Amarox

XCARD (APIXABAN)
2.5mg, 5mg Tablets
Prescriber Guide

This Prescriber Guide is not a substitute for the XCARD (APIXABAN) Summary of Product Characteristics (SPC). Please see SPC for full prescribing information.

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

This document is approved by the Executive Directorate of Pharmacovigilance at SFDA

Table of Contents

1- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors…….3
1.1 Dosing recommendations…….3
1.2 Patients with impairments ……..……..4

2- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults……..….6
2.1 Dosing recommendations…….6
2.2 Patients with impairments……6z
2.3 Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy…….7.
2.4 Patients with active cancer ……7

3- Switching to and from Xcard (Apixaban)…….8
4- Populations potentially at higher risk of bleeding……...8
5- Use of coagulation tests…….9

Patient Alert Card

A Patient Alert Card must be provided to each patient who is prescribed Xcard (Apixaban) 2.5 mg or 5 mg, and the importance and consequences of anticoagulant therapy should be explained. The Patient Alert Card is included inside the Xcard (Apixaban) 2.5 mg and 5 mg packs together with the package leaflet.

Specifically, the prescriber should talk to patients about the importance of treatment compliance, the signs or symptoms of bleeding, and when to seek attention from a healthcare professional.

This Patient Alert Card provides information to physicians, dentists and pharmacists on the anticoagulant therapy and contains important contact information in the event of emergencies.

Patients should be advised to carry the Patient Alert Card with them at all times and to show it to every healthcare professional including pharmacists. They should also be reminded about the need to inform healthcare professionals that they are taking Xcard (Apixaban) if they require surgery or invasive procedures.

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 of Xcard (Apixaban) is 5 mg taken orally twice daily (bid) with water, with or without food. Therapy should be continued long term

For patients who are unable to swallow whole tablets, Xcard (Apixaban) tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Xcard (Apixaban) tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube. Crushed Xcard (Apixaban) tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

Dose reduction

In patients with at least two of the following characteristics: age ≥80 years, body weight ≤60kg, or serum creatinine ≥1.5 mg/dL (133 µmol/L), the recommended dose of Xcard (Apixaban) is 2.5 mg taken orally bid.

Patients with exclusive criteria of severe renal impairment (creatinine clearance [CrCl] 15–29 ml/min) should also receive Xcard (Apixaban) 2.5 mg bid.

Missed dose

If a dose is missed, the patient should take Xcard (Apixaban) immediately and then continue with bid 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 bid
Mild (CrCl 51–80 ml/min) or moderate (CrCl 30–50 ml/min) renal impairment	5 mg bid. No dose adjustment required unless the patient fulfils criteria for dose reduction to 2.5 mg bid based on age, body weight and/or serum creatinine

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

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore, Xcard (Apixaban) should be used cautiously in this population. Prior to initiating Xcard (Apixaban), liver function testing should be performed.

Patients undergoing catheter ablation (NVAF):

Patient can continue Xcard (Apixaban) use while undergoing catheter ablation.

Patients undergoing cardioversion

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

Patient Status	**Patient qualifies for dose reduction?**	**Dosing regimen**
Not previously treated with anticoagulants	No	At least 5 doses of Xcard (Apixaban) 5 mg bid before cardioversion
	Yes	At least 5 doses of Xcard (Apixaban) 2.5 mg bid before cardioversion
Insufficient time prior to cardioversion to administer 5 doses of Xcard (Apixaban)	No	10 mg loading dose at least 2 hours before cardioversion, followed by 5 mg bid
	Yes	5 mg loading dose at least 2 hours before cardioversion, followed by 2.5 mg bid

Confirmation should be sought prior to cardioversion that the patient has taken Xcard (Apixaban) as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Patients with prosthetic heart valves

Safety and efficacy of Xcard (Apixaban) have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of Xcard (Apixaban) is not recommended in this setting.

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

Dosing recommendations

The recommended dose of Xcard (Apixaban) for the treatment of acute DVT and treatment of PE is 10 mg taken orally bid for the first 7 days followed by 5 mg taken orally bid with water, with or without food.

As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, and immobilisation).

The recommended dose of Xcard (Apixaban) for the prevention of recurrent DVT and PE is 2.5 mg taken orally bid with water, with or without food.

When prevention of recurrent DVT and PE is indicated, the 2.5 mg bid dose should be initiated following completion of 6 months of treatment with Xcard (Apixaban) 5 mg bid or with another anticoagulant.

DOSING SCHEDULE		**DAILY DOSE**
Treatment of acute DVT or PE (at least 3 months)	10 mg bid for the first 7 days	20 mg
	followed by 5 mg bid	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of anticoagulation treatment for DVT or PE	2.5 mg bid	5 mg

The duration of overall therapy should be individualized after careful assessment of the treatment benefit against the risk for bleeding.

For patients who are unable to swallow whole tablets, XCARD (APIXABAN) tablets may be crushed and suspended in water, or D5W, or apple juice or mixed with apple puree and immediately administered orally. Alternatively, XCARD (APIXABAN) tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube. Crushed XCARD (APIXABAN) tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

Missed dose

If a dose is missed, the patient should take Xcard (Apixaban) immediately and then continue with bid 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
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

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

Patients with elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore, Xcard (Apixaban) should be used cautiously in this population. Prior to initiating Xcard (Apixaban), liver function testing should be performed.

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

Xcard (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

Efficacy and safety of Xcard (Apixaban) in the treatment of DVT, treatment of PE, and prevention of recurrent DVT and PE in patients with active cancer have not been established.

Switching to and from Xcard (Apixaban)

Switching treatment from parenteral anticoagulants to Xcard (Apixaban) (and vice versa) can be done at the next scheduled dose.

These agents should not be administered simultaneously.

Switching from vitamin K antagonist (VKA) therapy to Xcard (Apixaban)

When converting patients from VKA therapy to Xcard (Apixaban), discontinue warfarin or other VKA therapy and start Xcard (Apixaban) when the international normalized ratio (INR) is <2.0.

Switching from Xcard (Apixaban) to VKA therapy

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

Populations potentially at higher risk of bleeding

Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. Xcard (Apixaban) should be used with caution in conditions with an increased haemorrhagic risk. Xcard (Apixaban) administration should be discontinued if severe haemorrhage occurs.

Lesion or condition considered a significant risk factor for major bleeding	
This includes: • Active clinically significant bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • 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	Circumstances where Xcard (Apixaban) is **contraindicated**

Interactions with other medicinal products affecting haemostasis	
Anticoagulants • Unfractionated heparins, low molecular weight heparins (e.g. enoxaparin, dalteparin), heparin derivatives (e.g. fondaparinux) • Oral anticoagulants (e.g. warfarin, rivaroxaban, dabigatran)	Concomitant treatment with Xcard (Apixaban) and any other anticoagulant agent is **contraindicated**, except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter

Platelet aggregation inhibitors, SSRIs/ SNRIs and NSAIDs • Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) • Acetylsalicylic acid (ASA) • Non-steroidal anti-inflammatory drugs (NSAIDs)	The concomitant use of Xcard (Apixaban) with antiplatelet agents increases the risk of bleeding Care is to be taken if patients are treated concomitantly with SSRIs/SNRIs or NSAIDs, including ASA

Medicinal products associated with serious bleeding are not recommended concomitantly with XCARD (APIXABAN), such as: thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g clopidogrel), dipyridamole, dextran and sulfinpyrazone.

Factors which may increase Xcard (Apixaban) exposure/increase Xcard (Apixaban) plasma levels	
Renal impairment	• Use is not recommended in patients with CrCl <15 ml/min or patients undergoing dialysis • No dose adjustment is required in patients with mild or moderate renal impairment **Patients with NVAF** • Patients with severe renal impairment (CrCl 15–29 ml/min) should receive the lower dose of Xcard (Apixaban) 2.5 mg bid • Patients with serum creatinine ≥1.5 mg/dL (133 µmol/L) associated with age ≥80 years or body weight ≤60 kg should receive the lower dose of Xcard (Apixaban) 2.5 mg bid
Elderly	• No dose adjustment required **Patients with NVAF** • No dose adjustment required except in combination with other factors
Low body weight ≤60 kg	• No dose adjustment required **Patients with NVAF** • No dose adjustment required except in combination with other factors
Concomitant use with strong inhibitors of both CYP3A4 and P-gp	• Xcard (Apixaban) is not recommended in patients receiving concomitant systemic treatment with, for example, azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir)
Concomitant use with agents not considered strong inhibitors of both	• No dose adjustment for Xcard (Apixaban) is required when coadministered with, for

CYP3A4 and P-gp	example, diltiazem, naproxen, clarithromycin, amiodarone, verapamil and quinidine
Factors which may reduce xcard (Apixaban) exposure/reduce ELIQUIS plasma levels	
Concomitant use with strong inducers of both CYP3A4 and P-gp	The concomitant use of Xcard (Apixaban) with strong inducers of both CYP3A4 and P-gp (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in Xcard (Apixaban) exposure and should be used with caution **Treatment of DVT or PE** • Xcard (Apixaban) is not recommended

Surgery and invasive procedures

Xcard (Apixaban) should be discontinued prior to elective surgery or invasive procedures with a risk of bleeding.
If surgery or invasive procedures cannot be delayed, exercise appropriate caution, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.
Although treatment with Xcard (Apixaban) does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of Xcard (Apixaban) exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.
In the event a patient treated with Xcard (Apixaban) requires an elective procedure, such as surgery or an invasive procedure associated with an increased risk of bleeding, Xcard (Apixaban) should be discontinued for a sufficient period of time prior to the procedure to reduce the risk of anticoagulant-related bleeding. The half-life of Xcard (Apixaban) is approximately 12 hours. Given that Xcard (Apixaban) is a reversible FXa inhibitor, its anticoagulant activity should abate within 24 to 48 hours of the last administered dose.

Discontinuation of Xcard (Apixaban) prior to elective surgery	
Low risk of bleeding (procedures for which bleeding, if it occurs, will be minimal, non-critical in its location and/or easily controlled by simple mechanical haemostasis)	At least 24 hours prior to elective surgery or invasive procedures
Moderate or high risk of bleeding (includes interventions for which the probability of clinically significant bleeding cannot be excluded, or for which the risk of bleeding would be unacceptable)	At least 48 hours prior to elective surgery or invasive procedures (>4 half-lives)

Temporary discontinuation

Discontinuing anticoagulants, including Xcard (Apixaban), for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with Xcard (Apixaban) must be temporarily discontinued for any reason, therapy should be restarted as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, 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 must be removed at least 5 hours prior to the first dose of Xcard (Apixaban).

Guidance on the use of Xcard (Apixaban) in patients with indwelling intrathecal or epidural catheters
There is no clinical experience with the use of Xcard (Apixaban) with indwelling intrathecal or epidural catheters. In case there is such need and based on the general pharmacokinetic characteristics of Xcard (Apixaban), a time interval of 20 to 30 hours (i.e., 2x half-life) between the last dose of Xcard (Apixaban) and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of Xcard (Apixaban) may be given at least 5 hours after catheter removal. As with all new anticoagulant drugs, experience with neuraxial blockade is limited and extreme caution is therefore recommended when using Xcard (Apixaban) in the presence of neuraxial blockade.
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 is necessary.

Management of overdose and haemorrhage

There is no antidote to Xcard (Apixaban). Overdose of Xcard (Apixaban) may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered.
In controlled clinical trials, orally-administered Xcard (Apixaban) in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg bid for 7 days or 50 mg once daily (od) for 3 days) had no clinically relevant adverse effects.
In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of Xcard (Apixaban) reduced mean AUC by 50% and 27%, respectively, and had no impact on Cmax. Mean half-life decreased from 13.4 hours when Xcard (Apixaban) was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after Xcard (Apixaban). Thus, administration of activated charcoal may be useful in the management of Xcard (Apixaban) overdose or accidental ingestion.
If life-threatening bleeding cannot be controlled by the above measures, administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered. Reversal of Xcard (Apixaban) pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 4-factor PCC 30 minute infusion in healthy subjects. However, there is no clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received Xcard (Apixaban). Currently there is no experience with the use of recombinant factor VIIa in individuals receiving Xcard (Apixaban). Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.
Depending on local availability, consultation of a coagulation expert should be considered in case of major bleeding.
Haemodialysis decreased AUC by 14% in subjects with end stage renal disease, when a single dose of Xcard (Apixaban) 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing Xcard (Apixaban) overdose.

Use of coagulation tests

Routine clinical monitoring is not required with Xcard (Apixaban). However, a calibrated quantitative anti-FXa assay may be useful in exceptional situations where knowledge of Xcard (Apixaban) exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.

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 pharmacodynamic effects of Xcard (Apixaban). In the thrombin generation assay, Xcard (Apixaban) reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Anti-FXa assays

Xcard (Apixaban) also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in multiple commercial anti-FXa kits, however results differ across kits. Anti-FXa activity exhibits a close direct linear relationship with Xcard (Apixaban) plasma concentration, reaching maximum values at the time of Xcard (Apixaban) peak plasma concentrations. The relationship between Xcard (Apixaban) plasma concentration and anti-FXa activity is approximately linear over a wide dose range of Xcard (Apixaban).

Below table shows the predicted steady state exposure and anti-Factor Xa activity. In non-valvular atrial fibrillation patients taking Xcard (Apixaban) for the prevention of stroke and systemic embolism, the results demonstrate a less than 1.7-fold fluctuation in peak-to-trough levels. In patients taking Xcard (Apixaban) for the treatment of DVT and PE or prevention of recurrent DVT and PE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

Predicted Xcard (Apixaban) Steady-state Exposure and Anti-Xa Activity				
	Xcard (Apixaban) C_{max} (ng/mL)	**Xcard (Apixaban) C_{min} (ng/mL)**	**Xcard (Apixaban) Anti-Xa Activity Max (IU/mL)**	**Xcard (Apixaban) Anti-Xa Activity Min (IU/mL)**
	Median [5th, 95th Percentile]			
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg twice daily	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg twice daily	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

Call for Reporting:

As a reminder, there is a need to report any suspected adverse reactions to:

National Pharmacovigilance & Drug Safety Centre at Saudi Food and Drug Authority (SFDA):

SFDA call centre: 19999

E-mail: npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa

Marketing Authorization Holder Contact Information:

Saudi Amarox Industrial Company

Ms. Razan almalki
Pharmacovigilance Specialist
Al Jamiyah Street – Al Malaz – Riyadh Code 12629, Saudi Arabia.
Phone: +966 11 226 8850
Mobile: +966 531215235
Email: r.almalki@amaroxpharma.com