For Use of a Registered Medical Practitioner only

WARNING: (A) PREMATURE DISCONTINUATION OF XAPILIS INCREASES THE RISK OF THROMBOTIC EVENTS (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF XAPILIS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including XAPILIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if XAPILIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with XAPILIS who are receiving neuraxial anaesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

1. Generic Name and Brand Name

Apixaban Tablets 2.5 mg
Xapilis™ 2.5

Apixaban Tablets 5 mg
Xapilis™ 5

2. Qualitative and quantitative composition

Xapilis™ 2.5
Each film coated tablet contains**:**
Apixaban……..2.5 mg
Excipients……q.s.
Colours: Ferric Oxide USP-NF (Yellow), Titanium Dioxide I.P.

Xapilis™ 5
Each film coated tablet contains**:**
Apixaban 5 mg
Excipients q.s.
Colours: Ferric Oxide USP-NF (Red), Titanium Dioxide I.P.

3. Dosage form and strength

Tablets and 2.5 mg & 5 mg

4. Clinical particulars

4.1 Therapeutic indication

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 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.

4.2 Posology and method of administration

Posology

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

The recommended dose of Apixaban for most patients is 5 mg taken orally twice daily.

The recommended dose of Apixaban 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

Prophylaxis of Deep Vein Thrombosis Following 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.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

The recommended dose of Apixaban is 10 mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of Apixaban is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE

Missed Dose

If a dose of Apixaban is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Temporary Interruption for Surgery and Other Interventions

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping Apixaban and prior to the intervention is not generally required. Apixaban should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established.

Converting from or to Apixaban

Switching from warfarin to Apixaban*:* Warfarin should be discontinued and Apixaban started when the international normalized ratio (INR) is below 2.0.

Switching from Apixaban to warfarin: Apixaban affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue Apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of Apixaban would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching from Apixaban *to anticoagulants other than warfarin (oral or parenteral):* Discontinue Apixaban and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of Apixaban.

Switching from anticoagulants other than warfarin (oral or parenteral) to Apixaban*:* Discontinue the anticoagulant other than warfarin and begin taking Apixaban at the usual time of the next dose of the anticoagulant other than warfarin.

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.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving Apixaban doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when Apixaban is coadministered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, Itraconazole, ritonavir)

In patients already taking 2.5 mg twice daily, avoid coadministration of Apixaban with combined P-gp and strong CYP3A4 inhibitors

Method of administration

For 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 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

4.4 Special warnings and precautions for use

Hemorrhage 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

An agent to reverse the anti-factor Xa activity of apixaban is available.

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 (2.1%) 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 multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).

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.

Patients with prosthetic heart valves

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

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

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.

Elderly patients

Increasing age may increase haemorrhagic risk

Body weight

Low body weight (< 60 kg) may increase haemorrhagic risk

Patients with 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)

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

4.5 Drugs interactions

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to Apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to Apixaban and increase the risk of stroke and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving Apixaban 5 mg or 10 mg twice daily, the dose of Apixaban should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, Iitraconazole, ritonavir)

For patients receiving Apixaban at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with Apixaban

Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of APIXABAN with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to Apixaban.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.
APPRAISE-2, a placebo-controlled clinical trial of APIXABAN in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with APIXABAN compared to placebo. The rate

of ISTH major bleeding was 2.8% per year with APIXABAN versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with APIXABAN versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on APIXABAN from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with Apixaban

4.6 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

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

Like all medicines, this medicine can cause side effects, although not everybody gets them. Apixaban can be given for three different medical conditions. The known side effects and how frequently they occur for each of these medical conditions may differ and are listed separately below. For these conditions, the most common general side effect of this medicine is bleeding which may be potentially life threatening and require immediate medical attention.

The following side effects are known if you take Apixaban to prevent blood clots from forming after hip or knee replacement operations.

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
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
Hepatobiliary disorders			
Liver function test abnormal, asparate 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
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 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

4.9 Overdose

Overdose of Apixaban increases the risk of bleeding. In controlled clinical trials, orally administered Apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, 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. Thus,

administration of activated charcoal may be useful in the management of Apixaban overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of Apixaban is available.

5. Pharmacological properties

5.1 Mechanism of action

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on Platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, Apixaban decreases thrombin generation and thrombus development.

5.2 Pharmacodynamic properties

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, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF.

This test is not recommended for assessing the anticoagulant effect of Apixaban.

Effect of PCCs on Pharmacodynamics of Apixaban

There is no clinical experience to reverse bleeding with the use of 4-factor PCC products in individuals who have received Apixaban.

Effects of 4-factor PCCs on the pharmacodynamics of apixaban were studied in healthy subjects. Following administration of apixaban dosed to steady state, endogenous thrombin potential (ETP) returned to pre-apixaban levels 4 hours after the initiation of a 30-minute PCC infusion, compared to 45 hours with placebo. Mean ETP levels continued to increase and exceeded pre-apixaban levels reaching a maximum (34%-51% increase over pre-apixaban levels) at 21 hours after initiating PCC and remained elevated (21%-27% increase) at the end of the study (69 hours after initiation of PCC). The clinical relevance of this increase in ETP is unknown.

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel. A 50% to 60% increase in anti-FXa activity was observed when Apixaban was coadministered with enoxaparin or naproxen.

Specific Populations

Renal impairment: Anti-FXa activity adjusted for exposure to Apixaban was similar across renal function categories.

Hepatic impairment: Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

Cardiac Electrophysiology
Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

5.3 Pharmacokinetic properties
Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

Absorption
The absolute bioavailability of Apixaban is approximately 50% for doses up to 10 mg of Apixaban Food does not affect the bioavailability of Apixaban. Maximum concentrations (Cmax) of Apixaban appear 3 to 4 hours after oral administration of Apixaban. At doses ≥ 25 mg, Apixaban displays dissolution-limited absorption with decreased bioavailability. Following oral administration of 10 mg of Apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was similar to that after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of Apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the Cmax and AUC were 20% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets. Following administration of a crushed 5 mg Apixaban tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube, exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose

Distribution
Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 Liters.

Metabolism
Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.

Unchanged Apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Excretion
Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces. Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

6 Nonclinical properties

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-foetal development and juvenile toxicity.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of Apixaban on blood coagulation parameters. In the toxicity studies little to no increase of bleeding tendency was found.

However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

In rat milk, a high milk to maternal plasma ratio (Cmax about 8, AUC about 30) was found, possibly due to active transport into the milk.

7 Description

Xapilis 2.5:

Xapilis 2.5 is supplied for oral administration, as a film coated tablet of Apixaban. Each film coated tablet of Xapilis 2.5 contains Apixaban 2.5 mg.

Xapilis 5:

Xapilis 5 is supplied for oral administration, as a film coated tablet of Apixaban. Each film coated tablet of Xapilis 5 contains Apixaban 5 mg.

8 Pharmaceutical particulars

8.3 Incompatibilities

Not applicable

8.4 Shelf life

Refer pack

8.5 Packaging information

Refer Pack

8.6 Storage and handing instructions

Refer Pack

9 Patient counseling information

Advise patients of the following:

- Not to discontinue Apixaban without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with Apixaban. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking Apixaban, and/or any other product known to affect bleeding (including non - prescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas. If any of these symptoms occur, advise the patient to seek emergent medical attention.

- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with Apixaban.

10 Details of manufacturer

Refer Pack for manufacturer details

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 &
211 to 216 2nd Floor, Pimplas,
Dist. Thane, Bhiwandi - 421 302, Maharashtra, India.

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11 Details of permission or License number with date

Refer Pack for Permission/License details

12 Date of Revision

Version No. 2.0, dated 07/05/2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com