



XAVI
APIXABAN

1. NAME OF THE MEDICINAL PRODUCT

XAVI 2.5 mg Film-Coated Tablets

XAVI 5 mg Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.5 mg: Each film-coated tablet contains 2.5 mg of apixaban.

5 mg: Each film-coated tablet contains 5 mg of apixaban.

Excipients with known effect:

Each 2.5 mg film-coated tablet contains 75.43 mg lactose.

Each 5 mg film-coated tablet contains 150.86 mg lactose.

3. PHARMACEUTICAL FORM

2.5 mg: Yellow, round tablets, debossed with "L51" on one side and plain on the other side.

5mg: Pink, oval tablets, debossed with "L52" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For 2.5 mg

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

For 2.5 mg and 5 mg

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA), age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (WHIA Class ≥ II), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults for haemodynamically unstable PE patients.

4.2 Posology and method of administration

Posology

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 (VTEr)

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 (VTEr)

	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 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.

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 co-administration of apixaban with VKA therapy, an INR should be obtained prior to the next scheduled dose of apixaban. Co-administration of apixaban and VKA therapy should be continued until the INR is ≥ 2.

Elderly

VTEp and VTEr - No dose adjustment required.

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

Renal impairment

In patients with mild or moderate renal impairment, the following recommendations apply:

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp) - for Apixaban 2.5mg, for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEr), no dose adjustment is necessary.
- for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary.

In patients with severe renal impairment (creatinine clearance 15–29 mL/min) the following recommendations apply:

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp) - for Apixaban 2.5mg, for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEr) apixaban is to be used with caution;
- for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg twice daily.

In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended.

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 ≥ 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 VTEr - 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. transeophageal 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.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of its 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 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.

4.4 Special warnings and precautions for use

Haemorrhage risk

As with other anticoagulants, patients taking apixaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Apixaban administration should be discontinued if severe haemorrhage occurs.

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.

Interaction with other medicinal products affecting haemostasis

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

The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding.

Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory medicinal products (NSAIDs), including acetylsalicylic acid.

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with apixaban.

In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with apixaban.

In a clinical study of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical study, there was limited (21%) use of concomitant dual antiplatelet therapy.

A clinical study enrolled patients with atrial fibrillation with ACS and/or undergoing PCI and a planned treatment period with a P2Y12 inhibitor, with or without ASA, and oral anticoagulant (either apixaban or VKA) for 6 months. Concomitant use of ASA increased the risk of ISTH (International Society on Thrombosis and Hemostasis) major or CRNM (Clinically Relevant Non-Major) bleeding in apixaban-treated subjects from 16.4% per year to 33.1% per year.

In a clinical study of high-risk post-acute coronary syndrome patients without atrial fibrillation, characterised by major cardiac and non-cardiac comorbidities, who received ASA or 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 I studies did not show a relevant increase in platelet 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.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply:

- 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 should be used with caution;
- for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

Hip fracture surgery

Apixaban has not been studied in the reported clinical studies 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 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4 and P-gp

Co-administration 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 co-administered 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

Co-administration 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 co-administered with ASA 325 mg once a day. Apixaban co-administration 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 I studies did not show a relevant increase in platelet 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 that are co-administered with apixaban. Apixaban should be used with caution when co-administered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicinal products typically increase the bleeding risk.

There is limited experience of co-administration with other platelet aggregation inhibitors (such as GIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfapyrazone) or thrombolytic agents. As such agents increase the bleeding risk, co-administration of these medicinal products with apixaban is not recommended.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or fentanyl. Co-administration 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 fentanyl 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 (IC₅₀ > 45 μM) and weak inhibitory effect on the activity of CYP2C19 (IC₅₀ > 20 μM) 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 co-administered 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

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

Naproxen

Co-administration 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

Co-administration 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.

4.6 Fertility, pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Common adverse reactions were haemorrhage, contusion, epistaxis, and haematoma.

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)
Blood and lymphatic system disorders			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
Immune system disorders			
Hypersensitivity, allergic oedema and Anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon*
Angioedema	Not known	Not known	Not known
Nervous system disorders			
Brain haemorrhage†	Not known	Uncommon	Rare
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
Vascular disorders			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon
Intraabdominal haemorrhage	Not known	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	Not known	Rare	Rare
Gastrointestinal disorders			
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
Retropitoneal haemorrhage	Not known	Rare	Not known
Hepatobiliary disorders			
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon
Gammaglutamyltransferase increased	Uncommon	Common	Common
Alanine aminotransferase increased	Uncommon	Uncommon	Common
Skin and subcutaneous tissue disorders			
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
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	Rare	Uncommon
Renal and urinary disorders			
Haematuria	Uncommon	Common	Common
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common
General disorders and administration site conditions			
Application site bleeding	Not known	Uncommon	Uncommon
Investigations			
Occult blood positive	Not known	Uncommon	Uncommon
Injury, poisoning and procedural complications			
Contusion	Common	Common	Common
Traumatic haemorrhage	Not known	Uncommon	Uncommon
Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage	Uncommon	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 post-haemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding.

4.9 Overdose

There is no antidote to apixaban available in Malaysia. 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.

For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, 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, 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

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. Available 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

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa 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 clotting in human plasma.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa 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-Factor Xa 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 3 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-Factor Xa activity

	Apix. C _{max} (ng/mL)	Apix. C _{min} (ng/mL)	Apix. anti-Factor Xa activity max (IU/mL)	Apix. anti-Factor Xa activity min (IU/mL)
Median [5th, 95th percentile]				
Prevention of VTE: elective hip or knee replacement surgery				
2.5mg twice daily	77 [41, 146]	51 [23, 109]	13 [0.67, 2.4]	0.84 [0.37, 1.8]
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 [69, 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.

5.2 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.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was comparable to exposure after oral administration of 2 whole 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets with 30 g of apple puree, the C_{max} and AUC were 21% and 16% lower, respectively, when compared to administration of 2 whole 5 mg tablets. The reduction in exposure is not considered clinically relevant.

Following administration of a crushed 5 mg apixaban tablet suspended in 80 mL of GSW and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical studies involving apixaban tablets administered as a single oral 5 mg apixaban tablet dose.

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 routes 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-FXa 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

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 < 50 kg 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-FXa 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose anhydrous
Croscarmellose sodium
Poloxamer 407
Magnesium Stearate
Film coat
Hypromellose
Lactose monohydrate
Titanium dioxide
Triacetin
Iron oxide yellow for 2.5 mg
Iron oxide red for 5 mg

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Product should not be used beyond the expiry date imprinted on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and content of container

2.5mg:
10's Alu-PVC/PVDC Blister Pack
5mg:
10's Alu-PVC/PVDC Blister Pack
14's Alu-PVC/PVDC Blister Pack

6.6 Special precautions for disposal

Any unused medicinal product or waste should be disposed of in accordance with local requirements.

KEEP MEDICINE OUT OF REACH OF CHILDREN

JAUHI UBAT-UBATAN DARIPADA KANAK-KANAK

For further information, please consult your doctor or your pharmacist.

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PRODUCT REGISTRATION HOLDER

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