

Apixaban

Prescriber Guide

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

A digital version of the Prescriber Guide is available on the eMC website: <http://www.medicines.org.uk/emc>.

The educational pack is aimed at increasing awareness about the potential risk of bleeding/bleeding or thrombosis due to overdose or underdose during treatment with apixaban and providing guidance on how to manage that risk.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse events should be reported. Reporting forms and information can be found at <http://www.mhra.gov.uk/yellowcard> or search for MHRA Yellow Card in the Google Play or Apple App Store.

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Patient Alert Card

A Patient Alert Card must be provided to each patient who is prescribed apixaban 1 mg/ml oral suspension, and the importance and consequences of anticoagulant therapy should be explained. The Patient Alert Card is included inside the apixaban 1 mg/ ml pack 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 healthcare professionals 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. They should also be reminded about the need to inform healthcare professionals that they are taking apixaban if they require surgery or invasive procedures.

Additional copies of the Patient Alert Card can be obtained by contacting Glenmark Pharmaceuticals Europe Ltd at medical_information@glenmarkpharma.com

Therapeutic indication

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors¹

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 \geq II).

■ Dosing recommendations

The recommended dose of apixaban is 5 mg (5 ml) taken orally twice daily. Therapy should be continued long-term (Figure 1).

Figure 1

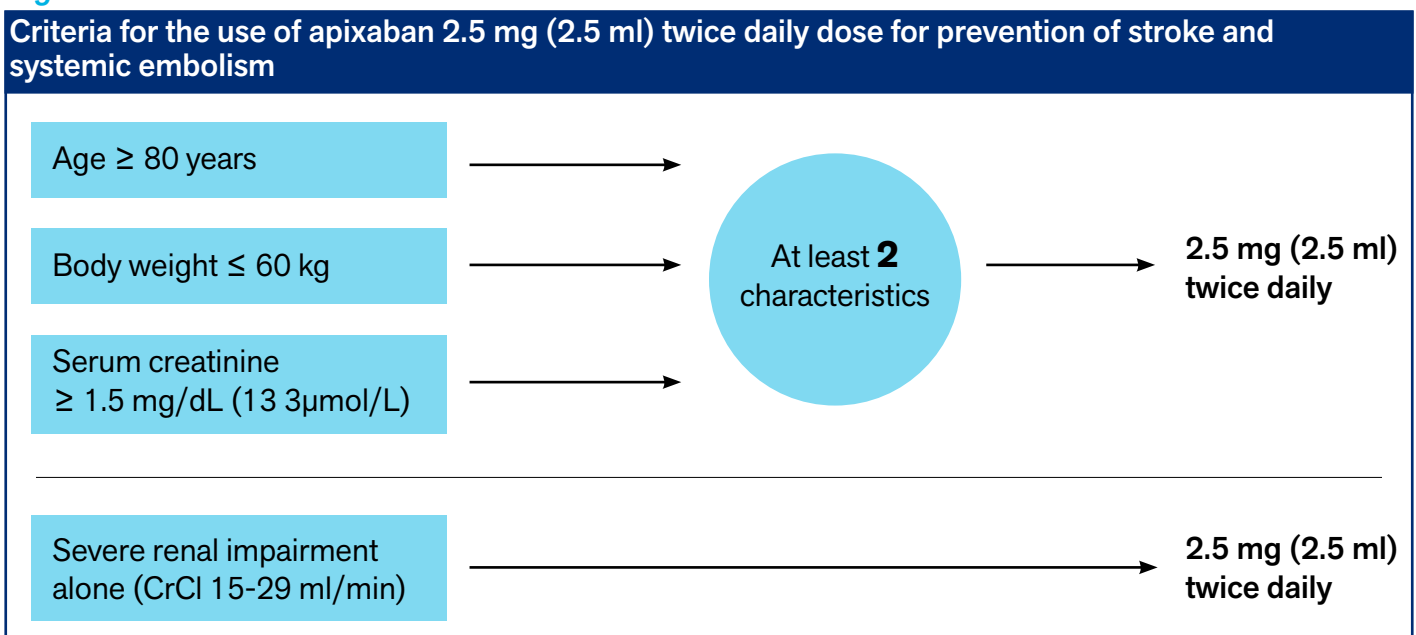


■ Dose reductions

In patients with at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 μ mol/L), the recommended dose of apixaban is 2.5 mg (2.5 ml) taken orally twice daily (Figure 2).

Patients with exclusive criteria of severe renal impairment (creatinine clearance [CrCl] 15–29 ml/min) should also receive apixaban 2.5 mg (2.5 ml) twice daily (Figure 2).

Figure 2



■ 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

Table 1:

Dose recommendation of apixaban for prevention of stroke and systemic embolism in patients with 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 (2.5 ml) twice daily
Mild (CrCl 51-80 ml/min) or moderate (CrCl 30-50 ml/min) renal impairment	5 mg (5 ml) twice daily. No dose adjustment required unless the patient fulfils criteria for dose reduction to 2.5 mg (2.5 ml) twice daily based on age, body weight and/or serum creatinine (refer to dosing section, p. 4)

■ Patients with hepatic impairment

Table 2:

Dose recommendation of apixaban for prevention of stroke and systemic embolism in patients with 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

Prior to initiating apixaban, liver function testing should be performed. 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 studies. Therefore, 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.

For patients not previously treated with anticoagulants, exclusion of left atrial thrombus using an image-guided approach (e.g. transesophageal echocardiography [TEE] or computed tomographic scan [CT]) prior to cardioversion should be considered, in accordance with established medical guidelines. For patients in whom a prior intracardiac thrombus has been detected, established medical guidelines should be followed prior to cardioversion.

Table 3:

Dose recommendation of apixaban for prevention of stroke and systemic embolism in patients undergoing cardioversion		
Patient status	Patient qualifies for dose reduction?	Dose regimen
Initiating treatment with apixaban	No	5 mg (5 ml) twice daily for at least 2.5 days (5 single doses) before cardioversion
	Yes	2.5 mg (2.5 ml) 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 (10 ml) loading dose at least 2 hours before cardioversion, followed by 5 mg (5 ml) twice daily
	Yes	5 mg (5ml) loading dose at least 2 hours before cardioversion, followed by 2.5 mg (2.5 ml) twice daily

For all patients undergoing cardioversion, confirmation should be sought prior to cardioversion that the patient has taken apixaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Therapeutic indication

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults^{1,2}

■ Dosing recommendations



The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg (10 ml) taken orally twice daily for the first 7 days followed by 5 mg (5ml) taken orally twice daily.

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

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg (2.5 ml) taken orally twice daily.

Figure 3

Dose recommendation of apixaban for treatment/prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Dosing Schedule	 Morning	 Evening	Daily Dose
Treatment of acute DVT or PE (at least 3 months)			
Day 1-7 10mg (10ml) twice daily	10mg (10ml)	10mg (10ml)	20 mg (20 ml)
Day 8 onwards 5mg (5ml) twice daily	5mg (5ml)	5mg (5ml)	10 mg (10 ml)
Prevention of recurrent DVT and/or PE following completion of 6 months anticoagulation treatment			
2.5mg (2.5ml) twice daily	2.5mg (2.5ml)	2.5mg (2.5ml)	5 mg (5 ml)

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

■ 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

Table 4:

Dose recommendation of apixaban for treatment/prevention of DVT and PE in patients with 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

Table 5:

Dose recommendation of apixaban for prevention of stroke and systemic embolism in patients with 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

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

■ Haemodynamically 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 events. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made.

Therapeutic indication

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery¹

■ Dosing recommendations

The recommended dose of apixaban is 2.5 mg (2.5 ml) taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window.

In patients undergoing **hip replacement surgery**, the recommended duration of treatment is **32 to 38 days**.

In patients undergoing **knee replacement surgery**, the recommended duration of treatment is **10 to 14 days**.

■ 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

Table 6:

Dose recommendation of apixaban for prevention of VTE in patients with 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

Table 7:

Dose recommendation of apixaban for prevention of VTE in patients with 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

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

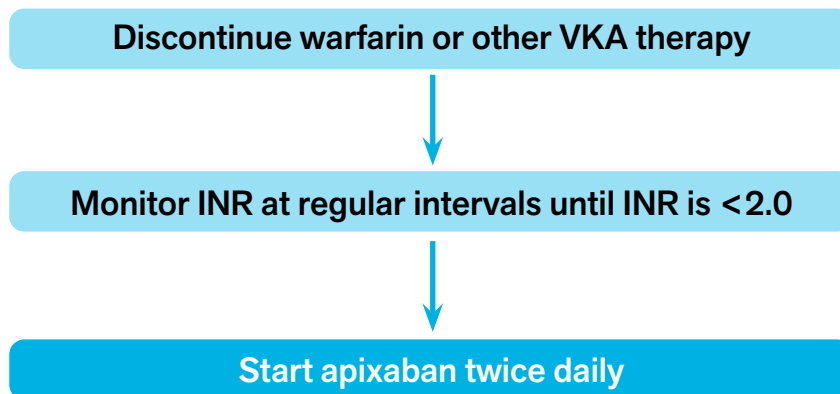
Switching to and from apixaban¹

Switching treatment from parenteral anticoagulants to apixaban (and vice versa) 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 patients from VKA therapy to apixaban, discontinue warfarin or other VKA therapy and start apixaban when the international normalised ratio (INR) is <2.0 (Figure 4).

Figure 4



■ 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 bleeding¹

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. Apixaban administration should be **discontinued** if severe haemorrhage occurs.

Table 8 Lesion or condition where the use of apixaban is contraindicated

Lesion or condition if considered a significant risk factor for major bleeding and where use is contraindicated
<p>This includes</p> <ul style="list-style-type: none"> ▪ 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

Table 9

Interactions with other medicinal products affecting haemostasis	
<p>Anticoagulants</p> <ul style="list-style-type: none"> ▪ Unfractionated heparin (UHF), low molecular weight heparins (e.g., enoxaparin, dalteparin), heparin derivatives (e.g., fondaparinux) ▪ Oral anticoagulants (e.g., warfarin, rivaroxaban, dabigatran) 	<p>Due to an increased bleeding risk, concomitant treatment with apixaban and any other anticoagulant agent is contraindicated, except under specific circumstances of switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter, or when UFH is given during catheter ablation for atrial fibrillation</p>
<p>Platelet aggregation inhibitors, SSRIs/ SNRIs and NSAIDs</p>	<p>The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding</p> <p>Apixaban should be used with caution when co-administered with selective serotonin reuptake inhibitors (SSRIs)/ serotonin norepinephrine reuptake inhibitors (SNRIs), non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA) and/or P2Y12 inhibitors (e.g., clopidogrel)</p> <p>There is limited experience of co-administration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfipyrazone) or thrombolytic agents. As such agents increase the bleeding risk, co-administration of these medicinal products with apixaban is not recommended</p>

Table 10

Factors which may increase apixaban exposure/increase apixaban plasma levels	
Renal impairment	<p>See sections on patients with renal impairment under dosing recommendations for each separate indication</p> <ul style="list-style-type: none"> 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 <p>Patients with NVAf</p> <ul style="list-style-type: none"> Patients with severe renal impairment (CrCl 15–29 ml/min) should receive the lower dose of apixaban 2.5 mg (2.5 ml) twice daily 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 apixaban 2.5 mg (2.5 ml) twice daily
Elderly	<ul style="list-style-type: none"> No dose adjustment required <p>Patients with NVAf</p> <ul style="list-style-type: none"> No dose adjustment required except in combination with other factors
Low body weight ≤ 60 kg	<ul style="list-style-type: none"> No dose adjustment required <p>Patients with NVAf</p> <ul style="list-style-type: none"> No dose adjustment required except in combination with other factors
Concomitant use with strong inhibitors of both CYP3A4 and P-gp	<ul style="list-style-type: none"> Apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as 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 CYP3A4 and P-gp	<ul style="list-style-type: none"> No dose adjustment for apixaban is required when co-administered with, for example, amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine and verapamil

Table 11

Factors which may reduce apixaban exposure/reduce apixaban plasma levels	
Concomitant use with strong inducers of both CYP3A4 and P-gp	<ul style="list-style-type: none"> The concomitant use of apixaban with strong inducers of both CYP3A4 and P-gp (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced apixaban plasma concentrations and should be used with caution <p>Treatment of DVT or PE</p> <ul style="list-style-type: none"> Apixaban is not recommended

Surgery and invasive procedure^{1,2}

Apixaban should be discontinued prior to elective surgery or invasive procedures (excluding cardioversion or catheter ablation) with a risk of bleeding (see table below).

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.

In the event a patient treated with apixaban requires an elective procedure, such as surgery or an invasive procedure associated with an increased risk of bleeding, 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 apixaban is approximately 12 hours. Given that apixaban is a reversible factor Xa inhibitor, its anticoagulant activity should abate within 24 to 48 hours from the last administered dose.

Table 12

Discontinuation of apixaban prior to elective surgery/invasive procedure	
Low risk of bleeding (includes interventions for which bleeding, if it occurs, will be minimal, noncritical in its location and/or easily controlled by simple mechanical haemostasis)	At least 24 hours prior to elective surgery or invasive procedure
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 procedure

Temporary discontinuation¹

Discontinuing anticoagulants, including 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 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 puncture¹

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 apixaban.

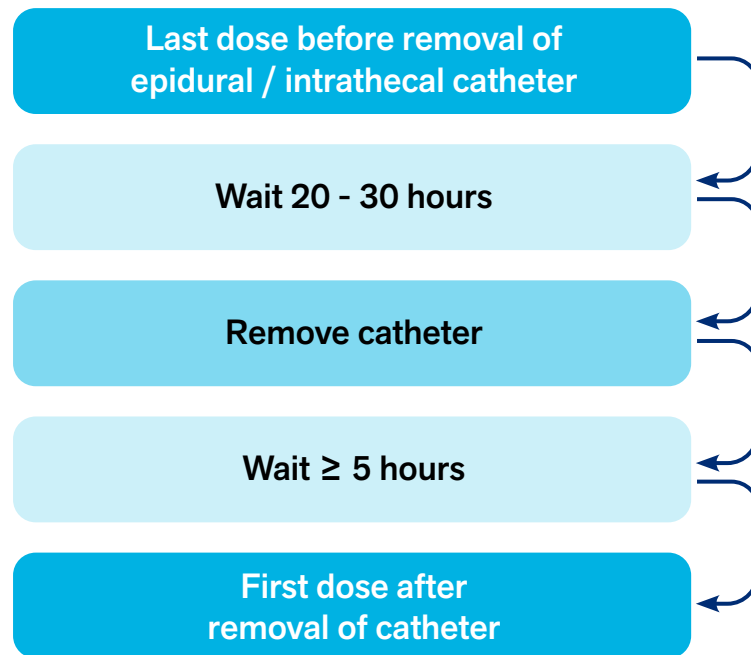
■ Guidance on the use of apixaban in patients with indwelling intrathecal or epidural catheters

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

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.

Figure 5

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



Management of overdose and haemorrhage¹

Overdose of 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, the transfusion of fresh frozen plasma, or the administration of a reversal agent for factor Xa inhibitors should be considered.

In controlled clinical studies, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse reactions.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of apixaban reduced mean AUC by 50% and 27%, respectively, and had no impact on C_{max}. Mean half-life decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of overdose or accidental ingestion.

For situations when reversal of anticoagulation is needed due to 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. Reversal of 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 apixaban. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving 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 apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Use of coagulation tests¹

Routine clinical monitoring is not required with apixaban treatment. However, a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of 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 apixaban.

In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

■ Anti-FXa assays

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. Data from clinical studies are only available for the Rotachrom® Heparin chromogenic assay. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is approximately linear over a wide dose range of apixaban.

Table 12 shows the predicted steady-state exposure and anti-FXa activity for each indication. In patients taking apixaban for the prevention of VTE following hip or knee replacement surgery, the results demonstrate a less than 1.6-fold fluctuation in peak-to-trough levels. In NVAf patients taking 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 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.

Table 13

Predicted apixaban steady-state exposure and anti-Factor Xa activity				
	apixaban C _{max} (ng/mL)	apixaban C _{max} (ng/mL)	apixaban anti- Factor Xa activity max (IU/mL)	apixaban anti- Factor Xa activity min (IU/mL)
	Median [5th, 95th percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg (2.5 ml) twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAf				
2.5 mg (2.5 ml) twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg (5 ml) 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				
2.5 mg (2.5 ml) twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg (5 ml) twice daily	132 [59, 302]	63 [22, 177] 1	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg (10 ml) twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

* Dose adjusted population based on at least 2 of 3 dose reduction criteria as shown in Figure 2.

References

1. Apixaban 1 mg/ml Oral Suspension Summary of Product Characteristics. Available at www.medicines.org.uk/emc
2. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis. *Archives of Cardiovascular Disease* 2011; 104: 669–676.

