APIXABAN IS A HIGH RISK MEDICINE **USE WITH CAUTION AND ENSURE THE DIRECTIONS WITHIN THIS PROTOCOL ARE FOLLOWED CAREFULLY**	
Areas where applicable	SESLHD Hospitals
Areas where not applicable	None
Authorised Prescribers:	Medical Officers and Nurse Practitioners Apixaban may only be commenced on the advice of a Senior Medical Officer
Indications for use	• Prevention of venous thromboembolism (VTE) after total knee replacement (TKR) or total hip replacement (THR) surgery. • Prevention of stroke or systemic embolism in non-valvular atrial fibrillation in patients with at least one of the following risk factors: *Age ≥ 75 years, Hypertension, Diabetes Mellitis, Heart failure or left ventricular dysfunction (left ventricular ejection fraction < 35%), previous stroke, transient ischaemic attack or systemic embolism.* • Acute and extended treatment of VTE, and prevention of recurrent VTE. **NOTE: All other indications are NON-FORMULARY at SESLHD. Patients should not be newly commenced on apixaban for other indications without prior approval from the local Drug and Therapeutics Committee**
Patient Selection	Before initiating apixaban undertake clinical evaluation of the patient to ensure it is a suitable and safe therapy: • Ensure no contraindications, drug interactions or significant cautionary factors are present. • Discuss treatment options and confirm patient agreement with choice of therapy. • Consider patient's capacity to manage the medication safely, e.g. compliance with prescribed dosing frequency. • Note: apixaban is suitable for packaging into a dose administration aid (e.g. Webster Pak or Dosette box) if required. • Perform the following: a. Full Blood Count to exclude significant thrombocytopenia or anaemia b. Biochemical Profile including liver function and renal function assessment. Creatinine clearance should be calculated using the Cockcroft Gault equation (requires patient gender, age, ideal body weight and serum creatinine). eGFR should NOT be used for this purpose. c. Coagulation profile (PT/APTT) to exclude underlying defect in haemostasis.

Important Safety Considerations	**<u>Duplication of anticoagulants</u>** Errors involving duplication of anticoagulant therapy are common. Before prescribing or administering apixaban, clinicians must ensure that the patient is not currently prescribed any other anticoagulant medications. In eMEDs, an alert is triggered if there is an attempt to order a second anticoagulant drug when one is already prescribed in the system. Prescribers must be aware of the limitations of electronic alerts and always be vigilant to the presence of other anticoagulants, including those that may be prescribed on the IV fluid chart. Alerts may not be triggered in other electronic medication management systems. Prescribers should annotate all orders for apixaban with the word "ANTICOAGULANT" and always include the indication for prescribing.
Contraindications	• **Significant active bleeding and organ lesions at risk of bleeding** (e.g. 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) • **Mechanical heart valves** • **Indwelling spinal or epidural catheter and during the first 6 hours after removal** • **Renal impairment:** calculated CrCl < 25 mL/min • **Congenital or acquired coagulation disorder or platelet disorder** (thrombocytopenia, platelets <100 x 10^9/L or functional platelet defects) • **Hepatic disease**: Child-Pugh B or C with coagulopathy (caution: Child Pugh A or B without coagulopathy) • **Pregnancy or breast feeding:** in women of child bearing age a pregnancy test should be performed • **Infective endocarditis** (where the risk of rupture/haemorrhage has not yet been surgically managed) • **Concomitant treatment with any other anticoagulant agent** (except under the circumstances of switching therapy to or from apixaban or when heparin is given at doses necessary to maintain a patent central venous or arterial catheter) • **Concomitant treatment with strong inhibitors of both CYP3A4 and P-gp** (such as azole antifungals or HIV protease inhibitors)

Precautions

- **Increased bleeding risk**: carefully assess risk vs benefit and consider use of alternative anticoagulant
  - History of intracranial haemorrhage, spinal, retroperitoneal or atraumatic intra-articular bleeding
  - History of retinal bleeding, vascular proliferative retinopathy or eye surgery
  - History of bronchiectasis or pulmonary haemorrhage
  - Recent malignancy or irradiation
  - Uncontrolled hypertension i.e. systolic BP >180mmHg or diastolic BP > 110mmHg
  - Thrombocytopenia (platelets < 100 $x10^9$/L - discuss with haematology)
  - Age >75 years and the presence of other risk factors for bleeding (including drug interactions)
  - Weight < 50 kg (dose adjustment may be required)
- **Malignancy:** Low molecular weight heparin is the current preferred treatment for VTE related to active malignancy
- **Antiphospholipid syndrome related VTE:** inadequate data in this group of patients. Warfarin remains the standard of care.
- **Poor compliance:** missing apixaban doses results in inadequate and inconsistent anticoagulation due to the short half-life; consider use of warfarin
- **Upper limb thrombosis or unusual site thrombosis** such as cerebral vein thrombosis, portal and splenic vein thrombosis (NOACS have not been studied in these groups)
- **Drug interactions:** see below

Always consult the haematology team if unsure of the appropriateness of apixaban

Important Drug Interactions

Drug-drug interactions

Class or medicine *(Not an exhaustive list*)*	Advice	Effect on rivaroxaban or apixaban activity	Comment
Anticonvulsants: phenytoin carbamazepine, phenobarbitone	Caution	Reduced activity	
Azole antifungals e.g. itraconazole voriconazole, posaconazole	Contraindicated	Increased activity	Potent CYP3A4 and P-gp inhibitors
HIV protease inhibitors e.g. ritonavir	Contraindicated	Increased activity	Potent CYP3A4 and P-gp inhibitors
Macrolides e.g. clarithromycin, azithromycin	Caution	Increased activity	
Rifampicin	Caution	Reduced activity	
St John's Wort	Caution	Reduced activity	
Verapamil	Uncertain	Increase in activity	Clinical significance uncertain

* SSRI and SNRI are not listed in the Product Information; however concurrent use may theoretically increase risk of bleeding (Recommendation based on expert opinion of the Anticoagulant Medicines Working Party)

Antithrombotic interactions: the appropriateness of the combination of apixaban and antiplatelet drugs should be confirmed with a senior medical officer.

<table>
<tr><td></td><td colspan="2">
<table>
<tr><th>Action</th><th>Example
(Not an exhaustive list)</th><th>Advice</th><th>Effect on bleeding rates</th><th>Comment</th></tr>
<tr><td rowspan="3">Antiplatelet</td><td>NSAIDS
Aspirin
Clopidogrel
Prasugrel
Dipyridamole</td><td>Caution</td><td>Increased bleeding rates seen in studies</td><td>Similar to antiplatelets/ warfarin combinations</td></tr>
<tr><td>Ticagrelor</td><td>Apixaban: Caution
Rivaroxaban: Caution
Dabigatran: Relative contraindication</td><td>Increased risk of bleeding</td><td></td></tr>
<tr><td>Dual-antiplatelets</td><td>Relative contraindication</td><td>Increased risk of bleeding</td><td>Seek specialist advice</td></tr>
<tr><td>Anticoagulant</td><td>Warfarin, heparin, Low Molecular Weight Heparin (LMWH)</td><td>Contraindicated (unless transitioning between anticoagulants)</td><td>Increased</td><td></td></tr>
</table>
</td></tr>
<tr><td rowspan="6">Dosage</td><td>Indication</td><td>Recommended Dose

NOTE: Apixaban is contraindicated if CrCl < 25mL/min</td></tr>
<tr><td>Prevention of VTE in patients having total knee replacement</td><td>2.5mg TWICE daily, starting 12 to 24 hours after surgery

Recommended duration of therapy is 10-14 days.</td></tr>
<tr><td>Prevention of VTE in patients having hip replacement surgery</td><td>2.5mg TWICE daily, starting 12 to 24 hours after surgery

Recommended duration of therapy is 32-38 days</td></tr>
<tr><td>Prevention of stroke and systemic embolism in Non-valvular Atrial Fibrillation with at least 1 additional risk factor (see above)</td><td>5mg TWICE daily

A reduced dose of 2.5mg TWICE daily is recommended in patients with two of the following three characteristics
- Age ≥ 80 years
- Weight ≤ 60kg
- Serum creatinine ≥ 133micromol/L</td></tr>
<tr><td>Acute treatment of DVT and PE</td><td>10 mg TWICE daily for 7 days then REDUCE to 5 mg TWICE daily.

Continue for a minimum of 3 months (and up to 12 months)</td></tr>
<tr><td>Prevention of recurrent DVT and PE
or
Extended treatment of DVT and PE</td><td>2.5 mg TWICE daily after at least 6 months of therapeutic treatment for DVT or PE</td></tr>
<tr><td>Transitioning between anticoagulants</td><td colspan="2">Detailed advice regarding transitioning between apixaban and other anticoagulants is available in the CEC NOAC Guidelines.

The process of transitioning between anticoagulants should be done under the close guidance of a Senior Medical Officer.</td></tr>
</table>

Prescription Requirements	All medication orders for apixaban must include: - Drug, dose, route and indication - the intended duration of therapy when prescribed for treatment or prevention of VTE - the word “ANTICOAGULANT” printed clearly
Administration Instructions	Apixaban is administered orally, twice daily (with or without food) Apixaban is available in 2.5mg and 5mg tablets. Take care to avoid missed doses. The missed dose should be taken as soon as possible on the same day, then twice day dosing resumed. Do not double dose to compensate for missed doses.

Monitoring Requirements	**Routine monitoring** Patients should be monitored for signs of bleeding and educated on how to self-monitor (see 'Patient Education' section). If a patient on apixaban experiences a fall, observe and monitor closely for signs of bleeding in accordance with SESLHDPR/380 Falls prevention and management for people admitted to acute and sub-acute care. In patients with normal renal function, renal function should be checked at least annually, and more often if the patient's clinical circumstances change. In patients with impaired renal function, with risk factors for bleeding or taking interacting medications, more regular monitoring is required. Even a small decline in renal function can result in a significantly increased risk of bleeding in these patients. **Investigations for bleeding** • Routine coagulation tests cannot be used to assess the degree of anticoagulation. • Apixaban levels can be assessed using a specific anti-Xa assay • Drug levels may be useful to assist in determining if there has been an overdose or if therapeutic anticoagulation is contributing to bleeding. • Drug assays may be requested on the pathology request form. One citrate blue top tube should be collected; noting that the patient is on apixaban, their current dose and the time of last dose. • Results should be interpreted in consultation with the haematology team. Note: There is no role for routine monitoring of drug levels or anticoagulant effect. Doses should NOT be adjusted in response to laboratory tests.
Management of Complications	**Management of bleeding** Refer to flowchart in Appendix A Note: No effective reversal agent for apixaban is available in Australia at the current time. Due to high plasma protein binding apixaban is not dialyzable.
Storage requirements	Apixaban must not be stored in clinical areas where use is infrequent and any dispensed products that are no longer required should be removed from these areas at the earliest opportunity. In areas where apixaban is stored outside of pharmacy, shelf labelling should be used to identify it as an anticoagulant medicine.

Peri-procedural management of anticoagulation

Routine Surgery

The bleeding risk of surgery, timing of the last dose and half-life of the drug adjusted for renal function will determine duration of treatment cessation before surgery.

It is recommended that the following laboratory results are reviewed preoperatively:

- CrCl (calculated using the Cockcroft-Gault equation)
- FBC
- LFT

For urgent or high bleeding risk elective surgery the following laboratory results should **also** be reviewed:

- PT, TT, APTT
- Consider Anti-Xa level in consultation with haematology team.

Specialist advice should be sought regarding when apixaban should be stopped prior to surgery. The following table is a guide:

Apixaban (Eliquis®) (2.5 mg or 5 mg twice a day)	Low bleeding risk surgery	High bleeding risk surgery
Normal/ mildly impaired renal function (CrCl >50 mL/min)	Last dose 24 hours before surgery	Last dose 48–72 hours before surgery
Moderately impaired renal function (CrCl 30-50 mL/min)	Last dose 48 hours before surgery	Last dose 72 hours before surgery
CrCl <30 mL/min	Seek specialist advice	

Urgent/Unplanned Surgery

- No agent can reverse apixaban. Consider delaying surgery until coagulation screen normal or sufficient time has passed for drug clearance. Consult with Haematology for urgent lifesaving surgery.
- If surgery must proceed, check apixaban Anti-Xa level, PT, APTT and fibrinogen. Also check EUC, calcium and perform a Group and Hold.
- If PT prolonged or Anti-Xa level significant and surgery cannot be delayed, consider use of Prothrombinex VF 50 international units/kg. Continue supportive measures such as maintenance of BP and urine output to optimise drug clearance and consider transfusion support for the management of bleeding.
- Epidural and spinal anaesthesia are contraindicated

Post-Procedure

ALWAYS LIASE WITH THE PROCEDURAL TEAM REGARDING SATISFACTION WITH HAEMOSTASIS PRIOR TO ANY ANTICOAGULATION COMMENCEMENT

General principles:

- For low bleeding risk procedures, consider restarting therapeutic anticoagulation 24 hours post operatively

	• For high bleeding risk procedures, consider restarting therapeutic anticoagulation 48 – 72 hours post operatively • In high-risk patients, consider prophylactic anticoagulation with enoxaparin or heparin, starting the evening following the procedure until therapeutic anticoagulation can be commenced. • If ongoing concerns for bleeding persist following high-risk procedures, consider restarting therapeutic anticoagulation initially with unfractionated heparin and converting to apixaban once stable.
Neuraxial anaesthesia in patients on apixaban	Neuraxial anaesthesia is contraindicated in patients who are therapeutically anticoagulated. Neuraxial anaesthesia cannot be performed until laboratory testing establishes the absence of apixaban effect. There is limited data on the safety of prophylactic doses of NOACs whilst a patient has an epidural catheter in situ. Use of apixaban for VTE prophylaxis is not recommended for patients who have an epidural catheter in situ. For patients with normal renal function receiving apixaban for VTE prophylaxis who require neuraxial anaesthesia: 1. The last dose of apixaban should be given 24 hours before planned insertion or removal of the epidural catheter 2. The first recommencement dose of apixaban should be given no earlier than 6 hours after catheter removal (longer of there are multiple punctures or traumatic insertion - seek haematology advice) 3. Apixaban is not recommended in patients undergoing anaesthesia with postoperative indwelling catheters Monitor carefully for symptoms and signs of neurological impairment due to an increased risk of epidural or spinal haematoma in patients receiving apixaban.
Pharmacist review	During business hours, pharmacists should prioritise patients prescribed apixaban for clinical review and provision of education. Within each SESLHD facility, mechanisms should be in place to assist pharmacists with identification of these patients. When clinically reviewing an order for apixaban, the pharmacist is responsible for ensuring the appropriateness of the drug, formulation, dose, route and frequency in the context of the individual patient's parameters. The pharmacist should also ensure that all prescribing requirements (above) have been met. Once satisfied with the order, the pharmacist should annotate the medication chart in the pharmacy section with their initials and the date. In electronic systems, the order should be electronically verified. Any interventions involving apixaban should be documented according to locally agreed process.

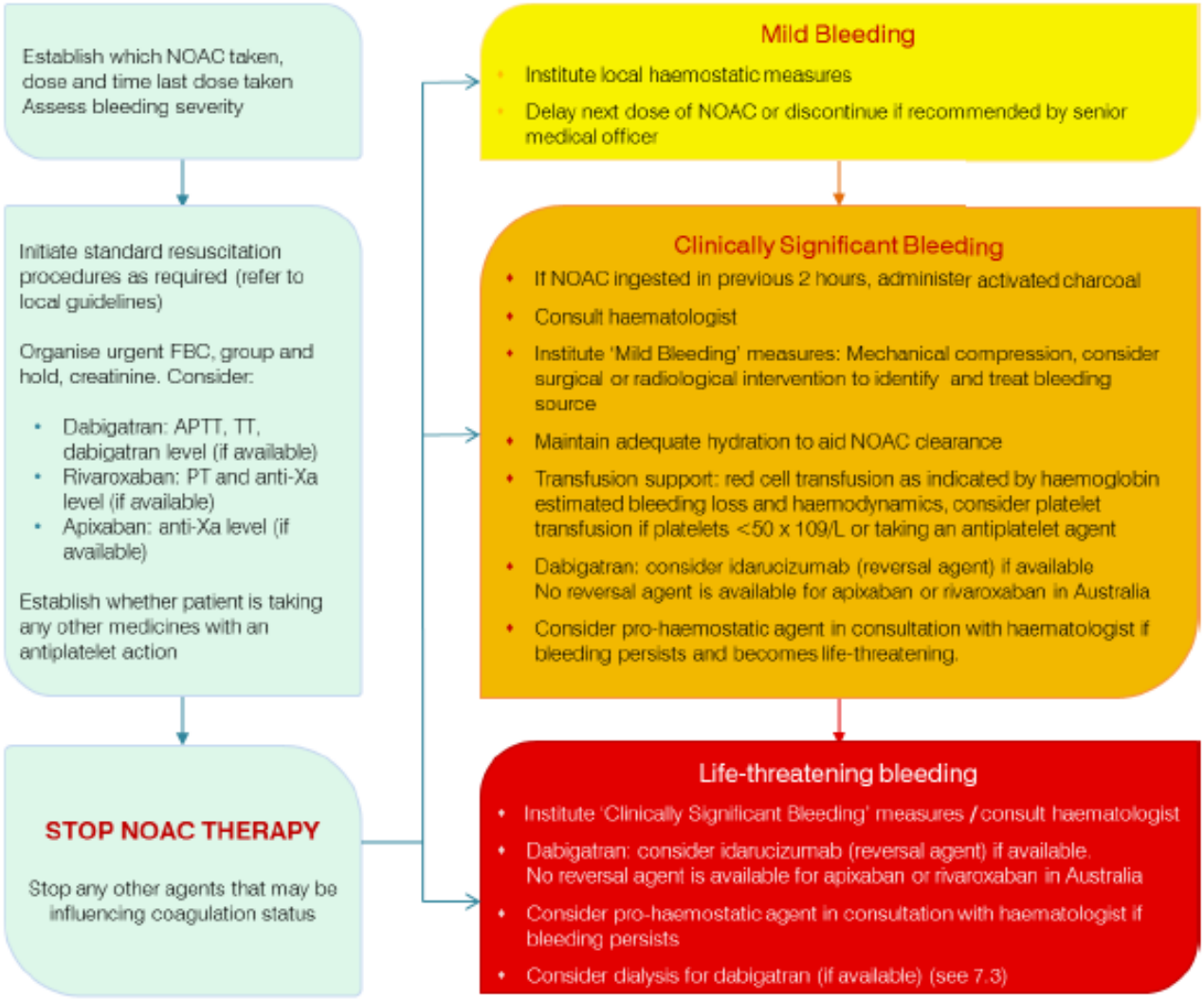
Patient Education	All patients initiated on apixaban MUST be educated regarding anticoagulation as they would be on warfarin. Patients admitted to hospital on apixaban should be assessed for their level of knowledge and receive further education as appropriate. Wherever possible, education should be provided by a clinical pharmacist. Pharmacy should be contacted as early as possible to request anticoagulant education. If a pharmacist is unavailable, the medical officer should provide written and verbal education. The patient must be provided with the specific patient booklets about apixaban (e.g. locally developed patient information booklets or CEC information leaflet)and an anticoagulation card to carry on their person (available from pharmacy) Patient education should include the following; 1. The reason the patient is being commenced on an anticoagulant 2. How to minimise risk of bleeding (lifestyle considerations, drug interactions e.g. NSAIDs), signs of bleeding and what to do in case of bleeding or a fall 3. Signs of venous thromboembolism 4. How to take apixaban and the importance of good compliance; missed doses lead to the loss of anticoagulation and the risk of thrombotic events. 5. How long to take it for. 6. Risk of bleeding with surgery or dental procedures, and the need to alert/seek advice from health practitioners if procedures are planned. 7. Need to attend GP for review, prescriptions for ongoing supply, and required renal function checks after initiation of apixaban. Provision of anticoagulant education must be documented in the patient's medical record.
Additional Resources	Guidelines on the management of Non-Vitamin K oral anticoagulants, summary information for each drug and patient information brochures are available from the CEC: https://www.cec.health.nsw.gov.au/keep-patients-safe/medication-safety/high-risk-medicines/anticoagulants
Basis of Protocol	1. Tran, H., et al., New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J, 2014 44(6): 525-36. 2. Granger, C.B., et al., Apixaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine, 2011 365(11): 981-992. 3. Agnelli, G., et al, Oral Apixaban for the treatment of Acute venous Thromboembolism New England Journal of Medicine, 2013 369(9): 799-808. 4. Agnelli, G et al. Apixaban for Extended Treatment of Venous Thromboembolism. New England Journal of Medicine, 2013 368:699-708

	5. Schulman, S et al. How I treat with anticoagulants in 2012: new and old anticoagulants and how and when to switch. Blood, 2012 119:3016-3023 6. Wood P et al. New Oral Anticoagulants: An emergency department overview. Emergency Medicine Australasia, 2013 25:503-514 7. ASTH NOAC guide: New Oral Anticoagulant – A practical guide on behalf of ASTH. Accessed 08/09/2014 at http://www.asth.org.au 8. Siegal D M et al, How I treat target – specific oral anticoagulant – associated bleeding. Blood, 2014 123:1152-1158 9. Spyropoulos A C et al. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood, 2012 120: 15: 2954-2962 10. CEC NOAC Guidelines: Non-Vitamin K Antagonist Oral Anticoagulant. Accessed 02/06/2021 at https://www.cec.health.nsw.gov.au/keep-patients-safe/medication-safety/high-risk-medicines/anticoagulants 11. Tran, H., et al. New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. Med J Aust 2019;210:227-35.
Groups consulted in development of this guideline	SESLHD NOACs Working Party.

AUTHORISATION	
Author (Name)	Dr Amanda Hugman Katie Hargreaves
Position	Haematologist Lead Pharmacist, Quality Use of Medicines
Department	Haematology, St George Hospital Clinical Governance Unit
Department Contact (for ongoing maintenance of Protocol/Guideline)	Katie.hargreaves@health.nsw.gov.au Amanda.hugman@health.nsw.gov.au

GOVERNANCE	
Enactment date: Reviewed:	July 2017 August 2021
Expiry date:	July 2023
Ratification date by SESLHD Drug and QUM Committee	5th August 2021
Chairperson, Drug and QUM Committee	Dr John Shephard
Version Number	2.0

Appendix A: Management of NOAC associated bleeding



Adapted from Tran et al (2014) with permission[α]