Apixaban Tablets

Eliquis®

1. GENERIC NAME

Apixaban

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each film-coated tablet contains: Apixaban 2.5 mg
Excipient: q.s.
Colour used: Titanium dioxide USP & Iron oxide yellow USP-NF

Each film-coated tablet contains: Apixaban 5 mg
Excipient: q.s.
Colour used: Titanium dioxide USP & Iron oxide red USP-NF

List of Excipients:

Tablet Core - anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate.

Film Coat - lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

3. DOSAGE FORM AND STRENGTH

2.5 mg & 5 mg Film coated Tablets

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 ischaemic 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

Prevention of VTE (VTEp): elective hip or knee replacement surgery
The recommended dose of apixaban is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

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

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

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

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
The recommended dose of apixaban is 5 mg taken orally twice daily.

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

Therapy should be continued long term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)
The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days, followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in Table 1 below (see also section 5.2).

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).

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 (see section 4.5). These medicinal products should not be administered simultaneously.

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

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

Elderly
VTEp and VTEt – No dose adjustment required (see sections 4.4 and 5.3).

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

Renal impairment

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

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics (see section 4.2):

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

Patients with end-stage renal disease on dialysis

Clinical efficacy and safety studies with apixaban did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of apixaban at the usually recommended dose (see section 4.2) will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study (see section 5.2). It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

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

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis (see section 4.2). Clinical efficacy and safety studies with apixaban did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis (see section 5.2).

Hepatic impairment

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

It is not recommended in patients with severe hepatic impairment (see sections 4.4. and 5.3).

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 and 5.3).

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 (see sections 4.4 and 5.3). Prior to initiating apixaban, liver function testing should be performed.

Body weight

VTEp and VTEt - No dose adjustment required (see sections 4.4 and 5.3).

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

Gender
No dose adjustment required (see section 5.3).

Patients undergoing catheter ablation (NVAF)
Patients can continue apixaban use while undergoing catheter ablation (see sections 4.3, 4.4 and 4.5).

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 5.2). 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 5.2).

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, 5.2).

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

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

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

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

Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (for cardioversion see section 4.2).

For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted (see sections 4.2, 4.3 and 4.5).

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 (see section 5.3). Alternatively, apixaban tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube (see section 5.3).

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 listed in section 2.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.3).
- 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), 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 and 4.5).

4.4. Special warnings and precautions for use

Increased risk of thrombotic events after premature discontinuation

Premature discontinuation of any oral anticoagulant, including apixaban, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from apixaban to warfarin in clinical trials in atrial fibrillation patients. If apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant (see sections 4.2 and 5.2).

Bleeding

Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding (see sections 4.2 and 4.8).

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) (see sections 4.5).

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

Reversal of anticoagulant effect

An agent to reverse the anti-factor Xa activity of apixaban is not available in India. The pharmacodynamic effect of apixaban can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies (see section 5.2). When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (Factor Xa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration (see sections 4.9).

Hemodialysis does not appear to have a substantial impact on apixaban exposure (see section 5.2). Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

Spinal/epidural anesthesia or puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

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

Patients with prosthetic heart valves

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

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

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

Increased risk of thrombosis in patients with triple positive antiphospholipid syndrome

Direct-acting oral anticoagulants (DOACs), including apixaban, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Hip fracture surgery

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

Laboratory parameters

Clotting tests [e.g., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)] are affected as expected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see section 5.2).

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 medicine.

4.5. Drugs interactions

Inhibitors of CYP3A4 and P-gp

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

The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) (see section 4.4)

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

Inducers of CYP3A4 and P-gp

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

Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised (see section 4.4).

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).

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

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

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

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

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are coadministered with apixaban. Apixaban should be used with caution when coadministered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

There is limited experience of coadministration 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, coadministration of these medicinal products with apixaban is not recommended (see section 4.4).

Other concomitant therapies

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

Effect of apixaban on other medicinal products

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (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 coadministered medicinal products that are metabolised by these enzymes. Apixaban is not a significant inhibitor of P-gp.

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

Digoxin

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

Naproxen

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

Atenolol

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

Activated charcoal

Administration of activated charcoal reduces apixaban exposure (see section 4.9).

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 (see section 6.1). 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 (see section 6.1). 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 (see section 6.1).

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

Summary of the safety profile

The safety of apixaban has been investigated in 7 Phase III clinical studies including more than 21,000 patients: more than 5,000 patients in VTEp studies, more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment (VTEt) studies, for an average total exposure of 20 days, 1.7 years and 221 days respectively (see section 5.2).

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

In the VTEp studies, in total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with apixaban was 10% in the apixaban vs enoxaparin studies.

In the NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and 9.6% in the apixaban vs acetylsalicylic acid study. In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

In the VTEt studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15.6% in the apixaban vs enoxaparin/warfarin study and 13.3% in the apixaban vs placebo study (see section 5.2).

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
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, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon
Gamma-glutamyltransferase increased	Uncommon	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)
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 (see sections 4.4 and 5.2).

Reporting of suspected adverse reactions

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

4.9. Overdose

Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

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

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

An agent to reverse the anti-factor Xa activity of apixaban is not available in India (see section 4.4). The pharmacodynamic effect of apixaban can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies (see section 5.2). 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. Mechanism of action

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

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

5.2. Pharmacodynamics properties

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (Factor Xa inhibition). As a result of Factor Xa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-Factor Xa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-Factor Xa kits, however results differ across kits. 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-to-trough levels. In patients taking apixaban for the treatment of DVT and PE or prevention of recurrent DVT and PE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

Table 3: Predicted apixaban steady-state exposure and anti-xa activity

	Apix. C_{max} (ng/mL)	**Apix. C_{min} (ng/mL)**	**Apix. anti-Xa activity max (IU/mL)**	**Apix. anti-Xa activity min (IU/mL)**
	Median [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]
Prevention of stroke and systemic embolism: NVAF				

	Apix. C_{max} (ng/mL)	**Apix. C_{min} (ng/mL)**	**Apix. anti-Xa activity max (IU/mL)**	**Apix. anti-Xa activity min (IU/mL)**
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]

* 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.

Clinical efficacy and safety

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

The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of VTE in a broad range of adult patients undergoing elective hip or knee replacement. A total of 8,464 patients were randomised in two pivotal, double-blind, multi-national studies, comparing apixaban 2.5 mg given orally twice daily (4,236 patients) or enoxaparin 40 mg once daily (4,228 patients). Included in this total were 1,262 patients (618 in the apixaban group) of age 75 or older, 1,004 patients (499 in the apixaban group) with low body weight (≤60 kg), 1,495 patients (743 in the apixaban group) with BMI ≥33 kg/m^2, and 415 patients (203 in the apixaban group) with moderate renal impairment.

The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement, and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement. Subjects received either apixaban 2.5 mg given orally twice daily (po bid) or enoxaparin 40 mg administered subcutaneously once daily (sc od). The first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Both apixaban and enoxaparin were given for 32-38 days in the ADVANCE-3 study and for 10-14 days in the ADVANCE-2 study.

Based on patient medical history in the studied population of ADVANCE-3 and ADVANCE-2 (8,464 patients), 46% had hypertension, 10% had hyperlipidemia, 9% had diabetes, and 8% had coronary artery disease.

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal DVT, non-fatal PE, and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 4).

Table 4: Efficacy results from pivotal phase III studies

Study	ADVANCE-3 (hip)			ADVANCE-2 (knee)		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po twice daily 35 ± 3 d	Enoxaparin 40 mg sc once daily 35 ± 3 d	p-value	Apixaban 2.5 mg po twice daily 12 ± 2 d	Enoxaparin 40 mg sc once daily 12 ± 2 d	p-value
Total VTE/all-cause death						
Number of events/subjects Event rate	27/1,949 1.39%	74/1,917 3.86%	< 0.0001	147/976 15.06%	243/997 24.37%	<0.0001
Relative risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Major VTE						
Number of events/subjects Event rate	10/2,199 0.45%	25/2,195 1.14%	0.0107	13/1,195 1.09%	26/1,199 2.17%	0.0373
Relative risk 95% CI	0.40 (0.15, 0.80)			0.50 (0.26, 0.97)		

The safety endpoints of major bleeding, the composite of major and CRNM bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 5). All the bleeding criteria included surgical site bleeding.

Table 5: Bleeding results from pivotal phase III studies*

	ADVANCE-3		ADVANCE-2	
	Apixaban 2.5 mg po twice daily 35 ± 3 d	Enoxaparin 40 mg sc once daily 35 ± 3 d	Apixaban 2.5 mg po twice daily 12 ± 2 d	Enoxaparin 40 mg sc once daily 12 ± 2 d
All treated	n = 2,673	n = 2,659	n = 1,501	n = 1,508
Treatment period[1]				
Major	22 (0.8%)	18 (0.7%)	9 (0.6%)	14 (0.9%)
Fatal	0	0	0	0
Major + CRNM	129 (4.8%)	134 (5.0%)	53 (3.5%)	72 (4.8%)
All	313 (11.7%)	334 (12.6%)	104 (6.9%)	126 (8.4%)
Post-surgery treatment period[2]				
Major	9 (0.3%)	11 (0.4%)	4 (0.3%)	9 (0.6%)
Fatal	0	0	0	0
Major + CRNM	96 (3.6%)	115 (4.3%)	41 (2.7%)	56 (3.7%)
All	261 (9.8%)	293 (11.0%)	89 (5.9%)	103 (6.8%)

* All the bleeding criteria included surgical site bleeding

[1] Includes events occurring after first dose of enoxaparin (pre-surgery)

[2] Includes events occurring after first dose of apixaban (post-surgery)

The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g., ALT levels) were numerically lower in patients on apixaban compared to enoxaparin in the phase II and phase III studies in elective hip and knee replacement surgery.

In the knee replacement surgery study during the intended treatment period, in the apixaban arm 4 cases of PE were diagnosed against no cases in the enoxaparin arm. No explanation can be given to this higher number of PE.

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

A total of 23,799 patients were randomised in the clinical program (ARISTOTLE: apixaban versus warfarin, AVERROES: apixaban versus ASA) including 11,927 randomised to apixaban. The program was designed to demonstrate the efficacy and safety of apixaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and one or more additional risk factors, such as:

- prior stroke or transient ischaemic attack (TIA)
- age ≥75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥II)

ARISTOTLE study

In the ARISTOTLE study a total of 18,201 patients were randomised to double-blind treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [4.7%], see section 4.2) or warfarin (target INR range 2.0-3.0), patients were exposed to study active substance for a mean of 20 months. The mean age was 69.1 years, the mean $CHADS_2$ score was 2.1 and 18.9% of patients had prior stroke or TIA.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 6) compared with warfarin.

Table 6: Efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N=9,120 n (%/yr)	**Warfarin N=9,081 n (%/yr)**	**Hazard ratio (95% CI)**	**p-value**
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
Stroke				
Ischaemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	
Haemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

For patients randomised to warfarin, the median percentage of time in therapeutic range (TTR) (INR 2-3) was 66%.

Apixaban showed a reduction of stroke and systemic embolism compared to warfarin across the different levels of center TTR; within the highest quartile of TTR according to center, the hazard ratio for apixaban vs warfarin was 0.73 (95% CI, 0.38, 1.40).

Key secondary endpoints of major bleeding and all cause death were tested in a pre-specified hierarchical testing strategy to control the overall type 1 error in the trial. Statistically significant superiority was also achieved in the key secondary endpoints of both major bleeding and all-cause death (see Table 7). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

Table 7: Secondary endpoints in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N = 9,088 n (%/year)	Warfarin N = 9,052 n (%/year)	Hazard ratio (95% CI)	p-value
Bleeding outcomes				
Major*	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	< 0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	< 0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	< 0.0001
Other endpoints				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66, 1.17)	

* Major bleeding defined per International Society on Thrombosis and Haemostasis (ISTH) criteria.

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study.

The efficacy results for prespecified subgroups, including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

The incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) was 0.76%/year with apixaban and 0.86%/year with warfarin.

The major bleeding results for prespecified subgroups including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the results for the overall population studied in the trial.

AVERROES study

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomised to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], see section 4.2) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study active substance for a mean of 14 months. The mean age was 69.9 years, the mean $CHADS_2$ score was 2.0 and 13.6% of patients had prior stroke or TIA.

Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), $CHADS_2$ score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medicinal product instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

AVERROES was stopped early based on a recommendation by the independent Data Monitoring Committee due to clear evidence of reduction of stroke and systemic embolism with an acceptable safety profile.

The overall discontinuation rate due to adverse reactions was 1.5% for apixaban and 1.3% for ASA in the AVERROES study.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism (see Table 8) compared to ASA.

Table 8: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study

	Apixaban N = 2,807 n (%/year)	**ASA N = 2,791 n (%/year)**	**Hazard ratio (95% CI)**	**p-value**
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischaemic or unspecified	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	
Haemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	
Stroke, systemic embolism, MI, or vascular death*†	132 (4.21)	197 (6.35)	0.66 (0.53, 0.83)	0.003
Myocardial infarction	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	
Vascular death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	
All-cause death†	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068

* Assessed by sequential testing strategy designed to control the overall type I error in the trial.
† Secondary endpoint.

There was no statistically significant difference in the incidence of major bleeding between apixaban and ASA (see Table 9).

Table 9: Bleeding events in patients with atrial fibrillation in the AVERROES study

	Apixaban N = 2,798 n(%/year)	**ASA N = 2,780 n (%/year)**	**Hazard ratio (95% CI)**	**p-value**
Major*	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal, n	5 (0.16)	5 (0.16)		
Intracranial, n	11 (0.34)	11 (0.35)		
Major + CRNM†	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

*Major bleeding defined per International Society on Thrombosis and Haemostasis (ISTH) criteria.
† Clinically relevant non-major

NVAF patients with ACS and/or undergoing PCI

AUGUSTUS, an open-label, randomised, controlled, 2 by 2 factorial design trial, enrolled 4614 patients with NVAF who had ACS (43%) and/or underwent PCI (56%). All patients received background therapy with a P2Y12 inhibitor (clopidogrel: 90.3%) prescribed per local standard of care.

Patients were randomised up to 14 days after the ACS and/or PCI to either apixaban 5 mg twice daily (2.5 mg twice daily if two or more of the dose-reduction criteria were met; 10% received lower dose) or VKA and to either ASA (81 mg once daily) or placebo. The mean age was 69.9 years, 94% of patients randomised had a CHA_2DS_2-VASc score > 2, and 47% had a HAS-BLED score > 3. For patients randomised to VKA, the proportion of time in therapeutic range (TTR) (INR 2-3) was 56%, with 32% of time below TTR and 12% above TTR.

The primary objective of AUGUSTUS was to assess safety, with a primary endpoint of ISTH major or CRNM bleeding. In the apixaban versus VKA comparison, the primary safety endpoint of ISTH major or CRNM bleeding at month 6 occurred in 241 (10.5%), and 332 (14.7%) patients in the apixaban arm and in the VKA arm respectively (HR=0.69, 95% CI: 0.58, 0.82; 2-sided $p<0.0001$ for non-inferiority and $p<0.0001$ for superiority). For VKA, additional analyses using subgroups by TTR showed that the highest rate of bleeding was associated with the lowest quartile of TTR. The rate of bleeding was similar between apixaban and the highest quartile of TTR.

In the ASA versus placebo comparison, the primary safety endpoint of ISTH major or CRNM bleeding at month 6 occurred in 367 (16.1%), and 204 (9.0%) patients in the ASA arm and in the placebo arm respectively (HR=1.88, 95% CI: 1.58, 2.23; two-sided $p<0.0001$).

Specifically, in apixaban-treated patients, major or CRNM bleeding occurred in 157 (13.7%), and 84 (7.4%) patients in the ASA arm and in the placebo arm respectively. In VKA-treated patients, major or CRNM bleeding occurred in 208 (18.5%), and 122 (10.8%) patients in the ASA arm and in the placebo arm respectively.

Other treatment effects were evaluated as a secondary objective of the study, with composite endpoints.

In the apixaban versus VKA comparison, the composite endpoint of death or re-hospitalisation occurred in 541 (23.5%) and 632 (27.4%) patients in the apixaban and in the VKA arm, respectively. The composite endpoint of death or ischemic event (stroke, myocardial infarction, stent thrombosis or urgent revascularisation) occurred in 170 (7.4%), and 182 (7.9%) patients in the apixaban and in the VKA arm, respectively.

In the ASA versus placebo comparison, the composite endpoint of death or re-hospitalisation occurred in 604 (26.2%) and 569 (24.7%) patients in the ASA and in the placebo arm, respectively. The composite endpoint of death or ischemic event (stroke, myocardial infarction, stent thrombosis or urgent revascularisation) occurred in 163 (7.1%), and 189 (8.2%) patients in the ASA and in the placebo arm, respectively.

Patients undergoing cardioversion

EMANATE, an open-label, multi-center study, enrolled 1500 patients who were either oral anticoagulant naïve or pre-treated less than 48 hours, and scheduled for cardioversion for NVAF. Patients were randomised 1:1 to apixaban or to heparin and/or VKA for the prevention of cardiovascular events. Electrical and/or pharmacologic cardioversion was conducted after at least 5 doses of 5 mg twice daily apixaban (or 2.5 mg twice daily in selected patients (see section 4.2)) or at least 2 hours after a 10 mg loading dose (or a 5 mg loading dose in selected patients (see section 4.2)) if earlier cardioversion was required. In the apixaban group, 342

patients received a loading dose (331 patients received the 10 mg dose and 11 patients received the 5 mg dose).

There were no strokes (0%) in the apixaban group (n= 753) and 6 (0.80%) strokes in the heparin and/or VKA group (n = 747; RR 0.00, 95% CI 0.00, 0.64). All-cause death occurred in 2 patients (0.27%) in the apixaban group and 1 patient (0.13%) in the heparin and/or VKA group. No systemic embolism events were reported.

Major bleeding and CRNM bleeding events occurred in 3 (0.41%) and 11 (1.50%) patients, respectively, in the apixaban group, compared to 6 (0.83%) and 13 (1.80%) patients in the heparin and/or VKA group.

This exploratory study showed comparable efficacy and safety between apixaban and heparin and/or VKA treatment groups in the setting of cardioversion.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)
The clinical program (AMPLIFY: apixaban versus enoxaparin/warfarin, AMPLIFY-EXT: apixaban versus placebo) was designed to demonstrate the efficacy and safety of apixaban for the treatment of DVT and/or PE (AMPLIFY), and extended therapy for the prevention of recurrent DVT and/or PE following 6 to 12 months of anticoagulant treatment for DVT and/or PE (AMPLIFY-EXT). Both studies were randomised, parallel-group, double-blind, multinational trials in patients with symptomatic proximal DVT or symptomatic PE. All the key safety and efficacy endpoints were adjudicated by an independent blinded committee.

AMPLIFY study
In the AMPLIFY study a total of 5,395 patients were randomised to treatment with apixaban 10 mg twice daily orally for 7 days followed by apixaban 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR≥ 2) and warfarin (target INR range 2.0-3.0) orally for 6 months.

The mean age was 56.9 years and 89.8% of randomised patients had unprovoked VTE events.

For patients randomised to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9. Apixaban showed a reduction in recurrent symptomatic VTE or VTE-related death across the different levels of center TTR; within the highest quartile of TTR according to center, the relative risk for apixaban vs enoxaparin/warfarin was 0.79 (95% CI, 0.39, 1.61).

In the study, apixaban was shown to be non-inferior to enoxaparin/warfarin in the combined primary endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death (see Table 10).

Table 10: Efficacy results in the AMPLIFY study

	Apixaban N=2,609 n (%)	Enoxaparin/Warfarin N=2,635 n (%)	Relative risk (95% CI)
VTE or VTE-related death	59 (2.3)	71 (2.7)	0.84 (0.60, 1.18)*
DVT	20 (0.7)	33 (1.2)	
PE	27 (1.0)	23 (0.9)	
VTE-related death	12 (0.4)	15 (0.6)	
VTE or all-cause death	84 (3.2)	104 (4.0)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3)	77 (2.9)	0.80 (0.57, 1.11)
VTE, VTE-related death, or major bleeding	73 (2.8)	118 (4.5)	0.62 (0.47, 0.83)

* Noninferior compared to enoxaparin/warfarin (p-value <0.0001)

Apixaban efficacy in initial treatment of VTE was consistent between patients who were treated for a PE [Relative Risk 0.9; 95% CI (0.5, 1.6)] or DVT [Relative Risk 0.8; 95% CI (0.5, 1.3)]. Efficacy across subgroups, including age, gender, body mass index (BMI), renal function, extent of index PE, location of DVT thrombus, and prior parenteral heparin use was generally consistent.

The primary safety endpoint was major bleeding. In the study, apixaban was statistically superior to enoxaparin/warfarin in the primary safety endpoint [Relative Risk 0.31, 95% confidence interval (0.17, 0.55), P-value <0.0001] (see Table 11).

Table 11: Bleeding results in the AMPLIFY study

	Apixaban N=2,676 n (%)	Enoxaparin/ Warfarin N=2,689 n (%)	Relative risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55)
Major + CRNM	115 (4.3)	261 (9.7)	0.44 (0.36, 0.55)
Minor	313 (11.7)	505 (18.8)	0.62 (0.54, 0.70)
All	402 (15.0)	676 (25.1)	0.59 (0.53, 0.66)

The adjudicated major bleeding and CRNM bleeding at any anatomical site were generally lower in the apixaban group as compared to the enoxaparin/warfarin group. Adjudicated ISTH major gastrointestinal bleeding occurred in 6 (0.2%) apixaban-treated patients and 17 (0.6%) enoxaparin/warfarin-treated patients.

AMPLIFY-EXT study

In the AMPLIFY-EXT study a total of 2,482 patients were randomised to treatment with apixaban 2.5 mg twice daily orally, apixaban 5 mg twice daily orally, or placebo for 12 months after completing 6 to 12 months of initial anticoagulant treatment. Of these, 836 patients (33.7%) participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

The mean age was 56.7 years and 91.7% of randomised patients had unprovoked VTE events.

In the study, both doses of apixaban were statistically superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death (see Table 12).

Table 12: Efficacy results in the AMPLIFY-EXT study

	Apixaban	**Apixaban**	**Placebo**	**Relative risk (95% CI)**	
	2.5 mg (N=840)	**5.0 mg (N=813)**	**(N=829)**	**Apix 2.5 mg vs. placebo**	**Apix 5.0 mg vs. placebo**
	n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15, 0.40)¥	0.19 (0.11, 0.33)¥
DVT*	6 (0.7)	7 (0.9)	53 (6.4)		
PE*	7 (0.8)	4 (0.5)	13 (1.6)		
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)		
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11, 0.33)	0.20 (0.11, 0.34)
Recurrent VTE or CV-related death	14 (1.7)	14 (1.7)	76 (9.2)	0.18 (0.10, 0.32)	0.19 (0.11, 0.33)
Nonfatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)
Nonfatal PE†	8 (1.0)	4 (0.5)	15 (1.8)	0.51 (0.22, 1.21)	0.27 (0.09, 0.80)
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)	0.28 (0.06, 1.37)	0.45 (0.12, 1.71)

¥ p-value < 0.0001

* For patients with more than one event contributing to the composite endpoint, only the first event was reported (e.g, if a subject experienced both a DVT and then a PE, only the DVT was reported)

† Individual subjects could experience more than one event and be represented in both classifications

Apixaban efficacy for prevention of a recurrence of a VTE was maintained across subgroups, including age, gender, BMI, and renal function.

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see Table 13).

Table 13: Bleeding results in the AMPLIFY-EXT study

	Apixaban	**Apixaban**	**Placebo**	**Relative risk (95% CI)**	
	2.5 mg (N=840)	**5.0 mg (N=811)**	**(N=826)**	**Apix 2.5 mg vs. placebo**	**Apix 5.0 mg vs. placebo**
		n (%)			
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69, 2.10)	1.62 (0.96, 2.73)
Minor	75 (8.9)	98 (12.1)	58 (7.0)	1.26 (0.91, 1.75)	1.70 (1.25, 2.31)
All	94 (11.2)	121 (14.9)	74 (9.0)	1.24 (0.93, 1.65)	1.65 (1.26, 2.16)

Adjudicated ISTH major gastrointestinal bleeding occurred in 1 (0.1%) apixaban-treated patient at the 5 mg twice daily dose, no patients at the 2.5 mg twice daily dose, and 1 (0.1%) placebo-treated patient.

5.3. 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 60 mL of G5W and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical studies involving healthy subjects receiving 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 (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 in clinical and nonclinical studies, respectively.

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

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major active substance-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

Elderly

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

Renal impairment

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

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36% when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14% in

these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment

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

Gender

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

Ethnic origin and race

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

Body weight

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

6.1 Animal toxicology or pharmacology

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 (C_{max} about 8, AUC about 30) was found, possibly due to active transport into the milk.

7. DESCRIPTION

Apixaban 2.5 mg - Yellow, round, biconvex film coated tablets with "893" debossed on one side and "2 1/2 " on the other side.

Apixaban 5 mg - Pink, oval shaped, biconvex film coated tablets with "894" debossed on one side and "5" on the other side.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

Not applicable.

8.2. Shelf-life

36 Months.

8.3 Packaging information

Apixaban 2.5 mg: Carton containing Alu-PVC/PVdC blisters of 10 film-coated tablets each [1 blister of 10 film-coated tablets each, 1x10 tablets / 3 blisters of 10 film-coated tablets each, 3x10 tablets].

Apixaban 5 mg: Carton containing Alu-PVC/PVdC blisters of 10 film-coated tablets each [2 blisters of 10 film-coated tablets each, 2x10 tablets / 3 blisters of 10 film-coated tablets each, 3x10 tablets].

Not all presentations may be available in the market.

8.4 Storage and handling instructions

Store below 30°C.
No special handling requirements.

9. PATIENT COUNSELLING 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 nonprescription 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 (see section 4.4). 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 (see section 4.6).
- How to take apixaban if they cannot swallow, or require a nasogastric tube (see section 4.2).
- What to do if a dose is missed (see section 4.2).

10. DETAILS OF MANUFACTURER

Manufactured by:

Pfizer Manufacturing Deutschland GmbH,
Betriebsstätte Freiburg,
Mooswaldallee 1, 79090 Freiburg, Germany

OR

M/s. Catalent Anagni S.r.l.,
Loc. Fontana del Ceraso snc - Strada, Provinciale 12 Casilina,
41, 03012 Anagni (FR) Italy

[NOTE: Please refer outer carton for precise "Manufactured by" details]

Imported and Marketed in India By:

M/s. Pfizer Limited,
The Capital-A Wing, 1802, 18th Floor, Plot No. C-70, G-block,
Bandra Kurla Complex, Bandra (East), Mumbai –Zone-4,
Maharashtra (India) – 400051

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Import-187/12 dated 03-Aug-2012
Import-102/2014 dated 16-May-2014
IMP-FF/SND/113/2015 dated 29-May-2015
Amendment to company name (Pfizer Limited) on Form 45 dated 15-Feb-2019

12. DATE OF REVISION

June 2022