Prescriber Guide
Apixaban EVA ®(Apixaban)

Objectives of this Guide:

This educational material is provided to further minimize the risk of bleeding that is associated with the use of apixaban and to guide healthcare professionals in managing that risk.

This Prescriber Guide is advised to be read carefully before prescribing, dispensing or administering the product.

This Prescriber Guide is not a substitute for the Apixaban EVA ® Summary of Product Characteristics (SmPC). Please consult the SmPC for full prescribing information.

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Patient Alert Card

A Patient Alert Card should be provided to every patient prescribed apixaban, and the importance and consequences of anticoagulant therapy explained. Patients should be counselled on treatment compliance, the signs and symptoms of bleeding, and when to seek medical attention. They should be advised to carry the card at all times, to show it to every healthcare professional, and to inform any healthcare professional that they are taking apixaban before surgery or invasive procedures. Additional copies of the Patient Alert Card can be obtained by contacting EVA pharma via: pv.ksateam@Evapharma.com

Therapeutic indication: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors

Risk factors for stroke in NVAF include prior stroke or transient ischaemic attack, age ≥75 years, hypertension, diabetes mellitus, and symptomatic heart failure (NYHA Class ≥II).

Dosing recommendations

The recommended dose is apixaban 5 mg twice daily, with or without food, continued long-term. For patients unable to swallow whole tablets, tablets may be crushed and suspended in water, 5% glucose in water (G5W), or apple juice, or mixed with apple puree, and given orally or via nasogastric tube; crushed tablets are stable for up to **4 hours.**

Dose reduction

A reduced dose of apixaban 2.5 mg twice daily is recommended in patients with at least two of the following:

- Age ≥80 years
- Body weight ≤60 kg
- Serum creatinine ≥1.5 mg/dL (133 µmol/L)

Patients with severe renal impairment (CrCl 15 to 29 ml/min) should also receive 2.5 mg twice daily.

Missed dose

If a dose is missed, the patient should take apixaban immediately and then continue with twice daily intake as before.

Patients with renal impairment

Renal impairment	
Dialysis	Not recommended
Renal failure (CrCl <15 ml/min)	Not recommended
Severe renal impairment (CrCl 15–29 ml/min)	Dose reduction to 2.5 mg twice daily
Mild (CrCl 51–80 ml/min) or moderate (CrCl 30–50 ml/min) renal impairment	5 mg twice daily. No dose adjustment required unless the patient fulfils criteria for dose reduction to 2.5 mg twice daily based on age, body weight and/or serum creatinine (refer to dosing section)

Patients with hepatic impairment

Hepatic impairment	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Contraindicated
Severe hepatic impairment	Not recommended
Mild or moderate hepatic impairment (Child Pugh A or B)	Use with caution (No dose adjustment required)

Liver function should be tested before initiating apixaban. Patients with ALT or AST above 2 x ULN, or total bilirubin at least 1.5 x ULN, were excluded from clinical studies, so apixaban should be used cautiously in this population.

Patients undergoing catheter ablation

Apixaban can be continued in patients undergoing catheter ablation for atrial fibrillation.

Patients undergoing cardioversion

Apixaban can be initiated or continued in NVAF patients who may require cardioversion.

In patients not previously anticoagulated, exclusion of left atrial thrombus by an image-guided approach (e.g. TEE or CT) should be considered before cardioversion, in line with established guidelines; where a prior intracardiac thrombus has been detected, established guidelines should be followed before cardioversion.

Patient status	Patient qualifies for dose reduction?	Dosing regimen
Initiating treatment with apixaban	No	5 mg twice daily for at least 2.5 days (5 single doses) before cardioversion
	Yes	2.5 mg twice daily for at least 2.5 days (5 single doses) before cardioversion
Insufficient time prior to cardioversion to administer 5 doses of apixaban	No	10 mg loading dose at least 2 hours before cardioversion, followed by 5 mg twice daily
	Yes	5 mg loading dose at least 2 hours before cardioversion, followed by 2.5 mg twice daily

Before cardioversion, confirmation should be sought that the patient has taken apixaban as prescribed. Decisions on initiation and duration of treatment should follow established guideline recommendations for anticoagulant treatment in cardioversion.

Therapeutic indication: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Dosing recommendations

For the treatment of acute DVT and PE, the recommended dose is apixaban 10 mg twice daily for the first 7 days, followed by 5 mg twice daily, with or without food. A short treatment duration (at least 3 months) should be based on major transient or reversible risk factors (e.g. recent surgery, trauma, immobilisation). For the prevention of recurrent DVT and PE, the recommended dose is 2.5 mg twice daily, initiated after completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant. The overall duration of therapy should be individualized after weighing the treatment benefit against the risk of bleeding. See below.

Dosing schedule	Morning	Night	Daily dose
Treatment of acute DVT or PE (at least 3 months)			
Day 1–7: 10 mg twice daily	5 mg 5 mg	5 mg 5 mg	20 mg
Day 8 onwards: 5 mg twice daily	5 mg	5 mg	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months anticoagulation treatment			
2.5 mg twice daily	2.5 mg	2.5 mg	5 mg

For patients unable to swallow whole tablets, tablets may be crushed and suspended in water, 5% glucose in water (G5W), or apple juice, or mixed with apple puree, and given orally or via nasogastric tube; crushed tablets are stable for up to **4 hours.**

Missed dose

If a dose is missed, the patient should take apixaban immediately and then continue with twice daily intake as before.

Patients with renal impairment

Renal impairment	
Dialysis	Not recommended
Renal failure (CrCl <15 ml/min)	Not recommended
Severe renal impairment (CrCl 15–29 ml/min)	Use with caution
Mild (CrCl 51–80 ml/min) or moderate (CrCl 30–50 ml/min) renal impairment	No dose adjustment required

Patients with hepatic impairment

Hepatic impairment	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Contraindicated
Severe hepatic impairment	Not recommended
Mild or moderate hepatic impairment (Child Pugh A or B)	Use with caution No dose adjustment required

Liver function should be tested before initiating apixaban. Patients with ALT or AST above 2 x ULN, or total bilirubin at least 1.5 x ULN, were excluded from clinical studies, so apixaban should be used cautiously in this population.

Hemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Apixaban is not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

Patients with active cancer

Patients with active cancer can be at high risk of both venous thromboembolism and bleeding. When apixaban is considered for DVT or PE treatment in these patients, the benefits should be carefully weighed against the risks.

Therapeutic indication: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery

Dosing recommendations

The recommended dose is apixaban 2.5 mg twice daily, with or without food, with the initial dose taken **12 to 24 hours after** surgery. In deciding the timing within this window, the benefit of earlier anticoagulation for VTE prophylaxis should be weighed against the risk of post-surgical bleeding. The recommended duration of treatment is 32 to 38 days after hip replacement, and 10 to 14 days after knee replacement.

For patients unable to swallow whole tablets, tablets may be crushed and suspended in water, 5% glucose in water (G5W), or apple juice, or mixed with apple puree, and given orally or via nasogastric tube; crushed tablets are stable for up to **4 hours.**

Missed dose

If a dose is missed, the patient should take apixaban immediately and then continue with twice daily intake as before.

Patients with renal impairment:

Renal impairment	
Dialysis	Not recommended
Renal failure (CrCl <15 ml/min)	Not recommended
Severe renal impairment (CrCl 15–29 ml/min)	Use with caution
Mild (CrCl 51–80 ml/min) or moderate (CrCl 30–50 ml/min) renal impairment	No dose adjustment required

Patients with hepatic impairment:

Hepatic impairment	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Contraindicated
Severe hepatic impairment	Not recommended
Mild or moderate hepatic impairment (Child Pugh A or B)	Use with caution No dose adjustment required

Liver function should be tested before initiating apixaban. Patients with ALT or AST above 2 x ULN, or total bilirubin at least 1.5 x ULN, were excluded from clinical studies, so apixaban should be used cautiously in this population.

Switching to and from apixaban

Switching between parenteral anticoagulants and apixaban (in either direction) can be done at the next scheduled dose. These medicinal products should not be administered simultaneously.

- **Switching from vitamin K antagonist (VKA) therapy to apixaban**

When converting from VKA therapy to apixaban, discontinue the warfarin or other VKA and start apixaban once the INR is below 2.0:

- Discontinue warfarin or other VKA therapy.
- Monitor INR at regular intervals until it is below 2.0.
- Start apixaban twice daily.

- **Switching from apixaban to VKA therapy**

When converting patients from apixaban to VKA therapy, continue administration of apixaban for at least 2 days after beginning VKA therapy. After 2 days of coadministration of apixaban with VKA therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue coadministration of apixaban and VKA therapy until the INR is ≥2.0.

Populations potentially at higher risk of bleeding

Several subgroups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. Apixaban should be used with caution in conditions with an increased haemorrhagic risk, and discontinued if severe haemorrhage occurs.

Lesions or conditions considered a significant risk factor for major bleeding, where use is contraindicated:

- Active clinically significant bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Current or recent gastrointestinal ulceration
- 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

Interactions with other medicinal products affecting haemostasis:

- **Anticoagulants (UFH, low molecular weight heparins such as enoxaparin or dalteparin, heparin derivatives such as fondaparinux, and oral anticoagulants such as warfarin, rivaroxaban, or dabigatran):** concomitant use with apixaban is contraindicated, except under specific switching circumstances, when UFH is given at doses to maintain patency of a central venous or arterial catheter, or when UFH is given during catheter ablation for atrial fibrillation.
- **Antiplatelet agents, SSRIs or SNRIs, and NSAIDs:** concomitant use increases bleeding risk. Use apixaban with caution with SSRIs or SNRIs, NSAIDs, acetylsalicylic acid, or P2Y12 inhibitors (e.g. clopidogrel).
- **Other platelet aggregation inhibitors (e.g. GPIIb/IIIa antagonists, dipyridamole, dextran, sulfinpyrazone) and thrombolytic agents:** experience is limited and, as these increase bleeding risk, concomitant use is not recommended.

Factors that may increase apixaban exposure (higher plasma levels):

- **Renal impairment:** see the renal impairment guidance under each indication. Use is not recommended if CrCl is below 15 ml/min or the patient is on dialysis; no dose adjustment is needed in mild or moderate impairment. In NVAF, use 2.5 mg twice daily in severe renal impairment (CrCl 15 to 29 ml/min), or where serum creatinine is at least 1.5 mg/dL (133 µmol/L) combined with age ≥80 years or body weight ≤60 kg.
- **Elderly:** no dose adjustment required (in NVAF, no adjustment except in combination with other factors).
- **Low body weight ≤60 kg:** no dose adjustment required (in NVAF, no adjustment except in combination with other factors).

- **Strong inhibitors of both CYP3A4 and P-gp:** apixaban is not recommended with systemic azole antimycotics (e.g. ketoconazole, itraconazole, voriconazole, posaconazole) or HIV protease inhibitors (e.g. ritonavir).
- **Agents that are not strong inhibitors of both CYP3A4 and P-gp:** no dose adjustment is needed with, for example, amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, or verapamil.

Factors that may reduce apixaban exposure (lower plasma levels):

- **Strong inducers of both CYP3A4 and P-gp (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort):** may reduce apixaban exposure by about 50% and should be used with caution. For treatment of DVT or PE, apixaban is not recommended.

Surgery and invasive procedures

Apixaban should be discontinued before elective surgery or invasive procedures with a risk of bleeding (this excludes cardioversion and catheter ablation). If the procedure cannot be delayed, appropriate caution should be exercised, weighing the increased bleeding risk against the urgency of intervention.

Apixaban should be discontinued for a sufficient period before the procedure to reduce the risk of anticoagulant-related bleeding. Its half-life is approximately **12 hours** and, as a reversible factor Xa inhibitor, its anticoagulant activity should abate within **24 to 48 hours** of the last dose.

Discontinuation before an elective procedure:

- **Low risk of bleeding** (interventions where bleeding, if it occurs, would be minimal, non-critical in location, or easily controlled by simple mechanical haemostasis): discontinue at least **24 hours** before the procedure.
- **Moderate or high risk of bleeding** (interventions where clinically significant bleeding cannot be excluded, or where the risk of bleeding would be unacceptable): discontinue at least **48 hours** before the procedure.

Temporary discontinuation

Discontinuing apixaban for active bleeding, elective surgery, or invasive procedures increases the risk of thrombosis. Lapses in therapy should be avoided; where apixaban must be temporarily discontinued for any reason, it should be restarted as soon as the clinical situation allows and adequate haemostasis has been established.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal or epidural) or spinal or epidural puncture is used, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma, which can result in long-term or permanent paralysis. Post-operative indwelling epidural or intrathecal catheters should be removed at least **5 hours** before the first dose of apixaban.

Guidance on the use of apixaban in patients with indwelling intrathecal or epidural catheters

There is no clinical experience with apixaban in patients with indwelling intrathecal or epidural catheters. Where such use is needed, and based on the pharmacokinetics of apixaban, an interval of **20 to 30 hours** (i.e. 2 x half-life) should elapse between the last dose and catheter withdrawal, and at least one dose should be omitted before withdrawal. The next dose may be given at least **5 hours** after catheter removal. As experience with neuraxial blockade is limited, extreme caution is recommended when using apixaban in this setting.

Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment are necessary.

The catheter timing sequence:

1. Give the last apixaban tablet before catheter removal.
2. Wait **20 to 30 hours.**
3. Remove the catheter.

4. Wait at least **5 hours.**
5. Give the first apixaban tablet after catheter removal.

Management of overdose and haemorrhage

Overdose of apixaban may increase the risk of bleeding. In the event of haemorrhagic complications, treatment should be discontinued and the source of bleeding investigated. Appropriate measures should be considered, such as surgical haemostasis, transfusion of fresh frozen plasma, or administration of a reversal agent for factor Xa inhibitors.

Administration of activated charcoal may be useful in the management of overdose or accidental ingestion, having been shown to reduce apixaban absorption and mean exposure when given within a few hours of ingestion.

Where reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available. Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered. There is no clinical experience with the use of 4-factor PCC or recombinant factor VIIa to reverse bleeding in patients who have received apixaban; re-dosing of recombinant factor VIIa may be considered and titrated to the improvement in bleeding. In cases of major bleeding, consultation of a coagulation expert should be considered, depending on local availability.

Haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Use of coagulation tests

Routine clinical monitoring is not required with apixaban. A calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure could inform clinical decisions, for example in overdose or emergency surgery.

Prothrombin time (PT), INR and activated partial thromboplastin time (aPTT)

Changes in prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) at the expected therapeutic dose are small and highly variable, and are not recommended for assessing the pharmacodynamic effect of apixaban.

Anti-FXa assays

Apixaban also shows anti-factor Xa activity, which has a close, approximately linear relationship with apixaban plasma concentration across a wide range and reaches its maximum at peak plasma concentration. Results differ across commercial kits.

Reporting Adverse Reactions:

Call for reporting:

- **The National Pharmacovigilance Centre (NPC - Saudi Food and Drug Authority (SFDA)):**
  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa
  - QR Code: Scan to report to the SFDA:
- **Pharmacovigilance department at Eva Pharma:**
  - E-Mail: pv.ksateam@Evapharma.com

References:

Summary of Product Characteristics (SmPC), APIXABAN EVA® (Apixaban) 2.5 mg and 5.0 mg film coated tablets.