Management consensus statement
There are no published data regarding the treatment of patients with active bleeding while receiving apixaban, therefore advice contained within is based on expert consensus.
About Eliquis® (apixaban)

Apixaban is a direct FXa inhibitor with rapid onset of action, a 12-hour half-life and only 25% renal excretion. Apixaban is indicated in Australia for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery and for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke. The recommended dose of apixaban for VTE prophylaxis is 2.5mg BD. The recommended dose of apixaban for stroke prevention in non-valvular atrial fibrillation (NVAF) is 5mg BD (2.5mg BD if ≥2 of the following; weight ≤60 kg, age ≥80 years, serum creatinine level ≥133 μm/L).²

The risk of stroke and bleeding must be assessed for each patient before commencing any anticoagulation therapy, including apixaban. Some of the patients excluded from the trials had baseline characteristics that were associated with increased risk of bleeding (e.g. recent major bleeding, renal insufficiency [CrCl <25mL/min], severe hepatic impairment, platelet count <100), and there are no or insufficient data on the use of apixaban in such patients. The clinical trials excluded aspirin doses >165mg/day or dual anti-platelet therapy. The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding. Apixaban should be used with caution when co-administered with NSAIDs (including ASA) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel in a clinical study in patients with acute coronary syndrome.²

There is no standardised assay to measure apixaban effect. As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamics effects of apixaban.² Apixaban also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in anti-FXa chromogenic assays, but these assays are not widely available.³
Switching to Eliquis® (apixaban)

Prior to initiating apixaban, liver function and renal function testing should be performed.

**Warfarin to apixaban**

When switching anticoagulation from warfarin to apixaban, it is important to avoid using both drugs at therapeutic doses simultaneously; it is recommended that the INR is monitored daily after the cessation of warfarin, and that apixaban is not started until the INR is <2.0, typically approximately three days after cessation of therapeutic warfarin.4

**Low molecular weight heparin (LMWH) to apixaban**

As both agents have a similar rapid onset of FXa inhibition and effective half-life, switching anticoagulation from LMWH (e.g. enoxaparin) to apixaban, and vice versa, can simply be done at the time of the next scheduled dose.2

Switching from Eliquis® (apixaban)

**Apixaban to warfarin**

When converting from apixaban to warfarin, continue apixaban for 48 hours after the first dose of warfarin. After 2 days of co-administration of apixaban with warfarin, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and warfarin until the INR is ≥2.0.

**Apixaban to low molecular weight heparin (LMWH)**

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An increased risk of stroke was observed during the transition from apixaban to warfarin in clinical trials in patients with non-valvular atrial fibrillation. Discontinuation of apixaban prior to the onset of an effective antithrombotic effect of VKA could result in an increased risk of thrombosis. If anticoagulation with apixaban must be discontinued for any reason other than pathological bleeding, consider coverage with another anticoagulant.
Bleeding management in patients receiving Eliquis® (apixaban)

In the ARISTOTLE study of apixaban in patients with atrial fibrillation, annual major bleeding events for apixaban compared to warfarin were 2.13% per year versus 3.09% per year (p<0.001). Intracranial haemorrhage events were 0.33% per year for apixaban, compared to 0.80% per year for warfarin (p<0.001).

Spontaneous bleeding may occur with most anticoagulants. In the absence of published data regarding the treatment of patients with active bleeding while receiving apixaban, the following advice for general management of bleeding events is based on expert consensus.

- Establish the primary source of bleeding wherever possible, and secure haemostasis with local measures.
- Most cases of minor bleeding will resolve after cessation of drug, standard supportive treatment, including transfusion, mechanical compression and other local measures.
- A specific antidote for apixaban is not available.
- If bleeding occurs within 6 hours of last apixaban dose, activated charcoal may reduce apixaban absorption, and hence anticoagulant effect. This should also be considered soon after overdose or accidental ingestion.
- Apixaban is highly (~87%) protein bound, and hence not expected to be dialysable. Based on studies of other factor Xa inhibitors in healthy volunteers, prothrombin complex concentrates (PCC) may reverse the anticoagulant effect, however the effect on clinical bleeding is not proven.
- There is no clinical evidence examining the use of recombinant FVIIa or bypassing agents (FEIBA) in bleeding patients receiving apixaban. In animal, in vitro and healthy volunteer studies, these agents have partially reversed the anticoagulant effect of apixaban and other factor Xa inhibitors. These agents can be considered for life-threatening bleeding, but carry a proven risk of thrombosis.
- There is no evidence to support the use of fresh frozen plasma (FFP), other than for volume replacement in case of major bleeding.
**FIGURE 1:** Considerations for the management of bleeding, based on expert consensus.

**ACTIVE BLEEDING**

- Establish timing of most recent dose
- Local measures; initiate standard measures to control bleeding, including first aid and notification of appropriate specialist team
- Measure baseline coagulation parameters (PT, aPTT, fibrinogen).
  N.B. These (standard) tests are relatively insensitive to apixaban

**CLINICALLY SIGNIFICANT BLEEDING**

- Local haemostatic measures
- Consider deferring next dose of apixaban
- Consult prescribing physician before re-commencing standard dose

**MAJOR BLEEDING**

- Local haemostatic measures
- Defer next dose of apixaban
- Consider activated charcoal if last apixaban dose <6 hrs
- Volume replacement or transfusion if required
- Consider tranexamic acid for mucosal or superficial bleeding (minor bleeding: 1g oral QID OR major bleeding: 15mg/kg bolus followed by 1mg/kg/hr until bleeding is controlled)
- If bleeding is not controlled by the above, consider PCC (Prothrombinex) at a dose of 25–50 U/kg and consult haematologist
- Consult prescribing physician before re-commencing apixaban

**LIFE-THREATENING BLEEDING**

- Local haemostatic measures
- Discontinue apixaban
- Volume replacement or transfusion if required
- Consider PCC (Prothrombinex) at a dose of 25–50 U/kg and consult haematologist
- Consider tranexamic acid for mucosal or superficial bleeding (minor bleeding: 1g oral QID OR major bleeding: 15mg/kg bolus followed by 1mg/kg/hr until bleeding is controlled)
- If bleeding persists despite measures above, consider recombinant FVIIa (NovoSeven)
  N.B. Risk of thromboembolic complications

Pfizer/BMS have no recommendation on the treatment of active bleeding in patients treated with apixaban. The advice contained in this diagram is based on expert consensus in the absence of published data. This advice is not proven with respect to apixaban.
Peri-operative management in patients receiving Eliquis® (apixaban)

In stable patients, apixaban has a predictable half-life of 8–12 hours, so there will be up to 50% activity at 12 hours and less than 25% activity at 24 hours after drug cessation (see FIGURE 2). This means that apixaban can be ceased for a shorter period of time prior to invasive procedures than warfarin, without the routine need to bridge with alternative anticoagulants such as heparin.

Planning for elective surgery or invasive procedures should involve balancing the intervention-associated bleeding risk and thrombotic risk associated with anticoagulant interruption in each individual. In general apixaban should be discontinued 2 to 3 days prior to elective surgery or invasive procedures. There is a small group of people at higher risk of thrombosis (e.g. CHADS2 >5, recent TIA or stroke) where an individualised approach is needed to minimise the period of subtherapeutic anticoagulation.

**FIGURE 2:** Mean apixaban (5mg) single dose plasma concentration profile.

Adapted from Frost et al. 2013

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Advice for assessing peri-procedural dosing

**High bleeding risk**

Procedures with a high risk of bleeding (e.g. neurosurgical, urological procedures, major abdominal or orthopaedic); Aim to achieve no residual apixaban effect at the time of the procedure, last dose of drug should be 3 days prior (5 missed doses including morning of surgery – see FIGURE 3).12

**Low bleeding risk**

Procedures with a low risk of bleeding (e.g. inguinal hernia repair, percutaneous biopsy, dental extractions); Aim to achieve minimal-mild residual apixaban effect at the time of the procedure, last dose of drug should be 2 days prior (3 missed doses including morning of surgery – see FIGURE 3).12

**Minimal bleeding risk**

For selected procedures with minimal risk of bleeding (e.g. cataract surgery, skin cancer excision); therapeutic anticoagulation may be continued.

**FIGURE 3:** Peri-procedural dosing schedule.

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<tr>
<th>HIGH RISK</th>
<th>DAY -5</th>
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<th>DAY -3</th>
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Skipped doses indicated by 🍒
Re-commencing Eliquis® (apixaban) after surgery

Re-commence apixaban dosing only once surgical haemostasis has been secured (typically 24 hours after surgery). In general, caution should be exercised with re-instituting therapeutic anticoagulation within the first 48 hours after surgery. Where there is a risk of post-operative venous thrombosis and the bleeding risk is high, consider a reduced dose of 2.5mg BD (recommended prophylactic dose) for the immediate post-operative period.

In patients with poor oral absorption or nil by mouth after surgery, parenteral anticoagulants may be needed until reliable oral absorption is established.

Neuraxial anaesthesia

Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of apixaban. Experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in this setting.

REFERENCES

Before prescribing, please review full Product Information available from Bristol-Myers Squibb Australia Pty Ltd by calling 1800 067 567.

**MINIMUM PRODUCT INFORMATION ELIQUIS®** (apixaban) 2.5 mg and 5 mg tablets. **Indications:** VTE prevention in adults after elective total hip or total knee replacement surgery, stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (NVAF) with at least one additional factor for stroke. **Contraindications:** Hypersensitivity to apixaban or tablet excipients; clinically significant active bleeding (intracranial, GI); impairment of haemostasis; hepatic disease associated with coagulopathy and clinically relevant bleeding risk, severe hepatic impairment (Child-Pugh C); severe renal impairment CrCl < 25 mL/min; organ lesion or conditions at risk of clinically significant major bleeding; strong inhibitors of both CYP3A4 and P-gp, concomitant anticoagulant treatments. See PI for details. **Precautions:** Haemorrhage risk: existing conditions with increased bleeding risk; fall in haemoglobin or blood pressure – search for bleeding site; discontinue if severe haemorrhage or complications; consider treatment. Increased risk of stroke when transitioning to warfarin (consider coverage with another anticoagulant); valvular heart disease; ischaemic stroke; renal or hepatic impairment; elevated liver enzymes or bilirubin. Concomitant NSAIDs. Other anti-platelets or antithrombotic agents not recommended. Spinal/epidural anaesthesia or puncture; indwelling catheters; neuraxial blockade. Hip fracture surgery. Pregnancy. Lactation. Children. Elderly patients on concomitant acetylsalicylic acid. Effects on clotting test. See PI for details. **Interactions with other Medicines:** Strong inducers of both CYP3A4 and P-gp. See PI for details. **Adverse Effects:** Most common: anaemia, haemorrhage (including eye, GI, rectal, gingival), haematoma, haematuria, epistaxis, contusion, nausea. Others include: thrombocytopenia, hypotension, haemorrhage: intra-abdominal, haemorrhoidal, mouth, vaginal, urogenital, operative, vessel/catheter/incision site, post-procedural bleeding, haematochezia, liver enzymes increased or abnormal, bilirubin increased, wound secretion, haemoptysis, hypersensitivity. See PI for details. **Dosage and Administration:** VTE prevention: 2.5 mg twice daily. Start 12 to 24 hours after surgery. Take for 32–38 days in hip replacement and 10–14 days for knee replacement. NVAF: 5 mg twice daily; 2.5 mg twice daily in patients with two of the following characteristics: ≥ 80 yrs; ≤ 60 kg; serum creatinine ≥ 133 μmol/L. See PI for details. V10503