1. NAME OF THE MEDICINAL PRODUCT

Xagulant 2.5 mg (Apixaban Film Coated Tablets)

Xagulant 5 mg (Apixaban Film Coated Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.5 mg

Each film-coated tablet contains 2.5 mg Apixaban.

Excipients with known effect:

Each 2.5 mg film-coated tablet contains 51.8 mg lactose (**see section 4.4 Special Warnings and Precautions for Use**).

5 mg

Each film-coated tablet contains 5.0 mg Apixaban.

Excipients with known effect:

Each 5 mg film-coated tablet contains 103.5 mg lactose (**see section 4.4 Special Warnings and Precautions for Use**).

For the full list of excipients, **see section 6.1 List of Excipients**.

3. PHARMACEUTICAL FORM

2.5 mg

Brown, film-coated, round, biconvex, beveled edge tablet debossed with X 2 on one side of the tablet and M on other side.

5 mg

Brown, film-coated, oval, biconvex, beveled edge tablet, debossed with X 5 on one side of the tablet and M on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

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 (NYHA Class ≥II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (**see section 4.4 Special Warnings and Precautions for Use**) 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 Xagulant 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 Xagulant is 5 mg taken orally twice daily.

Dose reduction

The recommended dose of Xagulant 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 Xagulant 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 Xagulant 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 Xagulant 5 mg twice daily or with another anticoagulant, as indicated in Table 1 below (**see also section 5.1 Pharmacodynamic Properties**).

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 individualised after careful assessment of the treatment benefit against the risk for bleeding (**see section 4.4 Special Warnings and Precautions for Use**).

Missed dose

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

Switching

Switching treatment from parenteral anticoagulants to Xagulant (and *vice versa*) can be done at the next scheduled dose (**see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**). These medicinal products should not be administered simultaneously.

Switching from vitamin K antagonist (VKA) therapy to Xagulant

When converting patients from vitamin K antagonist (VKA) therapy to Xagulant, warfarin or other VKA therapy should be discontinued and Xagulant started when the international normalised ratio (INR) is <2.

Switching from Xagulant to VKA therapy

When converting patients from Xagulant to VKA therapy, administration of Xagulant should be continued for at least 2 days after beginning VKA therapy. After 2 days of co-administration of Xagulant with VKA therapy, an INR should be obtained prior to the next scheduled dose of Xagulant. Co-administration of Xagulant and VKA therapy should be continued until the INR is ≥2.0.

Elderly

VTEp and VTEt – No dose adjustment required (**see sections 4.4 Special Warnings and Precautions for Use** and **5.2 Pharmacokinetic Properties**).

NVAF – No dose adjustment required, unless criteria for dose reduction are met (**see *Dose reduction* at the beginning of section 4.2 Posology and Method of Administration**).

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 2.5 mg, for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary (**see section 5.2 Pharmacokinetic Properties**).

- 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 (**see section 5.2 Pharmacokinetic Properties**).

In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply (**see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties**):

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp) – for apixaban 2.5 mg, for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) 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 (**see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties**).

Hepatic impairment

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (**see section 4.3 Contraindications**).

It is not recommended in patients with severe hepatic impairment (**see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties**).

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 (**see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties**).

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥1.5 x ULN were excluded. Therefore Xagulant should be used with caution in this population (**see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties**). Prior to initiating Xagulant, liver function testing should be performed.

Body weight

VTEp and VTEt - No dose adjustment required (**see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties**).

NVAF - No dose adjustment required, unless criteria for dose reduction are met (**see *Dose reduction* at the beginning of section 4.2 Posology and Method of Administration**).

Gender

No dose adjustment required (**see section 5.2 Pharmacokinetic Properties**).

Patients undergoing catheter ablation (NVAF)

Patients can continue apixaban use while undergoing catheter ablation (**see sections 4.3 Contraindications**, **4.4 Special Warnings and Precautions for Use and 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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 (**see section 5.1 Pharmacodynamic Properties**). 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 (**see above sections *Dose reduction* and *Renal impairment***).

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 (**see above sections *Dose reduction* and *Renal impairment***). The administration of the loading dose should be given at least 2 hours before cardioversion (**see section 5.1 Pharmacodynamic Properties**).

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 (**see sections 4.4 Special Warnings and Precautions for Use** and **5.1 Pharmacodynamic Properties**).

Paediatric population

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

Method of administration

Oral use.

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

For patients who are unable to swallow whole tablets, Xagulant 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 (**see section 5.2 Pharmacokinetic Properties**). Alternatively, Xagulant tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube (**see section 5.2 Pharmacokinetic Properties**).

Crushed Xagulant 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 the excipients listed in **section 6.1 List of Excipients**.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (**see section 5.2 Pharmacokinetic Properties**).

- 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 (**see section 4.2 Posology and Method of Administration**), 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 (**see sections 4.4 Special Warnings and Precautions for Use** and **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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 (**see sections 4.8 Undesirable Effects** and **4.9 Overdose**).

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 (**see section 5.1 Pharmacodynamic Properties**).

Interaction with other medicinal products affecting haemostasis

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (**see section 4.3 Contraindications**).

The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding (**see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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 drugs (NSAIDs), including acetylsalicylic acid.

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with apixaban (**see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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.

Concomitant use of ASA increased the major bleeding risk on apixaban and increased the bleeding risk on warfarin. There was limited use of concomitant dual antiplatelet therapy.

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.

A significant increase in risk of ISTH major bleeding was reported for apixaban compared to placebo.

Use of thrombolytic agents for the treatment of acute ischemic stroke

There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered apixaban (**see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Patients with prosthetic heart valves

The use of apixaban is not recommended in patients with prosthetic heart valves.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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 cardioversion **see section 4.2 Posology and Method of Administration**).

For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted (**see sections 4.2 Posology and Method of Administration, 4.3 Contraindications and 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Temporary discontinuation

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.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Apixaban. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary.

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.

There is no experience with the use of apixaban with indwelling intrathecal or epidural catheters. In case there is such need and based on the general PK characteristics of apixaban, a time interval of 20-30 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 new anticoagulant medicinal products, experience with neuraxial blockade is limited and extreme caution is therefore, recommended when using apixaban in the presence of neuraxial blockade.

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 pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of apixaban have not been established in these situations.

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 (**see also section 4.3 Contraindications**).

Patients with renal impairment

Apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15-29 mL/min) which may lead to an increased bleeding risk. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min) (**see sections 4.2 Posology and Method of Administration and 5.2 Pharmacokinetic Properties**).

For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥1.5 mg/dL (133 micromole/L) associated with age ≥80 years or body weight ≤60 kg should receive the lower dose of apixaban 2.5 mg twice daily (**see section 4.2 Posology and Method of Administration**).

In patients with creatinine clearance <15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore, apixaban is not recommended (**see sections 4.2 Posology and Method of Administration and 5.2 Pharmacokinetic Properties**).

Elderly patients

Increasing age may increase haemorrhagic risk (**see section 5.2 Pharmacokinetic Properties**).

Also, the co-administration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Body weight

Low body weight (<60 kg) may increase haemorrhagic risk (**see section 5.2 Pharmacokinetic Properties**).

Patients with hepatic impairment

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (**see section 4.3 Contraindications**).

It is not recommended in patients with severe hepatic impairment (**see section 5.2 Pharmacokinetic Properties**).

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (**see sections 4.2 Posology and Method of Administration and 5.2 Pharmacokinetic Properties**).

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 (**see section 5.2 Pharmacokinetic Properties**). Prior to initiating Xagulant, liver function testing should be performed.

Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)

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). These medicinal products may increase apixaban exposure by 2-fold (**see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**) or greater in the presence of additional factors that increase apixaban exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's Wort) may lead to a ~50% reduction in apixaban exposure. Diminished efficacy and a higher risk of bleeding were observed with co-administration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (**see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

- 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 is not recommended in patients undergoing hip fracture surgery.

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 (**see section 5.1 Pharmacodynamic Properties**).

Information about excipients

Xagulant 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 (23 mg) 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 Cmax.

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) (**see section 4.4 Special Warnings and Precautions for Use**).

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 Cmax. 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 Cmax, 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 Cmax 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 Cmax, 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 (**see section 4.4 Special Warnings and Precautions for Use**).

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 (**see section 4.3 Contraindications**).

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-administered 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) 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 Cmax, 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 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 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 (**see section 4.4 Special Warnings and Precautions for Use**).

There is limited experience of co-administration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfinpyrazone) or thrombolytic agents. As such agents increase the bleeding risk, co-administration of these medicinal products with apixaban is not recommended (**see section 4.4 Special Warnings and Precautions for Use**).

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. 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 Cmax 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 Cmax.

Effect of apixaban on other medicinal products

There was 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.

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 or Cmax. Therefore, apixaban does not inhibit Pgp 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 Cmax.

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 (**see section 4.9 Overdose**).

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no data from the use of apixaban in pregnant women. 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. 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

Apixaban have shown no effect on fertility.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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)**
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

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)
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
Intra-abdominal 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
Retroperitoneal haemorrhage	Not known	Rare	Not known

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)
Hepatobiliary disorders			
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
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

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)
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
Traumatic haemorrhage	Not known	Uncommon	Uncommon

* There were no occurrences of generalized 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 (**see sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties**).

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.

Administration of activated charcoal 2 and 6 hours after ingestion of a 20mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively, and had no impact on Cmax. 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. However, there is no 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. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

Pharmacodynamic effects

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 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. 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-Factor Xa activity is approximately linear over a wide dose range of apixaban.

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-totrough 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-totrough 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				
2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
	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)**
Prevention of stroke and systemic embolism: NVAF				

2.5 mg twice daily	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg twice daily	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg twice daily	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

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 (Cmax) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or Cmax 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 Cmax 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 60 mL of G5W and delivered via a nasogastric tube, exposure was similar to exposure seen in healthy subjects receiving a single oral 5 mg apixaban tablet dose.

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

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) 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.

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 Cmax.

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 1529 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

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

There is no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects.

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 <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-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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Lactose anhydrous
Microcrystalline cellulose
Sodium lauryl sulfate
Croscarmellose sodium
Magnesium stearate

Film coat:
Hypromellose
Polyethylene glycol
Sodium lauryl sulfate
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Please refer to outer carton.

6.4 Special Precautions for Storage

Do not store above 30°C. Store in the original container.

Keep out of the sight and reach of children.

6.5 Nature and Content of Container

For 2.5 mg:

Alu-PVC/PVdC blisters. Cartons of 2x10's and 3x10's film-coated tablets.

For 5 mg:

Alu-PVC/PVdC blisters. Cartons of 2x10's and 6x10's film-coated tablets.

Some product strengths or pack sizes may not be available in your country.

6.6 Special Precautions for Disposal

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

7. MANUFACTURER AND PACKAGER

Mylan Laboratories Limited
Plot No. H12 and H13,
Midc Waluj Industrial Area, Aurangabad
431136, India.

8. Product Registration Holder

Mylan Healthcare Sdn Bhd
15-03 & 15-04, Level 15, Imazium,
No. 8, Jalan SS 21/37, Damansara Uptown,
47400, Petaling Jaya, Selangor, Malaysia.

Date of Revision: March 2025

Font: Arial Size: 10