

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

Rx

Apixaban Tablets 2.5mg / 5mg

SANOXABAN™ 2.5mg / 5mg

Qualitative and Quantitative Composition

Composition:

Each film-coated tablet contains:

Apixaban 2.5 mg

Excipient: q.s.

Colour used: Titanium dioxide IP & Ferric oxide yellow USP-NF

Each film-coated tablet contains:

Apixaban 5 mg

Excipient: q.s.

Colour used: Titanium dioxide IP & Ferric oxide red USP-NF

Dosage Form and Strengths

2.5 mg & 5 mg Film coated Tablets

Clinical particulars

Indications

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), including those with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class \geq II). Compared to warfarin, apixaban also results in less bleeding, including intracranial hemorrhage.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adult patients.

Posology and Method of Administration

Prevention of VTE (VTEp): elective hip or knee replacement surgery

The recommended dose of apixaban is 2.5 mg 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.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf)

The recommended dose of apixaban is 5 mg taken orally twice daily.

Dose reduction : The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAf and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)

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

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in Table 1 below.

Table 1: Dose recommendation (VTEt)

	Dosing Schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be individualized 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.

Switching : 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 vitamin K antagonist (VKA) therapy to apixaban, warfarin or other VKA therapy should be discontinued and apixaban started when the international normalised ratio (INR) is <2 .

Switching from apixaban to VKA therapy : When converting patients from apixaban to VKA therapy, administration of apixaban should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of apixaban with VKA therapy, an INR should be obtained prior to the next scheduled dose of apixaban. Coadministration of apixaban and VKA therapy should be continued until the INR is ≥ 2 .

Elderly

VTEp and VTEt – No dose adjustment required.

NVAF – No dose adjustment required, unless criteria for dose reduction are met.

Renal impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with end-stage renal disease on dialysis

In patients with ESRD maintained on intermittent hemodialysis, administration of apixaban at the usually recommended dose will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in clinical studies. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in clinical studies.

Prophylaxis of deep vein thrombosis following hip or knee replacement surgery, and treatment of DVT and PE and reduction in the risk of recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis. Clinical efficacy and safety studies with apixaban did not enroll patients with ESRD on dialysis or patients with a CrCl <15 ml/min: therefore dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis.

Hepatic impairment

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment.

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin \geq 1.5 x ULN were excluded in clinical studies. Therefore apixaban should be used with caution in this population. Prior to initiating apixaban, liver function testing should be performed.

Body weight

VTEp and VTEt - No dose adjustment required.

NVAF - No dose adjustment required, unless criteria for dose reduction are met.

Gender

No dose adjustment required.

Patients undergoing catheter ablation (NVAF)

Patients can continue apixaban use while undergoing catheter ablation.

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 initiating treatment with apixaban, 5 mg should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation. The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 single doses) if the patient meets the criteria for dose reduction.

If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction. The administration of the loading dose should be given at least 2 hours before cardioversion.

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.

Patients with NVAF and acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI)

There is limited experience of treatment with apixaban at the recommended dose for NVAF patients when used in combination with antiplatelet agents in patients with ACS and/or undergoing PCI after haemostasis is achieved.

Paediatric population

The safety and efficacy of apixaban in children and adolescents below age 18 have not been established. No data are available.

Surgery and invasive procedures

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted.

Method of administration

Oral use

Apixaban should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, apixaban tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, apixaban tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube.

Crushed apixaban tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Lesion or condition if considered a significant risk factor for major bleeding. This may include 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.
- Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) 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.

Special warnings and precautions for use

Increased risk of thrombotic events after premature discontinuation

Premature discontinuation of any oral anticoagulant, including apixaban, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from apixaban to warfarin in clinical trials in atrial fibrillation patients. If apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Bleeding

Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue apixaban in patients with active pathological hemorrhage.

Reversal of anticoagulant effect

The pharmacodynamic effect of apixaban can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (Factor Xa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration.

Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

Spinal/epidural anesthesia or puncture

When neuraxial anesthesia (spinal/epidural anesthesia) 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 hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of apixaban. The next dose of apixaban should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of apixaban for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with prosthetic heart valves

The safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves. Therefore, use of apixaban is not recommended in these patients.

Acute PE in hemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.

Initiation of apixaban is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

Increased risk of thrombosis in patients with triple positive antiphospholipid syndrome

Direct-acting oral anticoagulants (DOACs), including apixaban, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-β₂-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Hip fracture surgery

Apixaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, it is not recommended in these patients.

Laboratory parameters

Clotting tests [e.g., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)] are affected as expected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability.

Information about excipients : Apixaban Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drugs interactions

Inhibitors of CYP3A4 and P-gp

Coadministration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max}.

The use of 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)..

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp (e.g., amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for apixaban is required when coadministered with agents that are not strong inhibitors of both CYP3A4 and P-gp. For example, diltiazem (360 mg once a day), considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4 fold increase in mean apixaban AUC and a 1.3 fold increase in C_{max}. Naproxen (500 mg, single dose), an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. Clarithromycin (500 mg, twice a day),

an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean apixaban AUC and C_{max} respectively.

Inducers of CYP3A4 and P-gp

Coadministration of apixaban with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and C_{max} , respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such medicinal products, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp apixaban should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE.

Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised.

Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants 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.

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was coadministered with ASA 325 mg once a day.

Apixaban coadministered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and ASA 162 mg once daily or with prasugrel (60 mg followed by 10 mg once daily) in Phase 1 studies did not show a relevant increase in template bleeding time or further inhibition of platelet aggregation compared to administration of the antiplatelet agents without apixaban. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of apixaban alone.

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max} , respectively. Corresponding increases in clotting tests were observed for apixaban. No changes were observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are coadministered with apixaban. Apixaban should be used with caution when coadministered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicinal products typically increase the bleeding risk.

There is limited experience of coadministration 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, coadministration of these medicinal products with apixaban is not recommended.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was coadministered with atenolol or famotidine. Coadministration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two medicinal products together, mean apixaban AUC and C_{max} were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max} .

Effect of apixaban on other medicinal products

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 ($IC_{50} >45 \mu M$) and weak inhibitory effect on the activity of CYP2C19 ($IC_{50} >20 \mu M$) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM . Therefore, apixaban is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes. Apixaban is not a significant inhibitor of P-gp.

In studies conducted in healthy subjects, as described below, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin

Coadministration of apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, did not affect digoxin AUC or C_{max} . Therefore, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen

Coadministration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max} .

Atenolol

Coadministration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta blocker, did not alter the pharmacokinetics of atenolol.

Activated charcoal

Administration of activated charcoal reduces apixaban exposure.

Use in special populations

Pregnancy

There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of apixaban during pregnancy.

Breast-feeding

It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from apixaban therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies in animals dosed with apixaban have shown no effect on fertility.

Effects on ability to drive and use machines

Apixaban has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

Common adverse reactions were haemorrhage, contusion, epistaxis, and haematoma (see Table 2 for adverse reaction profile and frequencies by indication).

Tabulated list of adverse reactions

Table 2 shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data) for VTEp, NVAf and VTEt respectively.

Table 2: Tabulated adverse reactions

System Organ Class	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)	Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors (NVAf)	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)
<i>Blood and lymphatic system disorders</i>			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
<i>Immune system disorders</i>			

Hypersensitivity, allergic oedema and Anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon*
Angioedema	Not known	Not known	Not known
<i>Nervous system disorders</i>			
Brain haemorrhage†	Not known	Uncommon	Rare
<i>Eye disorders</i>			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
<i>Vascular disorders</i>			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon
Intra-abdominal haemorrhage	Not known	Uncommon	Not known
<i>Respiratory, thoracic and mediastinal disorders</i>			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
<i>Respiratory tract haemorrhage</i>	Not known	Rare	Rare
<i>Gastrointestinal disorders</i>			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidal haemorrhage	Not known	Uncommon	Uncommon
Mouth haemorrhage	Not known	Uncommon	Common
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	Not known	Rare	Not known
<i>Hepatobiliary disorders</i>			
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon
Gamma-glutamyltransferase increased	Uncommon	Common	Common
Alanine aminotransferase increased	Uncommon	Uncommon	Common
<i>Skin and subcutaneous tissue disorders</i>			
Skin rash	Not known	Uncommon	Common
Alopecia	Rare	Uncommon	Uncommon
Erythema multiforme	Not known	Very rare	Not known
Cutaneous vasculitis	Not known	Not known	Not known
<i>Musculoskeletal and connective tissue disorders</i>			
Muscle haemorrhage	Rare	Rare	Uncommon
<i>Renal and urinary disorders</i>			
Haematuria	Uncommon	Common	Common
<i>Reproductive system and breast disorders</i>			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common
<i>General disorders and administration site conditions</i>			
Application site bleeding	Not known	Uncommon	Uncommon
<i>Investigations</i>			
Occult blood positive	Not known	Uncommon	Uncommon
<i>Injury, poisoning and procedural complications</i>			
Contusion	Common	Common	Common
Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site	Uncommon	Uncommon	Uncommon

haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage			
Traumatic haemorrhage	Not known	Uncommon	Uncommon

* There were no occurrences of generalised pruritus in CV185057 (long term prevention of VTE)

† The term “Brain haemorrhage” encompasses all intracranial or intraspinal haemorrhages (i.e., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).

The use of apixaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding.

Overdose

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 or the transfusion of fresh frozen plasma 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 (bid) for 7 days or 50 mg once daily (od) 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 apixaban AUC by 50% and 27%, respectively, and had no impact on C_{max} . Mean half-life of apixaban 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 apixaban overdose or accidental ingestion.

The pharmacodynamic effect of apixaban can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies. 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, a consultation of a coagulation expert should be considered in case of major bleedings.

Haemodialysis decreased apixaban AUC by 14% in subjects with end-stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Mechanism of action

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF02.

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

Pharmacodynamics properties

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (Factor Xa inhibition). As a result of Factor Xa 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 pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-Factor Xa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-Factor Xa kits, however results differ across kits.

Table 3 below shows the predicted steady state exposure and anti-Factor Xa 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 non-valvular atrial fibrillation 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 3: Predicted apixaban steady-state exposure and anti-xa activity

	Apix. C_{max} (ng/mL)	Apix. C_{min} (ng/mL)	Apix. anti-Xa activity max (IU/mL)	Apix. anti-Xa activity min (IU/mL)
	Median [5 th , 95 th percentile]			
<i>Prevention of VTE: elective hip or knee replacement surgery</i>				

2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
<i>Prevention of stroke and systemic embolism: NVAf</i>				
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]
<i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)</i>				
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]

* Dose adjusted population based on 2 of 3 dose reduction criteria in the ARISTOTLE study.

Although treatment with apixaban does not require routine monitoring of exposure, 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.

Pharmacokinetic properties

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Given the predictable, dose-proportional pharmacokinetic profile of apixaban, the bioavailability results from the conducted studies are applicable to lower apixaban doses.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (V_{ss}) is approximately 21 litres.

Biotransformation and elimination

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major active substance related

component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

Elderly

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher and no difference in C_{max} .

Renal impairment

There was no impact of impaired renal function on peak concentration of apixaban. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51–80 mL/min), moderate (creatinine clearance 30–50 mL/min) and severe (creatinine clearance 15–29 mL/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44%, respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-Factor Xa activity.

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36% when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14% in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment

In a study comparing 8 subjects with mild hepatic impairment, Child Pugh A score 5 (n = 6) and score 6 (n = 2), and 8 subjects with moderate hepatic impairment, Child-Pugh B score 7 (n = 6) and score 8 (n = 2), to 16 healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-Factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Gender

Exposure to apixaban was approximately 18% higher in females than in males.

Ethnic origin and race

The results across phase I studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects. Findings from a population pharmacokinetic analysis in patients who received apixaban were generally consistent with the phase I results.

Body weight

Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight >120 kg was associated with approximately 30% lower exposure and body weight <50kg was associated with approximately 30% higher exposure.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-Factor Xa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5-50 mg). The relationship between apixaban plasma concentration and anti-Factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

Storage and handling instructions

Do not store above 30°C.

Manufactured by

MSN Laboratories Private Limited, (Formulations Division)
Unit-II, Sy.No. 1277, 1319 to 1324, Nandigama (Village &
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