical Journal of the American Society of Nephrology 2022 17 p693-702. 14. Reed D, Palkimas S, Hockman R et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. Research Practice in Haemostasis 2018 p291-298. 15. Sarratt S, Nesbit R, Moye R et al. Safety outcomes of apixaban compared with warfarin in patients with end stage renal disease. Annals of Pharmacotherapy 2017 51 (6) p445-450. 16. Schafer J, Casey A, Dupre K et al. Safety and Efficacy of Apixaban versus warfarin in patients with advanced chronic kidney disease. Annals of Pharmacotherapy 2018 52 (11) p1078-1084. 17. Mavrakanas T, Garlo K, Charytan D et al. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clinical Journal of the American Society of Nephrology 2020 15 p1146-1154. 18. Strategies for the Management of Atrial Fibrillation in patients Receiving Dialysis (SAFE-D). NCT03987711. Available online at: https://clinicaltrials.gov/ct2/show/NCT03987711 (accessed 03/06/2022). 19. Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (AXADIA). NCT02933697. [online] Available here. 20. Eliquis (apixaban). Summary of product characteristics. [online] Available here.

NOTES:

a) SEL IMOC recommendations and minutes are available publicly via the website.

b) This SEL IMOC recommendation has been made on the cost effectiveness, patient outcome and safety data available at the time. The recommendation will be subject to review if new data becomes available, costs are higher than expected or new NICE guidelines or technology appraisals are issued.

c) Not to be used for commercial or marketing purposes. Strictly for use within the NHS.