

Apixaban (Eliquis®): Guidelines for Use in Adults

FDA Approved Indications

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of DVT and PE and to reduce the risk of recurrent DVT/PE following initial therapy
- For the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patient who have undergone hip or knee replacement surgery

Contraindications

- Active pathological bleeding
- Severe hypersensitivity reaction to apixaban (anaphylactic reactions)
- Severe hepatic impairment (Child-Pugh Class C)
- Epidural/spinal anesthesia
- Pregnancy

Mechanism of Action

- Apixaban is an orally bioavailable factor Xa inhibitor. It does not require a cofactor, such as anti-thrombin, for its antithrombotic activity. By inhibiting free and clot bound factor Xa, apixaban decreases thrombin generation and thrombus development. Apixaban also indirectly inhibits thrombin induced platelet aggregation.

Pharmacokinetics

Half-life: 12 hours

Time to peak: 3-4 hours

Bioavailability: ~50%, (unaffected by food)

Protein binding: ~87%

Metabolism: hepatic, predominantly via CYP3A4

Drug Interactions

Apixaban is a substrate of both CYP3A4 and P-gp. Both inhibitor and inducers of CYP3A4 and P-gp may change exposure to apixaban.

Table 1: Drug Interactions

Combined CYP3A4 and P-gp Strong Inhibitors

Reduce dose from 5 mg twice daily to 2.5 mg twice daily when administered with ketoconazole, itraconazole, ritonavir, or clarithromycin.

In patients already taking apixaban 2.5 mg twice daily or in patients who meet 2 of the following criteria: age \geq 80 years, body weight \leq 60kg or SCr $>$ 1.5 mg/dL, avoid co-administration with the above mentioned inhibitors.

Avoid use with strong dual Inducers of CYP3A4 and P-gp

rifampin, carbamazepine, phenytoin, St. John's Wort, phenobarbital, and primidone

Discontinuation of Therapy Before Surgery

Apixaban should be stopped at least 48 hours prior to elective surgery or invasive procedures with a moderate to high risk of bleeding. Discontinued at least 24 hours prior to surgery or procedures with a low risk of bleeding or where the bleeding would be in a non-critical location and easily controlled. Bridging anticoagulation during the 24-48 hours after stopping apixaban and prior to the intervention is not generally required. Restart apixaban post-op as soon as adequate hemostasis has been established. If oral therapy cannot be started, consider starting a parenteral agent (heparin, or enoxaparin).

Dosage (based on indication and renal function)

1. Nonvalvular atrial fibrillation

SCr <1.5mg/dL: 5mg by mouth twice daily unless patient has both of the following, then reduce the dose to 2.5mg by mouth twice daily: Age ≥ 80 years **AND** body weight ≤ 60 kg

SCr ≥1.5mg/dL: Reduce dose to 2.5mg twice daily if age ≥ 80 years **OR** body weight ≤ 60 kg

ESRD requiring hemodialysis: 5mg twice daily, reduce to 2.5mg twice daily if: Age ≥ 80 years **OR** body weight ≤ 60 kg.

***Caution:** These patients were excluded from clinical trials. Use only if potential benefit outweighs the risk.

2. DVT and/or PE

Treatment: 10mg by mouth twice daily for 7 days followed by 5mg by mouth twice daily for the remainder of treatment

Reduction in recurrence risk of DVT or PE after at least 6 months of initial treatment: 2.5mg by mouth twice daily

Renal impairment- No dose adjustments necessary, however patients with a SCr > 2.5 mg/dL or CrCl < 25 ml/min were excluded from the AMPLIFY clinical trials.

3. Prophylaxis of VTE Following Hip or Knee Replacement Surgery

2.5mg by mouth twice daily, beginning 12-24 hours post-op. Continue for 35 days following hip replacement surgery and 12 days following knee replacement surgery.

Renal impairment- No dose adjustments necessary, however patients with impaired renal function were excluded from the ADVANCE trials. Greater than 80% of patients in each trial had a CrCl > 60mL/min.

Table 2: Converting to or from Apixaban to Other Anticoagulants

Drug Conversion	Action
From warfarin → apixaban	Discontinue warfarin and start apixaban when the INR is < 2
From anticoagulant other than warfarin → apixaban	Discontinue current agent and start apixaban at the time the next dose would have been administered
From apixaban → warfarin:	If continuous anticoagulation is necessary, discontinue apixaban and begin warfarin and a parental anticoagulant at the time the next dose of apixaban would have been administered. Discontinue the parental anticoagulant when INR is therapeutic. Note: Apixaban can elevate the INR; therefore initial INR measurements during the transition from apixaban to warfarin may not be useful in determining the appropriate warfarin dose.
From apixaban → anticoagulant other than warfarin (parenteral or oral)	Discontinue apixaban and start the other anticoagulant at the time the next apixaban dose would have been administered

Monitoring

Routine monitoring of coagulation tests is not required. Assess renal function (Scr), liver function (LFTs), and complete blood count (CBC) at **baseline** and at least every 6-12 months thereafter to see if dose adjustment or alternative therapy is necessary. See the document titled "Direct Oral Anticoagulation Monitoring" posted to the Clinical Pathways and Guidelines page for more guidance. Though not recommended to assess effectiveness, the prothrombin time (PT), INR, and aPTT are prolonged with apixaban.

Management of Bleeding

Effects can be expected to persist for at least 24 hours after the last dose. Management of bleeds should be individualized.

Table 3: Strategies for the Management of Bleeding while on Apixaban

Bleed Category	Action
Minor Bleed	Hold apixaban. Provide supportive measures
Life-Threatening Bleed	<ul style="list-style-type: none">○ Discontinue apixaban○ Provide supportive measures (compression, surgical hemostasis, transfusions)○ Well documented <u>overdose</u>: Oral charcoal (give if ingestion occurred within 2 to 6 hours of presentation)○ Dialysis is not expected to have an impact on apixaban exposure.○ Kcentra® 50 units/kg may be considered^{4,5}. This does not reverse apixaban, but is an attempt to overwhelm the effect of the drug. See the "Oral Anticoagulation Reversal Algorithm" on the Clinical Pathways and Guidelines page for more information.

References:

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