PT PFIZER INDONESIA
LOCAL PRODUCT DOCUMENT
Generic Name: Apixaban
Trade Name: ELIQUIS
CDS Effective Date: April 19, 2019
Supersedes: July 21, 2017

1. NAME OF THE MEDICINAL PRODUCT

ELIQUIS 2.5 mg film-coated tablets.
ELIQUIS 5.0 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg and 5.0 mg apixaban, respectively.

3. PHARMACEUTICAL FORM

2.5 mg: Yellow, round, biconvex film-coated tablets debossed with "893" on one side and "2½" on the other side.
5.0 mg: Pink, oval shaped, biconvex film-coated tablets debossed with "894" on one side and "5" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Prevention of stroke: non-valvular atrial fibrillation
ELIQUIS is indicated to reduce the risk of stroke in patients with non-valvular atrial fibrillation with one or more risk factors, including patients unsuitable for warfarin/Vitamin K antagonist therapy (VKA).

Treatment of VTE
ELIQUIS is indicated for:
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).
- Prevention of recurrent DVT and PE.

4.2 Posology and method of administration
ELIQUIS can be taken with or without food.

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

Posology
Prevention of VTE: elective hip or knee replacement surgery
The recommended dose of ELIQUIS 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 32 to 38 days.

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

Prevention of stroke in patients with NVAF
The recommended dose of ELIQUIS is 5 mg taken orally twice daily.

Dose reduction

The recommended dose of ELIQUIS 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 and PE:
The recommended dose of ELIQUIS is 10 mg (2 x 5 mg) taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily for a maximum of 6 months.

Prevention of recurrent DVT and PE:
The recommended dose of ELIQUIS 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 for DVT or PE. The maximum duration of prevention of recurrent DVT and/or PE is 12 months.

Renal impairment
Prevention of VTE: elective hip or knee replacement surgery
No dose adjustment is necessary in patients with mild, moderate or severe (creatinine clearance 15 – 29 mL/min) renal impairment (see section 5.2). Because there is limited clinical experience in patients with creatinine clearance <15 mL/min and no data in patients undergoing dialysis, apixaban is not recommended in these patients.

Prevention of stroke: NVAF

No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2).

In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply (see sections 4.4 and 5.2):

Patients should receive the lower dose of apixaban 2.5 mg twice daily.

Patients with serum creatinine ≥1.5 mg/dL (133 micromole/L) associated with age ≥80 years or body weight ≤60 kg should also receive the lower dose of apixaban 2.5 mg twice daily.

In patients with creatinine clearance <15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore, apixaban is not recommended (see sections 4.4 and 5.2).

Treatment of VTE

No dose adjustment is necessary in patients with mild, moderate, or severe (creatinine clearance 15–29 mL/min) renal impairment (see section 5.2). Because there is limited clinical experience in patients with creatinine clearance <15 mL/min and no data in patients undergoing dialysis, apixaban is not recommended in these patients.

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment.

ELIQUIS is not recommended in patients with severe hepatic impairment.

Body weight

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required.

Treatment of VTE

No dose adjustment required.

Prevention of stroke: 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.

Paediatric and adolescent

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

Elderly
Prevention of VTE: elective hip or knee replacement surgery
No dose adjustment required.

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

Cardioversion (NVAF)
ELIQUIS can be initiated or continued in NVAF patients who may require cardioversion.

For patients not previously treated with anticoagulants, at least 5 doses of Apixaban 5 mg twice daily [2.5 mg twice daily in patients who qualify for a dose reduction (see section 4.2)] should be given before cardioversion to ensure adequate anticoagulation (see section 5.1).

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 section 4.2). The administration of the loading dose should be given at least 2 hours before cardioversion (see section 5.1).

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.

Treatment of VTE
No dose adjustment required.

Converting from or to parenteral anticoagulants
In general, switching treatment from parenteral anticoagulants to ELIQUIS (and *vice versa*) can be done at the next scheduled dose.

Converting from or to warfarin or other vitamin K antagonists (VKA)
When converting patients from warfarin or other VKA therapy to ELIQUIS, discontinue warfarin or other VKA therapy and start ELIQUIS when the international normalized ratio (INR) is below 2.0.

When converting from ELIQUIS to warfarin or other VKA therapy, continue ELIQUIS for 48 hours after the first dose of warfarin or other VKA therapy.

Surgery and invasive procedures

ELIQUIS 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. ELIQUIS 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. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. In non-valvular atrial fibrillation patients, bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Patients can continue taking ELIQUIS while being cardioverted.

For patients who are unable to swallow whole tablets, ELIQUIS tablets may be crushed and suspended in water and promptly administered orally. Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water and promptly delivered through a nasogastric tube (see section 5.2).

Crushed ELIQUIS tablets are stable in water for up to 4 hours.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients.

• Clinically significant active bleeding.

• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2)

• 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) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

4.4 Special warnings and precautions for use

Haemorrhage risk
As with other anticoagulants, patients taking ELIQUIS are to be carefully observed for signs of bleeding.

ELIQUIS is recommended to be used with caution in conditions with increased risk of haemorrhage, such as: congenital or acquired bleeding disorders; active ulcerative gastrointestinal disease; bacterial endocarditis; thrombocytopenia; platelet disorders; history of haemorrhagic stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery. ELIQUIS administration should be discontinued if severe haemorrhage occurs (see section 4.9).

Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see section 5.1).

In the event of hemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical hemostasis or the transfusion of fresh frozen plasma, should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered. Reversal of ELIQUIS pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, has been demonstrated after administration of 4-factor PCCs 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 ELIQUIS. Currently, there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban.

Temporary discontinuation of ELIQUIS
Discontinuing anticoagulants, including ELIQUIS, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Avoid lapses in therapy, and if anticoagulation with ELIQUIS must be temporarily discontinued for any reason, restart therapy as soon as possible.

Renal impairment
Prevention of VTE: elective hip or knee replacement surgery
Because there is limited clinical experience in patients with creatinine clearance <15 mL/min, apixaban is not recommended in these patients (see section 5.2).

Treatment of VTE
Because there is limited clinical experience in patients with creatinine clearance <15 mL/min and no data in patients undergoing dialysis, apixaban is not recommended in these patients (see section 5.2).

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

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

Elderly patients
Increasing age may increase haemorrhagic risk (see section 5.2).
Also, the co-administration of ELIQUIS with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

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

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

ELIQUIS is not recommended in patients with severe hepatic impairment (see section 5.2).

ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see section 5.2).

Interaction with strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)
The use of ELIQUIS is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir). These medicinal products may increase apixaban exposure by 2-fold (see section 4.5), or greater in the presence of additional factors that increase apixaban exposure (e.g., severe renal impairment).

Interaction with strong inducers of both CYP3A4 and P-gp
The concomitant use of ELIQUIS with strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with co-administration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone. In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (see section 4.5):

• for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke in patients with NVAF and for the prevention of recurrent DVT and PE, apixaban should be used with caution;
• for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

For the treatment of DVT or PE, ELIQUIS is not recommended in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp (see section 4.5). For prevention of recurrent DVT and PE, use caution when co-administering ELIQUIS with strong inducers of both CYP3A4 and P-gp (see section 4.5).

Interaction with other medicinal products affecting haemostasis
Care is to be taken if patients are treated concomitantly with medicinal products affecting Haemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents (see section 4.5).

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 ELIQUIS.

In a clinical trial 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 trial, there was limited (2.1%) use of concomitant dual antiplatelet therapy.

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

There is no clinical experience with the use of apixaban with indwelling intrathecal or epidural catheters. In case of such need and based on pharmacokinetic data, a time interval of 20-30 hours (i.e., twice the half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban may be given at least 5 hours after catheter

removal. As with all new anticoagulant drugs, experience with neuraxial blockade is limited and extreme caution is therefore, recommended when using apixaban in the presence of neuraxial blockade.

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, ELIQUIS is not recommended in these patients.

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

Information about excipients
ELIQUIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

Treatment of VTE
Initiation of ELIQUIS 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.

Patients with active cancer
Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made (see also section 4.3).

Patients with antiphospholipid syndrome
Direct acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS). In particular for patients who 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. The efficacy and safety of ELIQUIS in patients with APS have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on apixaban

Inhibitors of CYP3A4 and P-gp

Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max}. No dose adjustment for apixaban is required with concomitant ketoconazole therapy, however apixaban should be used with caution in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole or other strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

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

Inducers of CYP3A4 and P-gp

Co-administration of apixaban with rifampin, 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 in patients with NVAF and for the prevention of recurrent DVT and PE.

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

Anticoagulants

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.

Due to an increased bleeding risk, care is to be taken if patients are treated concomitantly with any other anticoagulants (see section 4.4).

Platelet aggregation inhibitors and NSAIDs
Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was co-administered with acetylsalicylic acid 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and acetylsalicylic acid 162 mg once daily did not show a relevant increase in bleeding time, platelet aggregation, or clotting tests (PT, INR, and aPTT) compared to administration of the antiplatelet agents without apixaban.

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 co-administered with apixaban. Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and/or platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Agents associated with serious bleeding are not recommended concomitantly with ELIQUIS, such as: thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran and sulfinpyrazone.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two drugs 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}.

Laboratory parameters
Clotting tests (e.g., PT, INR, and aPTT) are affected as expected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see section 5.1).

Paediatric population
Interaction studies have only been performed in adults.

Effect of apixaban on other drugs

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50>45 μM) and weak inhibitory effect on the activity of CYP2C19 (IC50>20 μM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM. Therefore, apixaban is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Apixaban is not recommended 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 newborns and infants cannot be excluded.

A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical experience

Prevention of VTE: elective hip or knee replacement surgery

The safety of apixaban has been evaluated in one phase II and three Phase III studies including 5,924 patients exposed to apixaban 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. As with other anticoagulants, bleeding may occur during apixaban therapy in the presence of associated risk factors such as organic lesions liable to bleed. Common adverse reactions were anemia, hemorrhage, contusion, and nausea. The overall incidences of adverse reactions of bleeding, anemia and abnormalities of transaminases (e.g., alanine aminotransferase 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. The adverse reactions should be interpreted within the surgical setting.

As with any anticoagulant, the use of ELIQUIS may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthemorrhagic anemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding (see sections 4.4 and 5.1).

Adverse reactions in the one phase II study and the three phase III studies are listed in Table 1 by system organ classification (MedDRA) and by frequency.

Table 1: Treatment-emergent adverse reactions in post-surgery orthopedic patients

Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Blood and lymphatic system disorders		
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	Thrombocytopenia (including platelet count decreases)	
Immune system disorders		
		Hypersensitivity
Eye disorders		
		Ocular hemorrhage (including conjunctival hemorrhage)
Vascular disorders		

Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	Hypotension (including procedural hypotension)	
Respiratory, thoracic and mediastinal disorders		
	Epistaxis	Hemoptysis
Gastrointestinal disorders		
Nausea	Gastrointestinal hemorrhage (including hematemesis and melaena), hematochezia	Rectal hemorrhage, gingival bleeding
Hepatobiliary disorders		
	Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal), aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased	
Musculoskeletal and connective tissue disorders		
		Muscle hemorrhage
Renal and urinary disorders		
	Hematuria (including respective laboratory parameters)	
Injury, poisoning and procedural complications		
Contusion	Post procedural hemorrhage (including post procedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage), wound secretion, incision site hemorrhage (including incision site hematoma), operative hemorrhage	

Prevention of stroke and systemic embolism: NVAF
The safety of apixaban has been evaluated in the ARISTOTLE and AVERROES studies, including 11284 patients exposed to apixaban 5 mg twice daily and 602 patients to

2.5 mg twice daily. The apixaban exposures were ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89.2 weeks on apixaban and 87.5 weeks on warfarin; total patient years for exposure was 15534 on apixaban and 15184 on warfarin. In AVERROES, the mean duration of exposure was approximately 59 weeks in both treatment groups; total patient years for exposure was 3193 on apixaban and 3150 on ASA.

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study, and was 1.5% for apixaban and 1.3% for ASA in the AVERROES study. The overall incidence of adverse reactions related to bleeding was numerically lower in patients on apixaban compared to warfarin in the ARISTOTLE study (24.3% vs. 31.0%). and was similar in patients on apixaban compared to ASA in the AVERROES study (9.6% vs. 8.5%).

Adverse reactions in the ARISTOTLE and AVERROES studies are listed in Table 2 by system organ classification (MedDRA) and by frequency. The frequency assignments in Table 2 are primarily based on the frequencies observed in the ARISTOTLE study. The adverse reactions observed in the AVERROES study were consistent with those observed in the ARISTOTLE study.

Table 2: Treatment-emergent adverse reactions in NVAF patients

Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Immune system disorders		
	Hypersensitivity (including drug hypersensitivity such as skin rash and anaphylactic reaction such as allergic edema)	
Nervous system disorders		
	Brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)	
Eye disorders		
Eye haemorrhage (including conjunctival haemorrhage)		
Vascular disorders		
Other haemorrhage, haematoma	Intra-abdominal haemorrhage	
Respiratory, thoracic and mediastinal disorders		

Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Epistaxis	Haemoptysis	Respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage, and pharyngeal haemorrhage)
Gastrointestinal disorders		
Gastrointestinal haemorrhage (including hematemesis and melaena), rectal haemorrhage, gingival bleeding	Haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage	Retroperitoneal haemorrhage
Renal and urinary disorders		
Haematuria		
Reproductive system and breast disorders		
	Abnormal vaginal haemorrhage, urogenital haemorrhage	
General disorders and administration site conditions		
	Application site bleeding	
Investigations		
	Occult blood positive	
Injury, poisoning and procedural complications		
Contusion	Traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage	

Treatment of VTE
The safety of apixaban has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to apixaban 10 mg twice daily, 3359 patients exposed to apixaban 5 mg twice daily, and 840 patients exposed to apixaban 2.5 mg twice daily. The mean duration of exposure to apixaban was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. The mean duration of exposure to apixaban was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study.

In the AMPLIFY study, adverse reactions related to bleeding occurred in 417 (15.6%) of apixaban-treated patients compared to 661 (24.6%) of enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the apixaban-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY-EXT study, adverse reactions related to bleeding occurred in 219 (13.3%) of apixaban-treated patients compared to 72 (8.7%) of placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the apixaban-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, hematoma, and menorrhagia.

Adverse reactions in the AMPLIFY and AMPLIFY-EXT studies are listed in Table 3 by system organ classification (MedDRA) and by frequency.

Table 3: Treatment-emergent adverse reactions in VTEtx patients

Common (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to < 1/1,000)
Blood and lymphatic system disorders		
		Haemorrhagic anaemia, haemorrhagic diathesis, spontaneous haematoma
Nervous system disorders		
		Cerebral haemorrhage, haemorrhagic stroke
Eye disorders		
	Conjunctival haemorrhage	Eye haemorrhage, retinal haemorrhage, scleral haemorrhage, vitreous haemorrhage
Ear and labyrinth disorders		
		Ear haemorrhage
Cardiac disorders		
		Pericardial haemorrhage
Vascular disorders		
Haematoma		Haemorrhage, intra-abdominal haematoma, shock haemorrhagic
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	Haemoptysis	Pulmonary alveolar haemorrhage
Gastrointestinal disorders		

Table 3: Treatment-emergent adverse reactions in VTEtx patients

Common (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to < 1/1,000)
Gingival bleeding	Rectal haemorrhage, haematochezia, haemorrhoidal haemorrhage, gastrointestinal haemorrhage, haematemesis	Melaena, anal haemorrhage, gastric ulcer haemorrhage, mouth haemorrhage, abdominal wall haematoma, Mallory-Weiss syndrome, gastric haemorrhage, peptic ulcer haemorrhage, small intestine haemorrhage
Skin and subcutaneous tissue disorders		
	Ecchymosis, skin haemorrhage	Petechiae, purpura, increased tendency to bleed, blood blister, skin ulcer haemorrhage
Musculoskeletal and connective tissue disorders		
		Muscle haemorrhage
Renal and urinary disorders		
Haematuria		Haemorrhage urinary tract
Reproductive system and breast disorders		
Menorrhagia	Vaginal haemorrhage, metrorrhagia	Menometrorrhagia, uterine haemorrhage, genital haemorrhage, breast haematoma, haematospermia, postmenopausal haemorrhage
General disorders and administration site conditions		
	Injection site haematoma, vessel puncture site haematoma	Injection site haemorrhage, infusion site haematoma
Investigations		
	Blood urine present, occult blood positive	Occult blood, red blood cells urine positive
Injury, poisoning, and procedural complications		
Contusion	Wound haemorrhage, post procedural haemorrhage, traumatic haematoma	Periorbital haematoma, vascular pseudoaneurysm, subcutaneous haematoma, procedural haematoma, post procedural haematoma, post

Table 3: Treatment-emergent adverse reactions in VTEtx patients

Common (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to < 1/1,000)
		procedural haematuria, extradural haematoma, renal haematoma, subdural haemorrhage

4.9 Overdose

There is no antidote to ELIQUIS. Overdose of ELIQUIS 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 trials, orally-administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg BID for 7 days or 50 mg QD for 3 days) [10 times the daily maximum recommended human dose] had no clinically relevant adverse effects.

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.

If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced

by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

Pharmacodynamic effects

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

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa enzyme activity in the Rotachrom Heparin chromogenic assay data from clinical studies. Anti-FXa 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 concentration and anti-FXa activity is linear over a wide dose range of apixaban. The dose- and concentration related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

Predicted steady-state peak and trough anti-FXa activity with apixaban 2.5 mg BID dosing are 1.3 IU/mL ($5^{th}/95^{th}$ percentile 0.67-2.4 IU/mL) and 0.84 IU/mL ($5^{th}/95^{th}$ percentile 0.37-1.8 IU/mL), respectively, demonstrating less than a 1.6-fold fluctuation in peak-to-trough anti-FXa activity over the dosing interval.

Based on results of the population PK/PD analysis in patients with atrial fibrillation, the predicted median (5th-95th percentile) steady state peak and trough anti-Xa activity with apixaban 5 mg twice daily are 2.55 (1.36-4.79) IU/mL and 1.54 (0.61-3.43) IU/mL, respectively. In patients who meet the criteria for a dose reduction to 2.5 mg twice daily, the corresponding estimated peak and trough values are 1.84 (1.02-3.29) IU/mL and 1.18 (0.51-2.42) IU/mL, respectively.

Table 4 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, the results demonstrate a less than 1.7-fold fluctuation in peak-to-trough levels. In patients taking apixaban for the treatment of VTE or prevention of recurrence of VTE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

Table 4: 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 BID	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				
2.5 mg BID*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg BID	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]

* 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 Trail Information

Prevention of VTE: 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 8464 patients were randomized in two pivotal, double-blind, multinational studies, comparing apixaban 2.5 mg given orally twice daily or enoxaparin 40 mg once daily. Included in this total were 1262 patients of age 75 or older, 1004 patients with low body weight (≤60 kg), 1495 patients with BMI ≥33 kg/m^2 and 437 patients with severe or moderate renal impairment. The ADVANCE-3 study included 5407 patients undergoing elective hip replacement, and the ADVANCE-2 study included 3057 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.

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 5).

Table 5: 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 bid 35 ± 3 d	Enoxaparin 40 mg sc od 35 ± 3 d	p-value	Apixaban 2.5 mg po bid 12 ± 2 d	Enoxaparin 40 mg sc od 12 ± 2 d	p-value
Total VTE/all-cause death						
Number of	27/1949	74/1917	<0.0001	147/976	243/997	<0.0001

events/subjects Event Rate	1.39%	3.86%		15.06%	24.37%	
Relative Risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Major VTE						
Number of events/subjects Event Rate	10/2199 0.45%	25/2195 1.14%	0.0107	13/1195 1.09%	26/1199 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 clinically relevant non-major (CRNM) bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 6). All the bleeding criteria included surgical site bleeding.

In both Phase III studies, bleeding was assessed beginning with the first dose of double-blind study drug, which was either enoxaparin or injectable placebo, given 9 to 15 hours before surgery. Bleeding during the treatment period included events that occurred before the first dose of apixaban, which was given 12 to 24 hours after surgery. Bleeding during the post-surgery treatment period only included events occurring after the first dose of study drug after surgery.

Over half the occurrences of major bleeding in the apixaban group occurred prior to the first dose of apixaban. Table 6 shows the bleeding results from the treatment period and the post-surgery treatment period.

Table 6: Bleeding results from pivotal phase III studies*

	ADVANCE-3		ADVANCE-2	
	Apixaban 2.5 mg po bid 35 ± 3 d	Enoxaparin 40 mg sc Od 35 ± 3 d	Apixaban 2.5 mg po Bid 12 ± 2 d	Enoxaparin 40 mg sc Od 12 ± 2 d
All treated	n=2673	n=2659	n=1501	n=1508
Treatment Period				
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				
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.

Prevention of stroke and systemic embolism: NVAF

The clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of stroke and systemic embolism in patients suitable for VKA (ARISTOTLE) and in patients unsuitable for VKA (AVERROES). Both studies were active-controlled (vs. warfarin in ARISTOTLE and vs. ASA in AVERROES), randomized, double-blind, parallel-arm, multi-national trials in patients with nonvalvular, persistent, paroxysmal, or permanent atrial fibrillation (AF) or atrial flutter (AFl) and one or more of the following additional risk factors:

- prior stroke or transient ischaemic attack (TIA) (also prior systemic embolism in ARISTOTLE)
- age ≥75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- decreased left ventricular ejection fraction (LVEF)
- documented peripheral arterial disease (AVERROES only)

Table 7: Patient demographic characteristics in the clinical studies

	ARISTOTLE	AVERROES
Randomized subjects	18,201	5598
Mean age	69.1	69.9
≥65 years	69.9%	69.3%
≥75 years	31.2%	33.8%
Gender		
Male	64.7%	58.5%
Female	35.3%	41.5%
Race		
White/Caucasian	82.6%	78.6%
Asian	14.5%	19.4%
Black/African American	1.2%	0.6%
Prior stroke or TIA	18.6%	13.6%
Hypertension	87.4%	86.4%
Diabetes	25.0%	19.6%
Heart failure	(or LVEF ≤40%) 35.4%	(or LVEF ≤35%) 33.7%
Mean $CHADS_2$ score	2.1	2.0
$CHADS_2 \leq 1$	34.0%	38.3%
$CHADS_2 = 2$	35.8%	35.2%
$CHADS_2 \geq 3$	30.2%	26.5%

ARISTOTLE STUDY

Patients were randomized to treatment with apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, 4.7% or warfarin (target INR range 2.0-3.0) and followed for a median of 89.86 weeks for apixaban and 87.79 weeks for warfarin. The apixaban 2.5 mg twice daily dose was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 micromole/L). 43% were VKA naive, defined as not previously received or have received ≤30 consecutive days of treatment with warfarin or another VKA. Coronary artery disease was present in 33.2% of patients.

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

The primary objective of the study was to determine if apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) was noninferior to warfarin for the prevention of stroke (ischemic, hemorrhagic, or unspecified) and systemic embolism. Assessments of superiority of apixaban versus warfarin were also prespecified for the primary endpoint and for death due to any cause.

The key study outcomes were prespecified and tested in a sequential, hierarchical manner to conserve overall type 1 error. Apixaban was tested compared to warfarin for: (1) non-inferiority on the composite endpoint of stroke and systemic embolism, (2) superiority on the composite endpoint of stroke and systemic embolism, (3) superiority on major bleeding, and (4) superiority on all-cause death.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (hemorrhagic or ischemic) and systemic embolism (see Table 8 and Figure 1). Statistically significant superiority was also achieved in all-cause death (see Table 8). Numeric reductions were observed for both CV and non-CV deaths.

Apixaban reduced the incidence of strokes compared to warfarin within each stroke severity category, including less severe strokes (Rankin score 0 to 2, HR=0.89 [CI=0.64, 1.26]) and the more clinically important fatal or disabling strokes (Rankin score 3 to 6, HR=0.71 [CI=0.54, 0.94]). The reduction in the stroke and systemic embolism incidence was seen regardless of the stroke risk at entry as categorized by $CHADS_2$ score.

Table 8: Key Efficacy Outcomes in Patients with Atrial Fibrillation in the ARISTOTLE Study

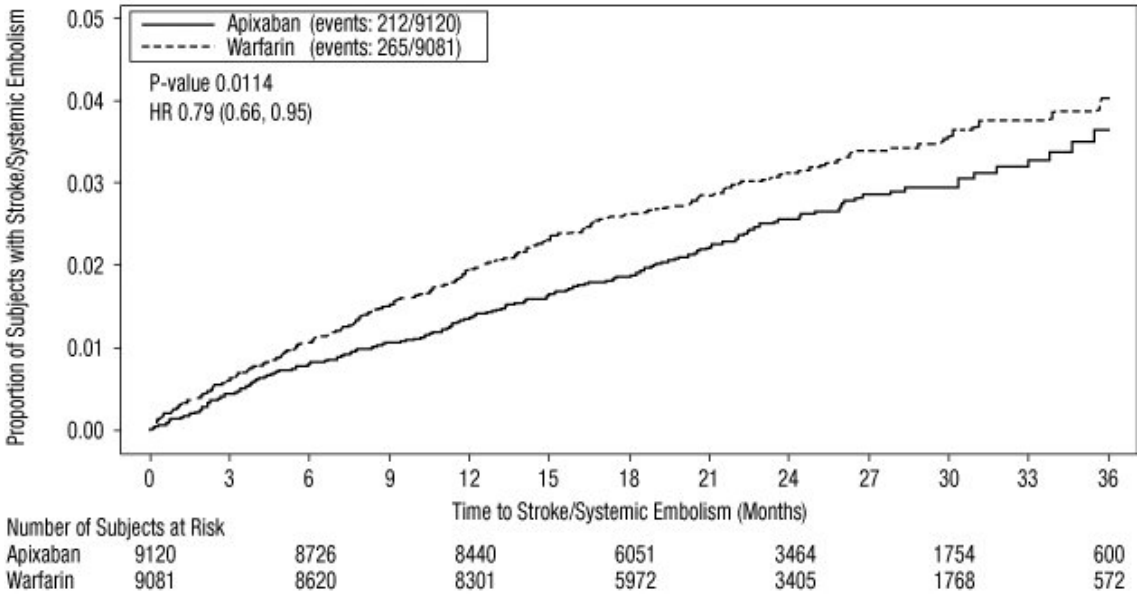
	Apixaban N=9120 n (%/yr)	**Warfarin N=9081 n (%/yr)**	**Hazard Ratio (95% CI)**	**p-value**
Stroke or systemic embolism*	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
Stroke				
Ischaemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	
Haemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	

	Apixaban N=9120 n (%/yr)	**Warfarin N=9081 n (%/yr)**	**Hazard Ratio (95% CI)**	**p-value**
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	
All-cause death*†	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465

* Assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.
† Secondary endpoint.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

The rate of myocardial infarction was similar between the apixaban and warfarin treatment groups (0.53%/year and 0.61%/year, respectively).

Figure 1: Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism in the ARISTOTLE study.



Centers were ranked post hoc by the percentage of time that warfarin-treated patients were in therapeutic range (INR 2-3). Findings for stroke/systemic embolism, major bleeds, and all-cause mortality are shown for centers above and below the median level of INR control in Table 9. The benefits of apixaban relative to warfarin were consistent in patients enrolled at centers with INR control below or above the median.

Table 9: Center INR Control in the ARISTOTLE Study

	Centers with INR control below the median of 66% Hazard Ratio (95% Confidence Interval)	Centers with INR control above the median of 66% Hazard Ratio (95% Confidence Interval)

Stroke/systemic embolism	0.78 (0.62, 0.98)	0.81 (0.61, 1.08)
Major bleed	0.56 (0.45, 0.70)	0.82 (0.68, 1.00)
All-cause mortality	0.86 (0.74, 1.00)	0.93 (0.79, 1.10)

AVERROES Study: Patients were randomized to treatment with apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, 6.4%) or ASA 81 to 324 mg once daily. The selection of an ASA dose of 81, 162, 243, or 324 mg was at the discretion of the investigator with 90.5% of subjects receiving either an 81 mg (64.3%) or 162 mg (26.2%) dose at randomization.

In the study, VKA therapy had been tried but discontinued in 40% of patients prior to enrolment. 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 medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

The primary objective of the study was to determine if apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) was superior to ASA (81-324 mg QD) for preventing the composite outcome of stroke or systemic embolism. Assessments of superiority of apixaban versus ASA were also pre-specified for major vascular events (composite outcome of stroke, systemic embolism, myocardial infarction or vascular death) and for death due to any cause.

AVERROES was stopped early upon the recommendation of the trial's independent Data Monitoring Committee which found that a predefined interim analysis revealed clear evidence of apixaban providing a clinically important reduction in stroke and systemic embolism and acceptable safety profile.

In the study, apixaban demonstrated statistically significant superiority in the primary endpoint of prevention of stroke (hemorrhagic or ischemic) and systemic embolism (see Table 10 and Figure 2). A clinically important reduction was observed in the key secondary composite endpoint of stroke, systemic embolism, myocardial infarction, or vascular death (see Table 10).

Apixaban reduced the incidence of strokes compared to ASA within each stroke severity category (modified Rankin score 0 to 2, HR=0.51 [CI=0.29, 0.91]; modified Rankin score 3 to 6, HR=0.43 [CI=0.28, 0.65]). The reduction in the stroke incidence was seen regardless of the stroke risk at entry as categorized by $CHADS_2$ score.

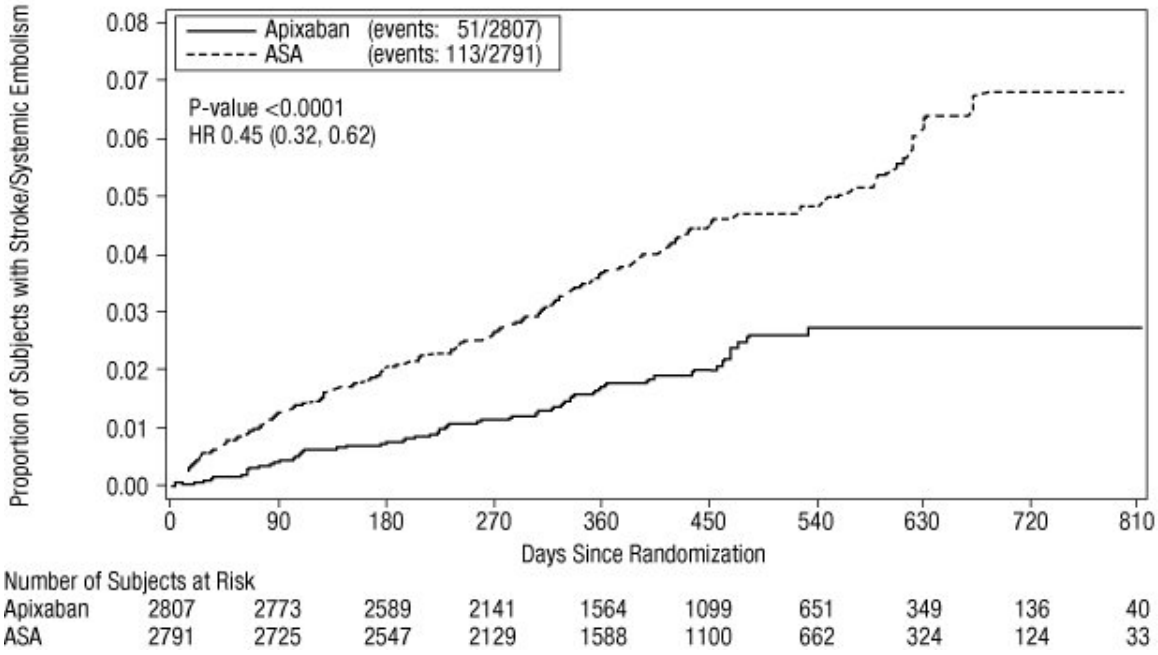
Apixaban also reduced the incidence of cardiovascular hospitalizations relative to ASA (HR =0.79, CI=0.69, 0.91).

Table 10: Key Efficacy Outcomes in Patients with Atrial Fibrillation in the AVERROES Study

	Apixaban N = 2807 n (%/year)	**ASA N = 2791 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.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Figure 2: Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism in the AVERROES study.



Number of Subjects at Risk

Apixaban	2807	2773	2589	2141	1564	1099	651	349	136	40
ASA	2791	2725	2547	2129	1588	1100	662	324	124	33

Bleeding in Patients with Atrial Fibrillation
In the ARISTOTLE and AVERROES studies, the primary safety endpoint was major bleeding, which was defined as acute clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites, intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; bleeding that is fatal. Intracranial hemorrhage included intracerebral (including hemorrhagic stroke), subarachnoid, and subdural bleeds.

Clinically relevant non-major bleeding (CRNM) was defined as acute clinically overt bleeding that does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least one of the following criteria: hospital admission for bleeding; physician guided medical or surgical treatment for bleeding; change in antithrombotic treatment (anticoagulant or antiplatelet) therapy.

ARISTOTLE Study: There was a statistically superior reduction in the incidence of ISTH major bleeding between the apixaban and warfarin treatment groups (see Table 11). There was also a substantial reduction in the incidence of ISTH major + CRNM and all bleeding.

Table 11: Bleeding Events in Patients with Atrial Fibrillation in the ARISTOTLE Study

	Apixaban N = 9088 n (%/year)	**Warfarin N = 9052 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

*Assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.
Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

Intracranial hemorrhage was reduced >50% with apixaban. GUSTO severe and TIMI major bleeding were reduced >40% with apixaban. Fatal bleeding was reduced >70% with apixaban.

Treatment discontinuation due to bleeding related adverse reactions occurred in 1.7% and 2.5% of patients treated with apixaban and warfarin, respectively.

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 incidence of ISTH major intraocular bleeding was higher with apixaban (0.18%/year) compared to warfarin (0.13%/year).

AVERROES Study: There was an increase in the incidence of major bleeding between the apixaban and ASA treatment group, which was not statistically significant (see Table 12). The frequency of fatal and intracranial bleeding was similar in the 2 treatment groups.

Table 12: Bleeding Events in Patients with Atrial Fibrillation in the AVERROES Study

	Apixaban N = 2798 n (%/year)	**ASA N = 2780 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

Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

Treatment discontinuation due to bleeding related adverse reactions occurred in 1.5% and 1.3% of patients treated with apixaban and ASA, respectively.

Paediatric Population
The European Medicines Agency has deferred the obligation to submit the results of studies with ELIQUIS in one or more subsets of the paediatric population in venous and arterial embolism and thrombosis (see section 4.2 for information on paediatric use).

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 randomized 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, 95% CI 0.0, 0.64) (nominal p-value = 0.0151). 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 (RR 1.98, 95% CI 0.19, 54.00). 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.

Subpopulation Analysis
In the ARISTOTLE study, the results for the primary efficacy endpoint and major bleeding results were generally consistent across all major subgroups including age, weight, $CHADS_2$ score, warfarin naive status, level of renal impairment, assignment to reduced dose apixaban, and ASA at randomization (see Figure 3).

Similarly, in the AVERROES study, the results for the primary efficacy endpoint and major bleeding results were consistent across all major subgroups including age.

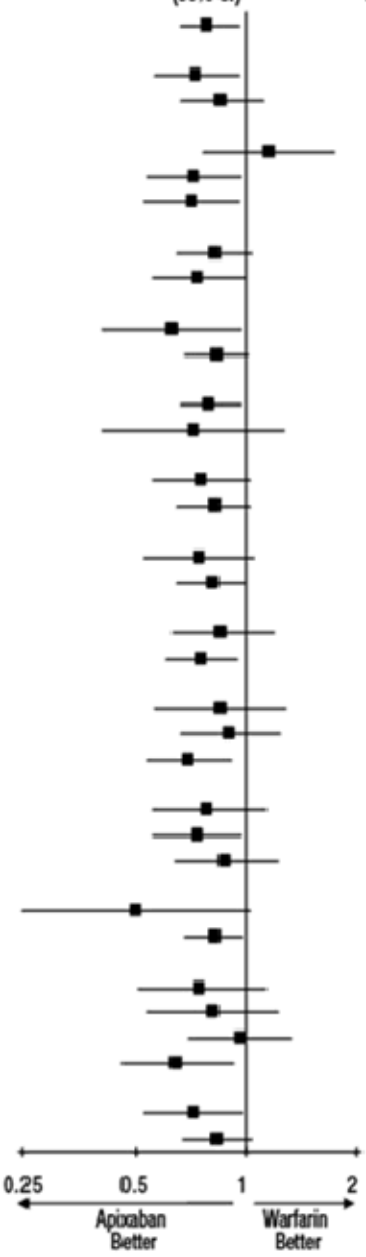
$CHADS_2$ score, level of renal impairment, and previous VKA use or VKA refusal (see Figure 4).

Notably, the efficacy and safety results for both studies in elderly patients (including those ≥75 years) were consistent with the overall population.

Figure 3: Stroke and Systemic Embolism (A), and Bleeding (B) Hazard Ratios by Baseline Characteristics - ARISTOTLE

A. Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	Warfarin	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Prior Warfarin/VKA Status				0.39
Experienced	10401	102 (1.1)	138 (1.5)	
Naive	7800	110 (1.5)	127 (1.8)	
Age				0.12
<65 yrs old	5471	51 (1.0)	44 (0.9)	
≥65 to <75 yrs old	7052	82 (1.3)	112 (1.7)	
≥75 yrs old	5678	79 (1.6)	109 (2.2)	
Gender				0.60
Male	11785	132 (1.2)	160 (1.5)	
Female	6416	80 (1.4)	105 (1.8)	
Weight				0.26
≤60 kg	1985	34 (2.0)	52 (3.2)	
>60 kg	16154	177 (1.2)	212 (1.4)	
Type of Atrial Fibrillation				0.70
Permanent/Persistent	15412	191 (1.4)	235 (1.7)	
Paroxysmal	2786	21 (0.8)	30 (1.1)	
Prior Stroke or TIA				0.71
Yes	3436	73 (2.5)	98 (3.2)	
No	14765	139 (1.0)	167 (1.2)	
Diabetes Mellitus				0.71
Yes	4547	57 (1.4)	75 (1.9)	
No	13654	155 (1.2)	190 (1.5)	
Heart Failure				0.50
Yes	5541	70 (1.4)	79 (1.6)	
No	12660	142 (1.2)	186 (1.6)	
$CHADS_2$ Score				0.45
≤1	6183	44 (0.7)	51 (0.9)	
=2	6516	74 (1.2)	82 (1.4)	
≥3	5502	94 (1.9)	132 (2.8)	
Level of Renal Impairment				0.72
Severe or Moderate	3017	54 (2.1)	69 (2.7)	
Mild	7587	87 (1.2)	116 (1.7)	
Normal	7518	70 (1.0)	79 (1.1)	
Apixaban Dose				0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)	
5 mg BID or placebo	17370	200 (1.3)	243 (1.5)	
Geographic Region				0.44
North America	4474	42 (1.0)	56 (1.3)	
Latin America	3468	43 (1.4)	52 (1.8)	
Europe	7343	75 (1.1)	77 (1.1)	
Asia/Pacific	2916	52 (2.0)	80 (3.1)	
Aspirin at Randomization				0.44
Yes	5632	70 (1.3)	94 (1.9)	
No	12569	142 (1.2)	171 (1.5)	



B. Major Bleeding

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	Warfarin	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Prior Warfarin/VKA Status				0.50
Experienced	10376	185 (2.1)	274 (3.2)	
Naïve	7764	142 (2.2)	188 (3.0)	
Age				0.64
<65 yrs old	5455	56 (1.2)	72 (1.5)	
≥65 to <75 yrs old	7030	120 (2.0)	166 (2.8)	
≥75 yrs old	5655	151 (3.3)	224 (5.2)	
Gender				0.08
Male	11747	225 (2.3)	294 (3.0)	
Female	6393	102 (1.9)	168 (3.3)	
Weight				0.22
≤60 kg	1978	36 (2.3)	62 (4.3)	
>60 kg	16102	290 (2.1)	398 (3.0)	
Type of Atrial Fibrillation				0.75
Permanent/Persistent	15361	283 (2.2)	402 (3.2)	
Paroxysmal	2776	44 (1.9)	60 (2.6)	
Prior Stroke or TIA				0.71
Yes	3422	77 (2.8)	106 (3.9)	
No	14718	250 (2.0)	356 (2.9)	
Diabetes Mellitus				0.003
Yes	4526	112 (3.0)	114 (3.1)	
No	13614	215 (1.9)	348 (3.1)	
Heart Failure				0.30
Yes	5527	87 (1.9)	137 (3.1)	
No	12613	240 (2.2)	325 (3.1)	
$CHADS_2$ Score				0.40
≤1	6169	76 (1.4)	126 (2.3)	
=2	6492	125 (2.3)	163 (3.0)	
≥3	5479	126 (2.9)	173 (4.2)	
Level of Renal Impairment				0.03
Severe or Moderate	3005	73 (3.2)	142 (6.4)	
Mild	7565	157 (2.5)	199 (3.2)	
Normal	7496	96 (1.5)	119 (1.8)	
Apixaban Dose				0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)	
5 mg BID or placebo	17314	307 (2.1)	425 (3.0)	
Geographic Region				0.16
North America	4463	106 (2.8)	137 (3.6)	
Latin America	3460	60 (2.1)	94 (3.5)	
Europe	7313	110 (1.7)	135 (2.2)	
Asia/Pacific	2904	51 (2.1)	96 (4.1)	
Aspirin at Randomization				0.40
Yes	5608	129 (2.7)	164 (3.7)	
No	12532	198 (1.9)	298 (2.8)	

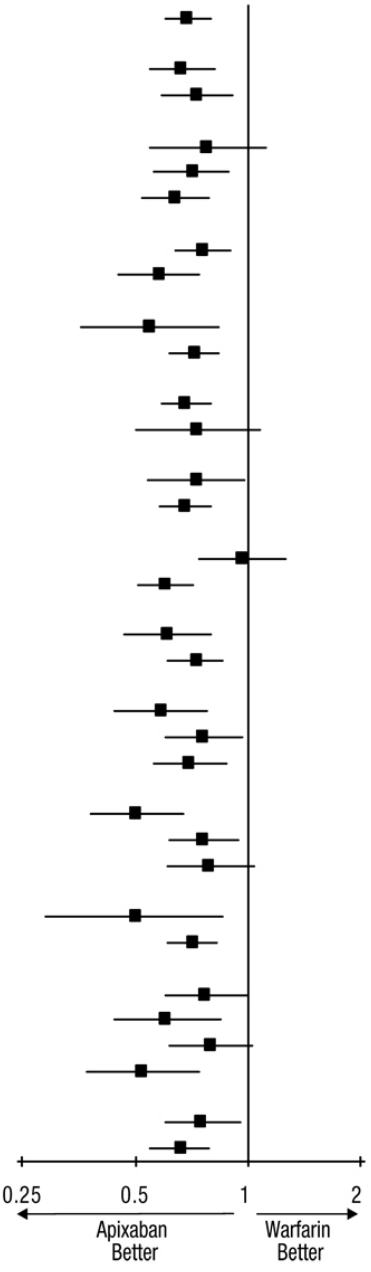
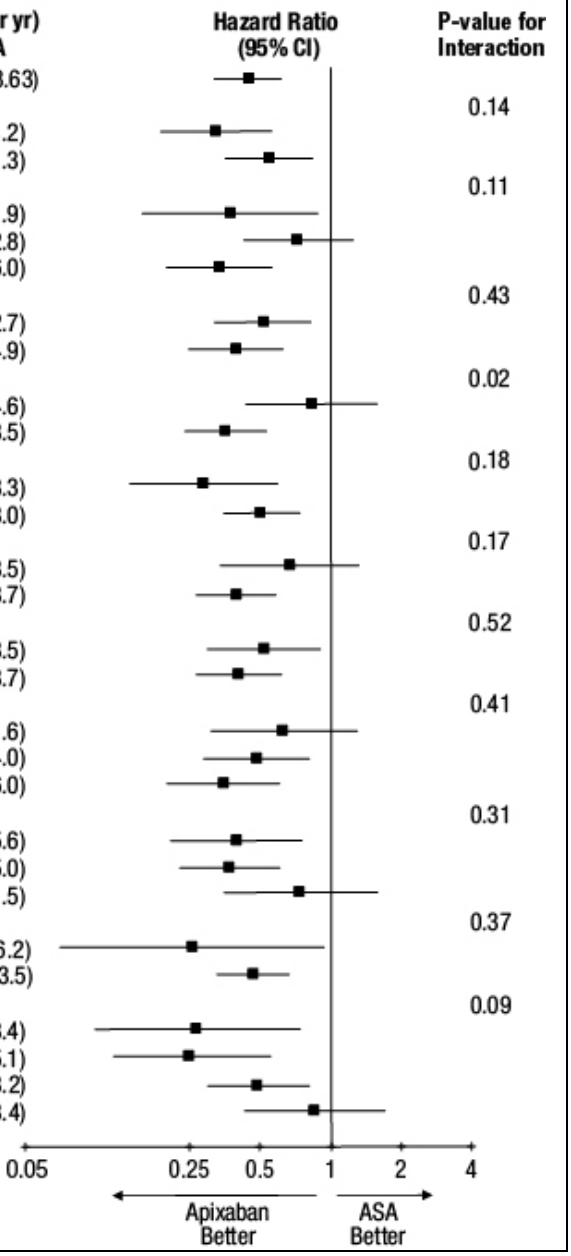


Figure 4: Stroke and Systemic Embolism (A), and Bleeding (B) Hazard Ratios by Baseline Characteristics - AVERROES

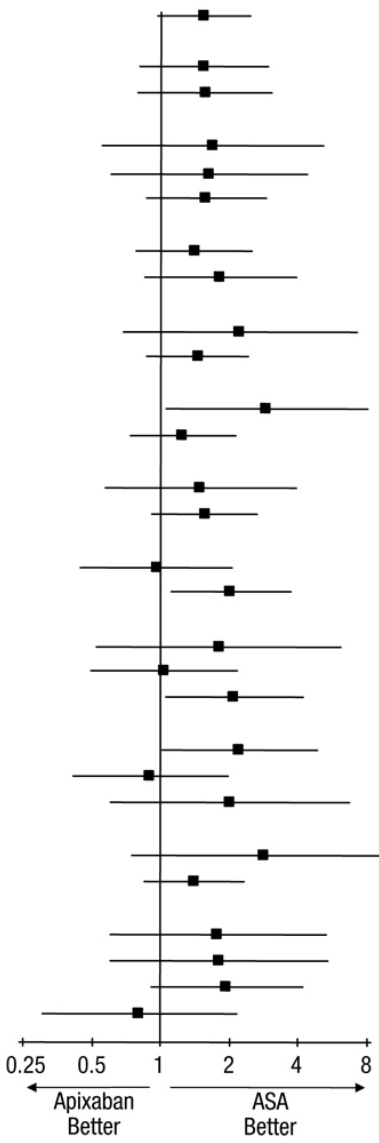
A. Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	ASA	P-value for Interaction
All Patients	5598	51 (1.62)	113 (3.63)	
Warfarin/VKA Unsuitable				0.14
Demonstrated	2215	17 (1.4)	52 (4.2)	
Expected	3383	34 (1.8)	61 (3.3)	
Age				0.11
<65 yrs old	1720	7 (0.7)	19 (1.9)	
≥65 to <75 yrs old	1987	24 (2.0)	29 (2.8)	
≥75 yrs old	1891	20 (2.0)	65 (6.0)	
Gender				0.43
Male	3277	26 (1.4)	49 (2.7)	
Female	2321	25 (1.9)	64 (4.9)	
Weight				0.02
≤60 kg	881	18 (3.9)	20 (4.6)	
>60 kg	4715	33 (1.2)	93 (3.5)	
Prior Stroke or TIA				0.18
Yes	764	10 (2.5)	33 (8.3)	
No	4834	41 (1.5)	80 (3.0)	
Diabetes Mellitus				0.17
Yes	1095	14 (2.4)	22 (3.5)	
No	4503	37 (1.4)	91 (3.7)	
Heart Failure				0.52
Yes	1810	19 (1.8)	35 (3.5)	
No	3788	32 (1.5)	78 (3.7)	
$CHADS_2$ Score				0.41
≤1	2142	12 (1.0)	19 (1.6)	
=2	1973	23 (2.0)	43 (4.0)	
≥3	1483	16 (2.1)	51 (6.0)	
Level of Renal Impairment				0.31
Severe or Moderate	1084	13 (2.3)	32 (5.6)	
Mild	2149	22 (1.8)	58 (5.0)	
Normal	1878	12 (1.1)	16 (1.5)	
Apixaban Dose				0.37
2.5 mg BID or placebo	361	3 (1.6)	12 (6.2)	
5 mg BID or placebo	5237	48 (1.6)	101 (3.5)	
Geographic Region				0.09
North America	804	5 (0.9)	18 (3.4)	
Latin America	1185	8 (1.3)	31 (5.1)	
Europe	2507	23 (1.6)	46 (3.2)	
Asia/Pacific	1102	15 (2.9)	18 (3.4)	



B. Major Bleeding

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	ASA	P-value for Interaction
All Patients	5578	45 (1.41)	29 (0.92)	
Warfarin/VKA Unsuitable				0.97
Demonstrated	2207	23 (1.8)	15 (1.2)	
Expected	3371	22 (1.1)	14 (0.7)	
Age				>0.99
<65 yrs old	1717	8 (0.8)	5 (0.5)	
≥65 to <75 yrs old	1979	11 (0.9)	6 (0.6)	
≥75 yrs old	1882	26 (2.7)	18 (1.7)	
Gender				0.59
Male	3269	27 (1.4)	19 (1.0)	
Female	2309	18 (1.4)	10 (0.8)	
Weight				0.55
≤60 kg	876	9 (1.9)	4 (0.9)	
>60 kg	4701	36 (1.3)	25 (0.9)	
Prior Stroke or TIA				0.15
Yes	763	15 (3.6)	5 (1.2)	
No	4815	30 (1.1)	24 (0.9)	
Diabetes Mellitus				0.93
Yes	1092	10 (1.7)	7 (1.1)	
No	4486	35 (1.4)	22 (0.9)	
Heart Failure				0.13
Yes	1803	13 (1.2)	13 (1.3)	
No	3775	32 (1.5)	16 (0.8)	
$CHADS_2$ Score				0.39
≤1	2133	7 (0.6)	4 (0.3)	
=2	1967	15 (1.3)	13 (1.2)	
≥3	1478	23 (3.0)	12 (1.4)	
Level of Renal Impairment				0.25
Severe or Moderate	1080	20 (3.5)	9 (1.6)	
Mild	2140	12 (1.0)	13 (1.1)	
Normal	1872	8 (0.7)	4 (0.4)	
Apixaban Dose				0.34
2.5 mg BID or placebo	360	8 (4.5)	3 (1.6)	
5 mg BID or placebo	5218	37 (1.2)	26 (0.9)	
Geographic Region				0.54
North America	800	9 (1.8)	5 (1.0)	
Latin America	1184	9 (1.4)	5 (0.8)	
Europe	2498	20 (1.4)	10 (0.7)	
Asia/Pacific	1096	7 (1.3)	9 (1.6)	



Treatment of VTE

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

Table 13: Patient demographic characteristics in the clinical studies

	AMPLIFY	**AMPLIFY-EXT**
Randomized patients	5395	2482
Mean age	56.9	56.7
>75 years	14.3%	13.3%
Gender (male)	58.7%	57.4%
Race		
White/Caucasian	82.7%	85.3%
Black/African American	3.8%	3.2%
Asian	8.4%	4.8%

Table 14: Patient risk factors for DVT/PE in the clinical studies

	AMPLIFY	**AMPLIFY-EXT**
Unprovoked events	89.8%	91.7%
Previous episode of PE or proximal VTE	16.2%	n/a*
Immobilization	6.4%	2.8%
Cancer (active)	2.7%	1.7%
Cancer (history)	9.7%	9.2%
Renal function		
Normal CrCl	64.5%	70.1%
CrCl 50 - ≤80 mL/min	20.3%	21.6%
CrCl 30 - ≤50 mL/min	5.7%	5.3%
CrCl ≤30 mL/min	0.5%	0.2%
History of prothrombotic genotype	2.5%	3.8%

* All patients in AMPLIFY-EXT were required to have a previous episode of PE or proximal VTE in order to enter the study.

AMPLIFY Study: Patients were randomized 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. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, or active bleeding were excluded from the studies. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9.

The primary objective of the study was to determine if apixaban was non-inferior to enoxaparin/warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death over 6 months of therapy.

In the study, apixaban was shown to be non-inferior to enoxaparin/warfarin in the combined endpoint of adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE related death (see Table 15).

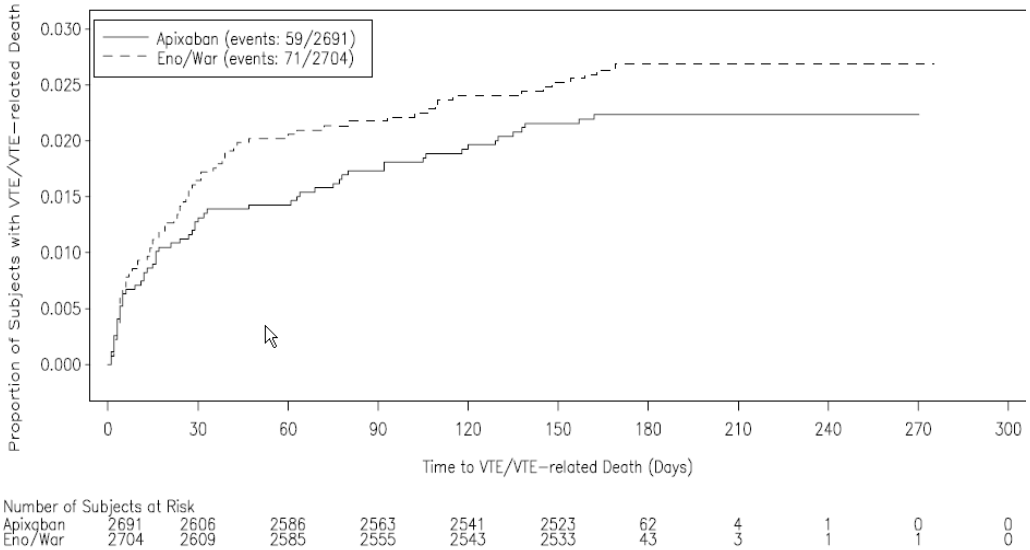
Table 15: Efficacy Results in the AMPLIFY Study

	Apixaban N=2609 n (%)	**Enoxaparin/ Warfarin N=2635 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)

* Non-inferior compared to enoxaparin/warfarin (P-value <0.0001).

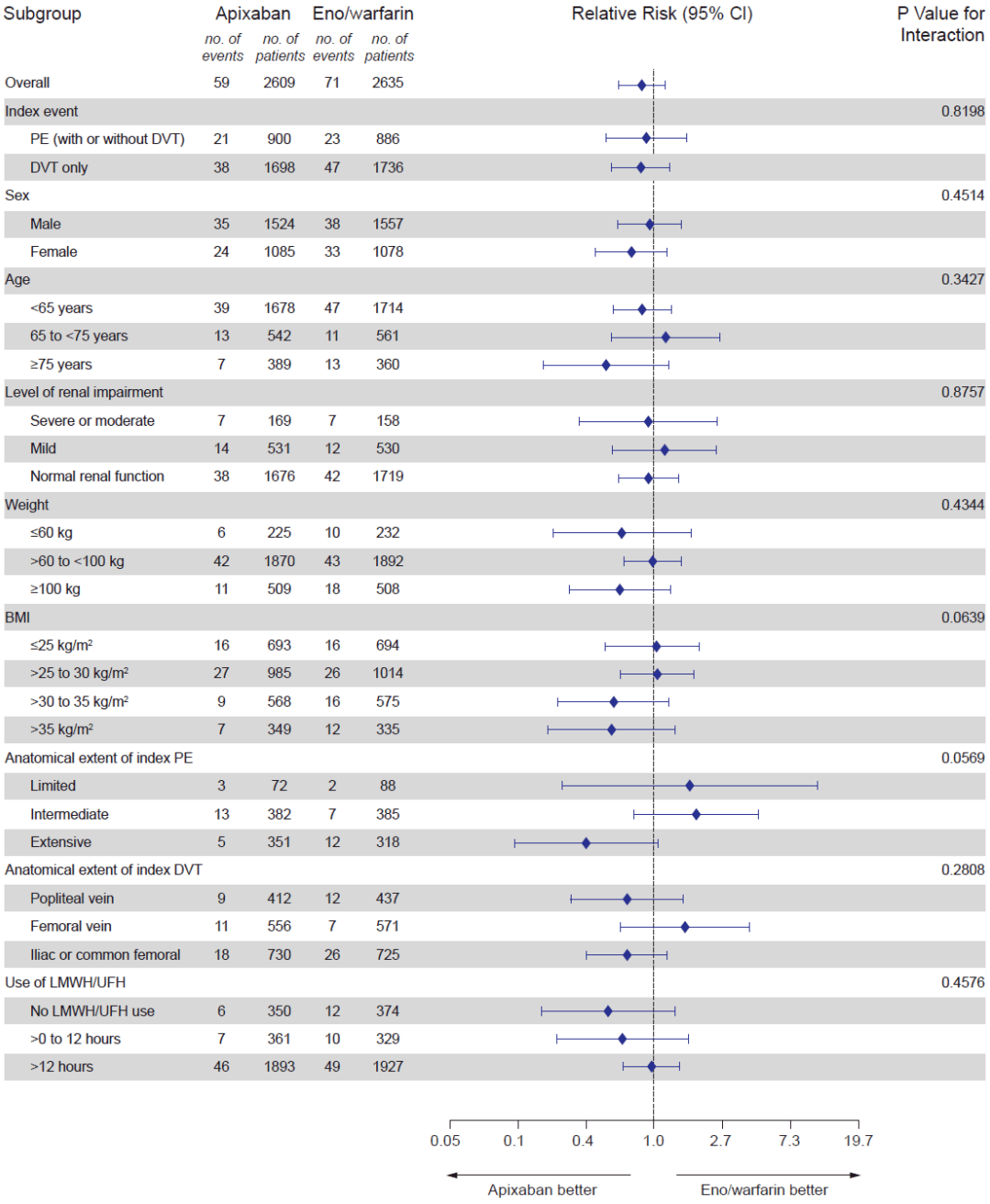
Figure 5 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups in the AMPLIFY study.

Figure 5: Kaplan-Meier Estimate of Time to First DVT or PE, or VTE-related Death in the AMPLIFY Study (Intent-to-Treat Population)



Apixaban efficacy in initial treatment of VTE was consistent between patients who were treated for a PE [Relative Risk 0.9, 95% confidence interval (0.5, 1.6)] or DVT [Relative Risk 0.8, 95% confidence interval (0.5, 1.3)]. Efficacy across subgroups, including age, gender, renal function, body mass index (BMI), extent of index PE, location of DVT thrombus, and prior parenteral heparin use was generally consistent (see Figure 6).

Figure 6: Recurrent Symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related Death Relative Risk by Baseline Characteristics



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 16).

Table 16: Bleeding Results in the AMPLIFY Study

	Apixaban N=2676 n (%)	**Enoxaparin/ Warfarin N=2689 n (%)**	**Relative Risk (95% CI*)**	**P-value**
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55)	<0.0001
CRNM†	103 (3.9)	215 (8.0)	0.48 (0.38, 0.60)	
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)	

* Confidence interval.
† CRNM = clinically relevant non-major bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

The adjudicated major bleeding and CRNM bleeding at any anatomical site was generally lower in the apixaban group 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.

During the 6 months of the study, fewer patients were hospitalized in the apixaban group [153 (5.7%)] compared to the warfarin treated patients [190 (7.1%)].

AMPLIFY-EXT Study: Patients were randomized 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. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

The primary objective of the study was to determine if apixaban was superior to placebo in the combined endpoint of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause death.

In the study, both doses of apixaban were statistically superior to placebo in the primary endpoint of symptomatic, recurrent VTE or all-cause death (see Table 17).

Table 17: Efficacy Results in the AMPLIFY-EXT Study

	Apixaban	**Apixaban**	**Placebo**	**Relative Risk (95% CI)**		**P-value**
	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 (%)					

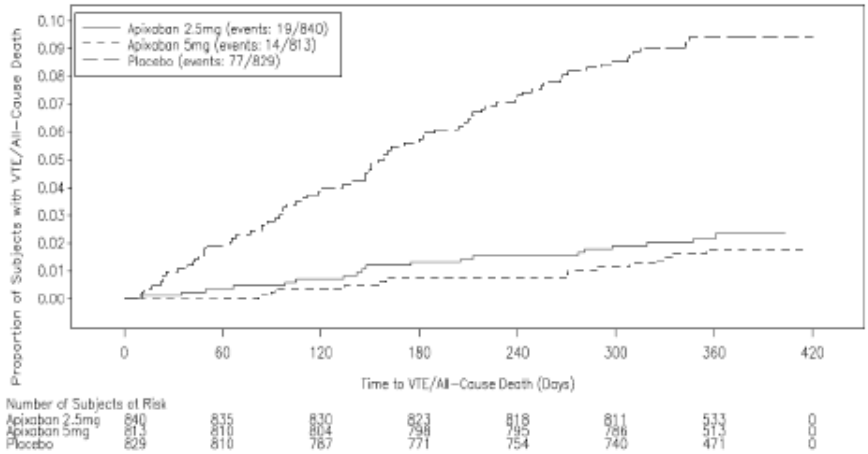
Table 17: Efficacy Results in the AMPLIFY-EXT Study

	Apixaban 2.5 mg (N=840)	Apixaban 5.0 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI) Apix 2.5 mg vs. Placebo	Relative Risk (95% CI) Apix 5.0 mg vs. Placebo	P-value
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)	<0.0001
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)	
Non-fatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)	
Non-fatal 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)	
CV-related death	2 (0.2)	3 (0.4)	10 (1.2)	0.20 (0.04, 0.90)	0.31 (0.09, 1.11)	

* 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.

Figure 7 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the three treatment groups in the AMPLIFY-EXT study.

Figure 7: Kaplan-Meier Estimate of Time to First DVT or PE, or All-cause Death in the AMPLIFY-EXT Study (Intent-to-Treat Population)



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 was similar between the apixaban and placebo groups. 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. The frequency of major + CRNM bleeding in the apixaban 5 mg twice daily group was not statistically different from the placebo group. The frequency of CRNM, minor bleeding, and all bleeding in the apixaban 5 mg twice daily group was statistically different from the placebo group (see Table 18).

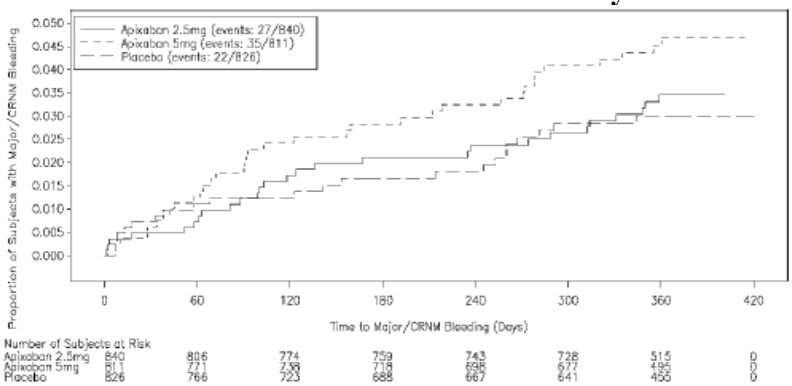
Table 18: Bleeding Results in the AMPLIFY-EXT Study

	Apixaban	**Apixaban**	**Placebo**	**Relative Risk (95% CI*)**	
	2.5 mg (N=840)	**5.0 mg** (N=811) n (%)	(N=826)	**Apix 2.5 mg** vs. Placebo	**Apix 5.0 mg** vs. Placebo
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)
CRNM†	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72, 2.33)	1.82 (1.05, 3.18)
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)

* Confidence interval.
† CRNM = clinically relevant non-major bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Figure 8 is a plot of the time from randomization to the occurrence of the first major or clinically relevant non-major bleeding event in the three treatment groups in the AMPLIFY-EXT study.

Figure 8: Kaplan-Meier Estimate of Major/Clinically Relevant Non-major Bleeding During the Treatment Period in the AMPLIFY-EXT Study



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.

During the 12 months of the study, fewer patients were hospitalized in the apixaban groups [42 (5%) in the 2.5 mg twice daily group; 34 (4.2%) in the 5 mg twice daily group] compared to the placebo treated patients [62 (7.5%)].

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was comparable to exposure after oral administration of 2 intact 5 mg tablets.

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

Metabolism 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 non-clinical 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 metabolized mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-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).

Renal impairment

There was no impact of impaired renal function on peak concentration of apixaban. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51 - 80 mL/min), moderate (creatinine clearance 30 – 50 mL/min) and severe (creatinine clearance 15 – 29 mL/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44% respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity. No dose adjustment is necessary in patients with mild, moderate or severe renal impairment. There are no data available in patients with creatinine clearance <15 mL/min or in patients undergoing dialysis, therefore apixaban is not recommended in these patients (see sections 4.2 and 4.4).

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 hemodialysis, compared to that seen in subjects with normal renal function. Hemodialysis, 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.

Hepatic impairment

Apixaban has not been studied in patients with severe hepatic impairment or active hepatobiliary disease.

Apixaban is not recommended in patients with severe hepatic impairment (see section 4.4).

In a study comparing subjects with mild and moderate hepatic impairment (classified as Child Pugh A and B, respectively) to 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. No

dose adjustment is required in patients with mild or moderate hepatic impairment; however, given the limited number of subjects studied, caution is advised when using ELIQUIS in this population (see sections 4.2 and 4.4).

Elderly
Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher. No dose adjustment is required, except as described in section 4.2.

Gender
Exposure to apixaban was approximately 18% higher in females than in males. No dose adjustment is required.

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 consistent with the phase I results. No dose adjustment is required.

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. No dose adjustment is required, except as described in section 4.2.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 – 50 mg). The relationship between apixaban concentration and factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients who received apixaban following elective hip or knee replacement surgery was consistent with that established in healthy subjects.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryofoetal development (see section 4.6). In the offspring of pregnant rats treated with apixaban there were decreases in mating and fertility. These effects were minimal and observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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.

6. PHARMACEUTICAL PROPERTIES

6.1 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)

6.2. Shelf life

36 months.

6.3. Special precautions for storage

Store below 30°C

7. MARKETING AUTHORISATION NUMBER

ELIQUIS 2.5 mg: Box of 2 blisters @ 10 tablets; Reg. No.: **DKI2190702117A1**

ELIQUIS 5.0 mg: Box of 1 blister @ 10 tablets; Reg. No.: **DKI2190702117B1**
Box of 2 blisters @ 10 tablets; Reg. No.: **DKI2190702117B1**

HARUS DENGAN RESEP DOKTER

8. MARKETING AUTHORISATION HOLDER NAME AND ADDRESS

Manufactured by:
Pfizer Ireland Pharmaceuticals, Little Cornell Newbridge, Co. Kildare, Ireland

Packed and released by:
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1, 79090
Freiburg, Germany

Imported by:
PT. Pfizer Indonesia,
Jakarta, Indonesia