PRODUCT MONOGRAPH

Pr SANDOZ® APIXABAN SDZ

Apixaban Tablets
2.5 mg and 5 mg

Anticoagulant

Sandoz Canada Inc.
110 Rue de Lauzon
Boucherville, Quebec
J4B 1E6

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet, 2.5 mg and 5 mg	Lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, hypromellose, magnesium stearate, titanium dioxide, triacetin. Tartrazine aluminum lake, sunset yellow FCF aluminum lake, iron oxide yellow (2.5 mg tablets only), iron oxide red (5 mg tablets only).

INDICATIONS AND CLINICAL USE

Sandoz Apixaban SDZ (apixaban) is indicated for:

- the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery.
- the prevention of stroke and systemic embolism in patients with atrial fibrillation.
- the treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.

Geriatrics (≥ 65 years of age):
Clinical studies in VTE prevention, stroke prevention in patients with atrial fibrillation (SPAF), treatment of DVT and PE, and prevention of recurrent DVT and PE included patients ≥ 65 years of age (see WARNINGS AND PRECAUTIONS, Renal Impairment, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS).

Pediatrics (< 18 years of age):
The safety and efficacy of apixaban in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use. Pharmacokinetic / pharmacodynamic data are available from a single-dose pediatric study (28 days to <18 years) (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

CONTRAINDICATIONS

- Clinically significant active bleeding, including gastrointestinal bleeding

- Lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (ischemic or hemorrhagic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis

- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see ACTION AND CLINICAL PHARMACOLOGY, Hepatic Impairment)

- Concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (P-gp) such as azole-antimycotics, e.g., ketoconazole, itraconazole, voriconazole, or posaconazole, and HIV protease inhibitors, e.g., ritonavir (see WARNINGS AND PRECAUTIONS, Drug Interactions, and DRUG INTERACTIONS, Inhibitors of both CYP 3A4 and P-gp)

- Concomitant treatment with any other anticoagulant, including
    - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
    - low molecular weight heparins (LMWH), such as enoxaparin and dalteparin,
    - heparin derivatives, such as fondaparinux, and
    - oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, except under circumstances of switching therapy to or from apixaban.

- Hypersensitivity to apixaban or to any ingredients of the formulation. For a complete listing of ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING SANDOZ APIXABAN SDZ, INCREASES THE RISK OF THROMBOTIC EVENTS.

To reduce this risk, consider coverage with another anticoagulant if Sandoz Apixaban SDZ is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

The following Warnings and Precautions are listed in alphabetical order.

Bleeding

The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. As with all anticoagulants, apixaban should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with apixaban. An unexplained fall in hemoglobin, hematocrit or blood pressure should lead to a search for a bleeding site. Patients should be advised of signs and symptoms of blood

loss and to report them immediately or go to an emergency room.

Patients at high risk of bleeding should not be prescribed Sandoz Apixaban SDZ (see CONTRAINDICATIONS).

Should severe bleeding occur, treatment with Sandoz Apixaban SDZ must be discontinued and the source of bleeding investigated promptly.

Close clinical surveillance (i.e., looking for signs of bleeding or anemia) is recommended throughout the treatment period. This may include looking for obvious signs of bleeding, e.g. hematomas, epistaxis, or hypotension, testing for occult blood in the stool, checking serum hemoglobin for significant decrease, etc., especially if other factors/conditions that generally increase the risk of hemorrhage are also present. (see Table 1 below).

Table 1 – Factors Which Increase Hemorrhagic Risk

Factors increasing apixaban plasma levels	Severe renal impairment (eCrCl < 30 mL/min)
	Concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp
Pharmacodynamic interactions	NSAID
	Platelet aggregation inhibitors, including ASA, clopidogrel, prasugrel, ticagrelor
	Selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs)
Diseases / procedures with special hemorrhagic risks	Congenital or acquired coagulation disorders
	Thrombocytopenia or functional platelet defects
	Uncontrolled severe arterial hypertension
	Active ulcerative gastrointestinal disease
	Recent gastrointestinal bleeding
	Recent intracranial hemorrhage
	Intraspinal or intracerebral vascular abnormalities
	Recent brain, spinal or ophthalmological surgery
	Bronchiectasis or history of pulmonary bleeding
Others	Age > 75 years

Concomitant use of apixaban with drugs affecting hemostasis increases the risk of bleeding.

Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAID), acetylsalicylic acid (ASA), platelet aggregation inhibitors, selective serotonin reuptake inhibitors (SSRI), or serotonin norepinephrine reuptake inhibitors (SNRIs) (see also DRUG INTERACTIONS).

Concomitant use of ASA or dual antiplatelet therapy with either apixaban or warfarin increases the risk of major bleeding in patients with atrial fibrillation. Other platelet aggregation inhibitors such as prasugrel and ticagrelor, have not been studied with apixaban in any patient population, and are not recommended as concomitant therapy (see DRUG INTERACTIONS).

In patients with atrial fibrillation and having a condition that warrants single or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made

before combining this therapy with apixaban.

In high-risk patients following acute coronary thrombosis, apixaban 5 mg bid, as an adjunct to standard anti-platelet treatment, has led to significantly increased bleeding (see ACTION AND CLINICAL PHARMACOLOGY, Post-acute coronary syndrome patients).

The use of thrombolytics should generally be avoided during acute myocardial infarction (AMI) or acute stroke in patients treated with apixaban, due to expected increased risk of major bleeding.

Cardiovascular

Patients with Valvular Disease

Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis. There are no data to support that apixaban 5 mg twice daily or 2.5 mg twice daily provides adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of apixaban is not recommended in this setting.

Of note, in the pivotal ARISTOTLE trial, that evaluated apixaban in the prevention of stroke in atrial fibrillation when compared to warfarin, 18% of patients had other valvular disease, including aortic stenosis, aortic regurgitation, and/or mitral regurgitation. In the AVERROES trial, that also evaluated apixaban in patients with atrial fibrillation but when compared to ASA, 23% had other valvular disease of a similar nature to that described just above in the ARISTOTLE trial.

Drug Interactions

Inhibitors of Both CYP 3A4 and P-glycoprotein (P-gp)

Co-administration of apixaban with ketoconazole (400 mg q.d.), a strong inhibitor of CYP 3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in apixaban C_{max}. Therefore, the use of apixaban is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole), and HIV protease inhibitors (e.g., ritonavir) (see CONTRAINDICATIONS). These drug products may increase apixaban exposure by two-fold (see DRUG INTERACTIONS, Inhibitors of Both CYP 3A4 and P-gp).

Inducers of Both CYP 3A4 and P-gp

The concomitant use of apixaban with strong inducers of CYP 3A4 and P-gp (e.g., rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) reduces apixaban exposure.

Combined use of apixaban with strong inducers of both CYP 3A4 and P-gp should generally be avoided since efficacy of apixaban may be compromised (see DRUG INTERACTIONS, Inducers of Both CYP 3A4 and P-gp). Paradoxically, increased bleeding has been noted in patients with atrial fibrillation taking concomitant inducers with either apixaban or warfarin (see DRUG INTERACTIONS, Inducers of Both CYP 3A4 and P-gp, Table 10).

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see CONTRAINDICATIONS). Apixaban is not recommended in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Hepatic Impairment). Apixaban should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Patients with elevated liver enzymes (ALT/AST > 2 x ULN, or total bilirubin ≥ 1.5 x ULN) were excluded in clinical trials. Therefore, apixaban should be used with caution in these patients.

Peri-Operative/Procedural Considerations

As with any anticoagulant, patients on apixaban who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of apixaban may be required.

Pre-Operative Phase

If an invasive procedure or surgical intervention is required, apixaban should be stopped at least 24 hours before the intervention, if possible, due to increased risk of bleeding, and based on clinical judgment of the physician. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention. Although there are limited data, in patients at higher risk of bleeding or in major surgery where complete hemostasis may be required, consider stopping apixaban at least 48 hours before surgery, depending on clinical circumstances. Apixaban should be restarted after surgery or interventional procedures as soon as it has been determined that adequate hemostasis has been established.

Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture

When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk for developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis.

The risk of these events is even further increased by the use of indwelling catheters or the concomitant use of drugs affecting hemostasis. Accordingly, indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of apixaban. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of apixaban should be delayed for 24 hours.

Patients who have undergone epidural puncture and who are receiving apixaban should be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.

The physician should consider the potential benefit versus the risk before neuraxial intervention

in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use apixaban only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 24 hours after the last administration of apixaban.

Post-Procedural Period
Apixaban should be restarted following an invasive procedure or surgical intervention as soon as adequate hemostasis has been established and the clinical situation allows, in order to avoid unnecessary increased risk of thrombosis.

Pulmonary
Apixaban is **not** recommended as an alternative to unfractionated heparin for the treatment of VTE in patients with pulmonary embolism who are hemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of apixaban have not been established in these clinical situations.

Patients with antiphospholipid syndrome
Direct acting oral anticoagulants (DOACs), including Apixaban, are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (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 Apixaban in patients with APS have not been established.

Renal

Anticoagulant-related nephropathy
There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following Apixaban, presenting as acute kidney injury. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and hematuria.

Renal Impairment
Determine estimated creatinine clearance (eCrCl) in all patients before instituting apixaban (see DOSAGE AND ADMINISTRATION).

Apixaban is not recommended in patients with creatinine clearance < 15 ml/min, or in those undergoing dialysis (see DOSAGE AND ADMINISTRATION, Renal Impairment, and ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment)

Stroke Prevention in Patients with Atrial Fibrillation
No dose adjustment is necessary in patients with mild or moderate renal impairment, or in those with eCrCl 25 - 30 mL/min, unless at least two (2) of the following criteria for dose reduction are met: age ≥ 80 years, body weight ≤ 60 kg, or patients with serum creatinine ≥ 133 micromol/L (1.5 mg/dL). In this case, patients should receive a reduced dose of apixaban 2.5 mg twice daily (see DOSAGE AND ADMINISTRATION).

In patients with eCrCl 15 - 24 mL/min, no dosing recommendation can be made as clinical data are very limited.

Special Populations

Pregnant Women

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. Apixaban is not recommended during pregnancy.

Nursing Women

It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. In rats, this resulted in high milk-to-maternal plasma ratios (apixaban AUC ~ 30, C_{max} ~ 8).

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.

Hip Fracture Surgery Patients

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

Pediatrics (< 18 years of age)

The efficacy and safety of apixaban in pediatric patients have not been established (see INDICATIONS AND CLINCIAL USE, Pediatrics); therefore, Health Canada has not authorized an indication for pediatric use. Data are available from a single-dose study which evaluated the pharmacokinetics and pharmacodynamics of apixaban in pediatric subjects aged between 28 days to < 18 years at risk for a venous or arterial thrombotic disorder (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).**

Geriatrics (≥ 65 years of age)

- *Prevention of VTE following elective hip or knee replacement surgery:* No dose adjustment is necessary in elderly patients. Of the total number of patients in clinical studies of apixaban in VTE prevention following major orthopedic surgery (N=5924), 50 percent were 65 and older, while 16 percent were 75 and older.

- *Stroke Prevention in Patients with Atrial Fibrillation (SPAF):* No dose adjustment is necessary in elderly patients, unless the criteria for dose reduction are met (see DOSAGE and ADMINISTRATION). Of the total number of patients in the ARISTOTLE and AVERROES studies, about 69 percent were 65 and older and about 32 percent were 75 and older in these trials.

- *Treatment of DVT and PE and Prevention of recurrent DVT and PE*: No dose adjustment is necessary in elderly patients. But caution is required when prescribing apixaban to

elderly patients (≥ 75 years of age). Of the total number of patients in clinical studies of apixaban in VTE treatment and prevention of recurrent DVT and PE (N=7877), about 35 percent were 65 and older, while about 14 percent were 75 and older, respectively.

Monitoring and Laboratory Tests

The pharmacodynamic effects of apixaban are reflective of the mechanism of action, namely Factor-Xa (FXa) inhibition. As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Due to their lack of sensitivity, PT or aPTT are not recommended to assess the pharmacodynamic effects of apixaban.

Although apixaban therapy will lead to an elevated INR, depending on the timing of the measurement (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics), the INR is not a valid measure to assess the anticoagulant activity of apixaban (see also DOSAGE AND ADMINISTRATION, Switching from apixaban to VKA, Considerations for INR Monitoring of VKA Activity during Concomitant apixaban Therapy). The INR is only calibrated and validated for vitamin K antagonists (VKA) and should not be used for any other anticoagulant, including apixaban.

Apixaban demonstrates anti-FXa activity as evident by reduction in Factor-Xa enzyme activity in the Rotachrom® Heparin Anti-Xa 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 plasma 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, for anti-FXa activity compared to that seen with standard clotting tests, such as PT and aPTT (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Although there is no need to monitor anticoagulation effect of apixaban during routine clinical practice, in certain infrequent situations such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of apixaban may be appropriate. Accordingly, a calibrated quantitative anti-FXa assay may be useful to inform clinical decisions in these circumstances. See ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Table 13, for predicted steady-state peak and trough anti-FXa activity in different indications and for different doses of apixaban.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Prevention of VTE following Elective Hip or Knee Replacement Surgery

The safety of apixaban 2.5 mg twice daily has been evaluated in one Phase II and three Phase III studies (ADVANCE 1, 2 and 3) including 5,924 patients exposed to apixaban after undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) and treated for up to 38 days.

Stroke Prevention in Patients with Atrial Fibrillation (SPAF)
The safety of apixaban has been evaluated in the ARISTOTLE and AVERROES studies, including 11,284 patients exposed to apixaban 5 mg twice daily, and 602 patients exposed to apixaban 2.5 mg twice daily. The duration of apixaban exposure was ≥ 12 months for 9,375 patients, and ≥ 24 months for 3,369 patients in the two studies. In ARISTOTLE, 9,088 patients were exposed to apixaban over a mean duration of 89.2 weeks, and 9,052 to dose-adjusted warfarin (INR 2.0 to 3.0) over a mean duration of 87.5 weeks. In AVERROES, 2,798 patients were exposed to apixaban, and 2,780 to ASA, over a mean duration of approximately 59 weeks in both treatment groups.

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study, and 1.5% for apixaban and 1.3% for ASA in the AVERROES study.

Treatment of DVT and PE and Prevention of recurrent DVT and PE
The safety of apixaban has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to apixaban 10 mg twice daily for up to 7 days, 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 10 mg twice daily followed by 5 mg twice daily was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. The mean duration of exposure to either 2.5 mg or 5 mg apixaban was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study.

Bleeding
Bleeding is the most relevant adverse reaction of apixaban. Bleeding of any type was observed in approximately 12% of patients treated with apixaban short-term following hip replacement surgery and about 6% following knee replacement surgery. In long-term treatment in patients having atrial fibrillation, bleeding of any type of severity occurred at a rate of 18% per year for patients exposed to apixaban in the ARISTOTLE trial, and 11% per year in the AVERROES trial.

Major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Prevention of VTE following Elective Hip or Knee Replacement Surgery
In all Phase III studies, bleeding was assessed beginning with the first dose of double-blind study drug. In studies that compared apixaban to the 40 mg once daily dose of enoxaparin, the first dose of either enoxaparin or injectable placebo was given 9 to 15 hours before surgery. Bleeding during the treatment period for these studies includes events that occurred before the first dose of apixaban, which was given 12-24 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 in these two studies occurred prior to the first dose of apixaban. For the study that compared apixaban with enoxaparin given every 12 hours, the first dose of both oral and injectable study drugs was 12-24 hours after surgery. For this study, the treatment period and post-surgery treatment period are identical. Table 2 shows the

bleeding results from the treatment period and the post-surgery treatment period.

Table 2 - Bleeding in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding endpoint[a]	ADVANCE-3 Hip replacement surgery		ADVANCE-2 Knee replacement surgery		ADVANCE-1 Knee replacement surgery	
	Apixaban 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	Apixaban 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	Apixaban 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post-surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post-surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post-surgery	First dose 12 to 24 hours post-surgery
All treated	n = 2673	n = 2659	n = 1501	n = 1508	n = 1596	n = 1588
Treatment Period[b]						
Major	22 (0.8%)	18 (0.7%)	9 (0.6%)	14 (0.9%)	11 (0.7%)	22 (1.4%)
Fatal	0	0	0	0	0	1 (< 0.1%)
Major +CRNM	129 (4.8%)	134 (5.0%)	53 (3.5%)	72 (4.8%)	46 (2.9%)	68 (4.3%)
All	313 (11.7%)	334 (12.6%)	104 (6.9%)	126 (8.4%)	85 (5.3%)	108 (6.8%)
Post-surgery Treatment Period						
Major	9 (0.3%)	11 (0.4%)	4 (0.3%)	9 (0.6%)	11 (0.7%)	22 (1.4%)
Fatal	0	0	0	0	0	1 (< 0.1%)
Major +CRNM	96 (3.6%)	115 (4.3%)	41 (2.7%)	56 (3.7%)	46 (2.9%)	68 (4.3%)
All	261 (9.8%)	293 (11.0%)	89 (5.9%)	103 (6.8%)	85 (5.3%)	108 (6.8%)

[a]All bleeding criteria included surgical site bleeding.
[b]Includes bleeding events which occurred before the first dose of apixaban.

Stroke Prevention in Patients with Atrial Fibrillation (SPAF)

Bleeding events observed in patients with atrial fibrillation are presented below in Tables 3 and 4.

Table 3 - Bleeding Events* in the ARISTOTLE Study

	Apixaban N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI)	p-value
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

Events for each endpoint were counted once per subject but subjects may have contributed events to more than one endpoint
* Dataset includes events occurring on-treatment plus the following two days; Assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.
** Clinically relevant non-major (CRNM) bleeding - clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician- guided medical or surgical treatment, or a change in antithrombotic therapy

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 major gastrointestinal bleeds, including upper GI, lower GI, and rectal bleeding, was reported at 0.8% per year with apixaban, and 0.9% per year with warfarin.

In the ARISTOTLE study, concomitant aspirin use with either apixaban or warfarin increased the risk of major bleeding 1.5 to 2 times when compared with those patients not treated with concomitant aspirin. Apixaban, like other anticoagulants, should be used with caution in patients treated concomitantly with antiplatelet agents.

Table 4 – Bleeding Events* in the AVERROES Study

	Apixaban N=2798 n (%/year)	**Aspirin N=2780 n (%/year)**	**Hazard Ratio vs Aspirin (95%CI)**	**p-value**
Major*	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal	5 (0.16)	5 (0.16)		
Intracranial	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 for each endpoint were counted once per subject but subjects may have contributed events to more than one endpoint.

* Dataset includes events occurring on-treatment, plus the following two days for patients that did not enter open-label extension

** Clinically relevant non-major (CRNM) bleeding, CRNM = clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician- guided medical or surgical treatment, or a change in antithrombotic therapy

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

Treatment of DVT and PE and Prevention of recurrent DVT and PE

Bleeding events observed in clinical studies of apixaban in VTE treatment and prevention of recurrent DVT and PE are presented below in Tables 5 and 6.

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.

Table 5 – Bleeding Events in the AMPLIFY Study

	Apixaban N=2676 n(%)	**Enoxaparin/Warfarin N=2689 n(%)**	**Relative Risk (95% CI)**	**P-value for superiority**
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)

† 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.

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.

Table 6 – Bleeding Events 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)	**Apixaban 2.5 mg** vs. Placebo	**Apixaban 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)

* P-value <0.05, compared to Placebo.
† 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Prevention of VTE following Elective Hip or Knee Replacement Surgery

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. Adverse reactions occurring in ≥ 1% of patients undergoing hip or knee replacement surgery in the one Phase II study and the three Phase III studies are listed in Table 7.

Table 7 –Adverse Reactions Occurring in ≥ 1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	Apixaban 2.5 mg BID PO n= 5924 (%)	**Enoxaparin 40 mg SC OD or 30 mg SC q12h n= 5904 (%)**

GASTROINTESTINAL DISORDERS		
Nausea	153 (2.6)	159 (2.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia (including post-operative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
VASCULAR DISORDERS		
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Contusion	83 (1.4)	115 (1.9)
Post procedural hemorrhage (including post procedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
HEPATOBILIARY DISORDERS		
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Stroke Prevention in Patients with Atrial Fibrillation (SPAF)

Common adverse reactions in patients with atrial fibrillation are shown in Table 8, below.

Table 8 – Adverse Reactions Occurring in ≥ 1% of Patients with Atrial Fibrillation in the ARISTOTLE and AVERROES Studies

	ARISTOTLE		**AVERROES**	
	Apixaban N=9088 n (%)	**Warfarin N=9052 n (%)**	**Apixaban N=2798 n (%)**	**ASA N=2780 n (%)**
EYE DISORDERS				
Eye hemorrhage (including conjunctival hemorrhage	211 (2.3)	326 (3.6)	22 (0.8)	11 (0.4)
GASTROINTESTINAL DISORDERS				
Gastrointestinal hemorrhage (including hematemesis and melena)	194 (2.1)	190 (2.1)	24 (0.9)	23(0.8)
Rectal hemorrhage	141 (1.6)	156 (1.7)	17 (0.6)	6 (0.2)
Gingival bleeding	113 (1.2)	223 (2.5)	19 (0.7)	9 (0.3)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS				
Contusion	456 (5.0)	745 (8.2)	49 (1.8)	61 (2.2)
RENAL AND URINARY DISORDERS				
Hematuria	340 (3.7)	409 (4.5)	31 (1.1)	17 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Epistaxis	560 (6.2)	685 (7.6)	54 (1.9)	52 (1.9)
VASCULAR DISORDERS				
Other hemorrhage	150 (1.7)	188 (2.1)	10 (0.4)	5 (0.2)

Hematoma	233 (2.6)	439 (4.8)	15 (0.5)	24 (0.9)

Treatment of DVT and PE and Prevention of recurrent DVT and PE
Common adverse reactions (≥1%) in VTE treatment patients are shown in Table 9, below

Table 9 – Adverse Reactions Occurring in ≥ 1% of Patients in the AMPLIFY and AMPLIFY-EXT Studies

	AMPLIFY		AMPLIFY-EXT	
	Apixaban N=2676 n (%)	**Enoxaparin/ Warfarin N=2689 n (%)**	**Apixaban N=1651 n (%)**	**Placebo N=826 n (%)**
GASTROINTESTINAL DISORDERS				
Gingival bleeding	26 (1.0)	50 (1.9)	21 (1.3)	3 (0.4)
Rectal haemorrhage	26 (1.0)	39 (1.5)	(< 1.0)	(< 1.0)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS				
Contusion	49 (1.8)	97 (3.6)	27 (1.6)	13 (1.6)
RENAL AND URINARY DISORDERS				
Hematuria	46 (1.7)	102 (3.8)	28 (1.7)	9 (1.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Epistaxis	77 (2.9)	146 (5.4)	42 (2.5)	9 (1.1)
Haemoptysis	32 (1.2)	31 (1.2)	(< 1.0)	(< 1.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
Menorrhagia	38 (1.4)	30 (1.1)	16 (1.0)	2 (0.2)
VASCULAR DISORDERS				
Haematoma	35 (1.3)	76 (2.8)	27 (1.6)	10 (1.2)

Prevention of VTE following Elective Hip or Knee Replacement Surgery
Less common adverse reactions observed in clinical trials in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥ 0.1% to < 1% are provided below.

Blood and lymphatic system disorders: thrombocytopenia

Gastrointestinal disorders: gastrointestinal hemorrhage, including hematemesis, melena, and hematochezia

Hepatobiliary disorders: liver function test abnormal, serum alkaline phosphatase increased, serum bilirubin increased

Injury, poisoning and procedural complications: wound secretion, incision site hemorrhage or hematoma, operative hemorrhage

Renal and urinary disorders: hematuria

Respiratory, thoracic and mediastinal disorders: epistaxis

Vascular disorders: hypotension

Less common adverse reactions observed in clinical trials in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of < 0.1% are provided below.

Gingival bleeding, hemoptysis, drug hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage.

Stroke Prevention in Patients with Atrial Fibrillation (SPAF)
Less common adverse reactions observed in the ARISTOTLE and AVERROES studies in apixaban-treated patients occurring at a frequency of ≥ 0.1% to < 1% are provided below.

Immune system disorders: Drug hypersensitivity, such as skin rash, anaphylactic reactions

Nervous system disorders: Intracranial hemorrhage, intraspinal hemorrhage or hematoma, subdural hemorrhage, subarachnoid hemorrhage

Vascular disorders: Intra-abdominal hemorrhage

Respiratory, thoracic and mediastinal disorders: Hemoptysis.

Gastrointestinal disorders: hemorrhoidal hemorrhage, hematochezia, retroperitoneal hemorrhage (< 0.1%)

Reproductive system and breast disorders: Abnormal vaginal hemorrhage, hematuria

Injury, poisoning and procedural complications: Post-procedural hemorrhage, traumatic hemorrhage, incision site hemorrhage

Investigations: Occult blood positive

Treatment of DVT and PE and Prevention of recurrent DVT and PE
Less common adverse reactions observed in the AMPLIFY and AMPLIFY-EXT trials in apixaban-treated patients occurring at a frequency of ≥ 0.1% to < 1% are provided below:

Eye disorders: Conjunctival haemorrhage, retinal haemorrhage

Gastrointestinal disorders: Haematochezia, haemorrhoidal haemorrhage, gastrointestinal, haemorrhage, haematemesis

Skin and subcutaneous tissue disorders: Ecchymosis, skin haemorrhage

Reproductive system and breast disorders: Vaginal haemorrhage, metrorrhagia, menometrorrhagia, genital haemorrhage

General disorders and administration site conditions: Injection site haematoma, vessel puncture site haematoma

Laboratory investigation: Blood urine present, occult blood positive

Injury, poisoning, and procedural complications: Wound haemorrhage, post procedural haemorrhage, traumatic haematoma

Post-Market Adverse Reactions

Renal and urinary disorders: Anticoagulant-related nephropathy (ARN)

DRUG INTERACTIONS

CYP Inhibition
Apixaban does not inhibit CYP 3A4 or any other major CYP isoenzymes. *In vitro* apixaban studies showed no inhibitory effect on the activity of CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C8, CYP 2C9, CYP 2D6 or CYP 3A4 (IC_{50} >45 mcM) and weak inhibitory effect on the activity of CYP 2C19 (IC_{50} >20 mcM) at concentrations that are significantly greater than peak plasma concentrations observed in patients.

CYP Induction
Apixaban does not induce CYP 3A4 or any other major CYP isoenzymes. Apixaban did not induce CYP 1A2, CYP 2B6, CYP 3A4/5 at a concentration up to 20 mcM.

P-gp Inhibition
Apixaban does not inhibit P-gp based on *in vitro* data.

Drug-Drug Interactions
Apixaban is metabolized mainly via CYP 3A4/5 with minor contributions from CYP 1A2, 2C8, 2C9, 2C19, and 2J2. Apixaban is a substrate of transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Inhibitors of Both CYP 3A4 and P-gp
Co-administration of apixaban with ketoconazole 400 mg q.d., a strong inhibitor of both CYP 3A4 and P-gp, led to a 2-fold increase in apixaban mean AUC and a 1.6-fold increase in apixaban C_{max}. The use of apixaban is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of **both** CYP 3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole, or posaconazole), and HIV protease inhibitors (e.g., ritonavir) (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, *Inhibitors of Both CYP 3A4 and P-gp*).

Active substances moderately inhibiting the apixaban elimination pathways, CYP 3A4 and/or P-gp, 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 q.d. led to a 1.4 and 1.3-

fold increase in mean apixaban AUC and C_{max}, respectively. Naproxen (500 mg, single dose), an inhibitor of P-gp, led to a 1.5 and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. Clarithromycin (500 mg, twice daily), 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. (see WARNINGS AND PRECAUTIONS, Bleeding, and DOSAGE AND ADMINISTRATION, Concomitant Use with CYP 3A4 and P-gp Inhibitors/Inducers).

Inducers of Both CYP 3A4 and P-gp

Co-administration of apixaban with rifampicin 600 mg q.d., a strong inducer of both CYP 3A4 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 inducers of both CYP 3A4 and P-gp (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations and should generally be avoided. (see WARNINGS AND PRECAUTIONS, Inducers of Both CYP 3A4 and P-gp, and DOSAGE AND ADMINISTRATION, Concomitant Use with CYP 3A4 and P-gp Inhibitors/Inducers).

Increased stroke rates, and paradoxically, increased major bleeding have been noted in patients with atrial fibrillation taking these drugs with either apixaban or warfarin.

Drug Products Affecting Hemostasis

The concomitant use of apixaban with drugs affecting hemostasis, including antiplatelet agents increases the risk of bleeding (see WARNINGS AND PRECAUTIONS, Bleeding). Care is to be taken if patients are treated concomitantly with drug products affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAID), acetylsalicylic acid (ASA), platelet aggregation inhibitors, selective serotonin reuptake inhibitors (SSRI), or serotonin norepinephrine reuptake inhibitors (SNRIs).

If concomitant antiplatelet therapy is contemplated, a careful assessment of the potential risks should be made against potential benefits, weighing risk of increased bleeding against expected benefit. In clinical trials conducted in patients with atrial fibrillation, the addition of ASA or dual antiplatelet therapy to apixaban did not decrease the incidence of stroke but increased the incidence of major bleeding (see ADVERSE REACTIONS, Bleeding, *Stroke Prevention in Patients with Atrial Fibrillation*, and DOSAGE AND ADMINISTRATION, Concomitant Use of Antiplatelet Agents).

For concomitant treatment with any other anticoagulant, see CONTRAINDICATIONS.

Table 10 - Summary of Drug-Drug Interactions

Proper Name	Reference	Effect	Clinical Comment
Ketoconazole	CT	Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP 3A4 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 contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of **both** CYP 3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole and ritonavir (see

Proper Name	Reference	Effect	Clinical Comment
			CONTRAINDICATIONS).
Diltiazem	CT	Diltiazem (360 mg once a day), considered a moderate CYP 3A4 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}. Other moderate inhibitors of CYP 3A4 and/or P-gp, such as amiodarone and dronedarone, are expected to have similar effect.	No dose adjustment for apixaban is required. Use with caution.
Naproxen	CT	A single dose of naproxen 500 mg, 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. A corresponding 63% increase in mean anti-Xa activity at 3 hours post-dose was observed when apixaban was co-administered with naproxen. Apixaban had no effect on naproxen AUC or C_{max}. No changes were observed in the usual effect of naproxen on (arachidonic acid-induced) platelet aggregation.	No dose adjustment for either agent is required. Use with caution.
Clarithromycin	CT	Clarithromycin (500 mg, twice daily), 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.	No dosage adjustment for apixaban is required. Use with caution.
Rifampin	CT	Co-administration of apixaban with rifampin, a strong inducer of both CYP 3A4 and P-gp, rifampin, led to an approximate 54% and 42% decrease in mean apixaban AUC and C_{max}, respectively.	Combined use with strong inducers of both CYP 3A4 and P-gp should generally be avoided, since efficacy of apixaban may be compromised (see WARNINGS AND PRECAUTIONS, Inducers of Both CYP 3A4 and P-gp.
Enoxaparin	CT	Enoxaparin had no effect on the pharmacokinetics of apixaban. 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.	Concomitant use of apixaban with enoxaparin is contraindicated (see CONTRAINDICATIONS).
Acetylsalicylic acid (ASA)	CT	Pharmacokinetic interactions were not evident when apixaban was co-administered with acetylsalicylic acid 325 mg once a day.	No dose adjustment for either agent is required, but bleeding risk is increased (see WARNINGS AND PRECAUTIONS, Bleeding, and ADVERSE REACTIONS, Bleeding, SPAF). Assess bleeding

Proper Name	Reference	Effect	Clinical Comment
			risk before co-administration, and use with caution, if deemed necessary.
Clopidogrel	CT	Pharmacokinetic interactions were not evident when apixaban was co-administered with clopidogrel 75mg OD or with the combination of clopidogrel 75 mg and acetylsalic acid 162 mg OD	Concomitant use of ASA or dual antiplatelet therapy with either apixaban or warfarin increases the risk of major bleeding in patients with atrial fibrillation. Assess bleeding risk before co-administration, and use with caution, if deemed necessary (see WARNINGS AND PRECAUTIONS, Bleeding).
Atenolol	CT	Coadministration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol or have a clinically relevant effect on apixaban pharmacokinetics. Following administration of the two drugs together, mean apixaban AUC and C_{max} were 15% and 18% lower than when administered alone.	No dose adjustment for either agent is required.
Famotidine		The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max}.	No dose adjustment for apixaban is required when co-administered with famotidine. These data indicate that apixaban pharmacokinetics are not likely to be altered by changes in gastric pH or co-administration with other organic cation transport inhibitors.
Digoxin	CT	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}.	No dose adjustment for digoxin is required. Apixaban does not inhibit P-gp mediated substrate transport.
Prasugrel	CT	No clinically relevant pharmacokinetic interactions were evident when apixaban (5mg bid) was co-administered with prasugrel (60 mg followed by 10 mg once daily).	Concomitant use of apixaban and prasugrel is **not** recommended (see WARNINGS AND PRECAUTIONS, Bleeding).
Charcoal (activated)	CT	Administration of activated charcoal (50 g charcoal and 96 g sorbitol in 240 ml of water) 2 hours and 6 hours after apixaban 20 mg, resulted in a mean 50% and 27% decrease in apixaban AUC, respectively.	May be useful in overdosage or accidental ingestion (see OVERDOSAGE).
Selective serotonin reuptake inhibitors	T, CT	Serotonin release by platelets plays an important role in	Sandoz Apixaban SDZ should be used with caution when co-

Proper Name	Reference	Effect	Clinical Comment
(SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs)		hemostasis. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.	administered with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) because these medicinal products typically increase the bleeding risk. Patients should be advised of signs and symptoms of blood loss and to report them immediately or go to an emergency room (see WARNINGS AND PRECAUTIONS).

Legend: CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Apixaban can be taken with or without food (see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY**,** Pharmacokinetics**,** *Absorption*).

Drug-Herb Interactions

The concomitant use of apixaban with strong inducers of **both** CYP 3A4 and P-gp inducers (e.g. St. John's Wort) may lead to reduced apixaban plasma concentrations. Combined use with strong inducers of both CYP 3A4 and P-gp should generally be avoided, since efficacy of apixaban may be compromised (see WARNINGS AND PRECAUTIONS, Inducers of Both CYP 3A4 and P-gp).

Drug-Laboratory Interactions

Clotting tests, e.g., PT (including INR), and aPTT, are affected as may be expected by the mechanism of action of apixaban (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Changes observed in these clotting tests at the expected therapeutic dose are relatively small, subject to noteworthy variability, and are not useful for assessing the anticoagulant effect of apixaban (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

DOSAGE AND ADMINISTRATION

As for any non-vitamin K antagonist oral anticoagulant (NOAC) drug, before initiating Sandoz Apixaban SDZ *(apixaban), ensure that the patient understands and is prepared to accept adherence to NOAC therapy, as directed.*

Sandoz Apixaban SDZ (apixaban) can be taken with or without food.

Sandoz Apixaban SDZ should be taken regularly**, as prescribed, to ensure optimal effectiveness. All temporary discontinuations should be avoided, unless medically indicated.**

For patients unable to swallow whole tablets, apixaban tablets may be crushed to a fine powder

using a mortar and pestle or an adequate device designed for this purpose, suspended in water or mixed with applesauce. The suggested procedures are shown in PART III, PROPER USE OF THIS MEDICATION−If you have trouble swallowing the tablet(s). The suspended crushed tablet(s) should be administered immediately after preparation (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics)

Determine estimated creatinine clearance (eCrCl) in all patients before instituting apixaban, and monitor renal function during apixaban treatment, as clinically appropriate. Determination of renal function by eCrCl should occur at least once per year, and especially during circumstances when renal function may be expected to be compromised, i.e., acute myocardial infarction (AMI), acute decompensated heart failure (AHF), increased use of diuretics, dehydration, hypovolemia, etc. Clinically relevant deterioration of renal function may require dosage adjustment or discontinuation of apixaban (see below, Renal Impairment).

Glomerular filtration rate may be estimated by calculating eCrCl, using the Cockroft-Gault formula:
eCrCl (mL/min)=

in males: $\frac{(140\text{-age}) \text{ (years)} \times \text{weight (kg)} \times 1.23}{\text{serum creatinine (mcmol/L)}}$ or, $\frac{(140\text{-age}) \text{ (yrs)} \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$

in females: $\frac{(140\text{-age}) \text{ (years)} \times \text{weight (kg)} \times 1.04}{\text{serum creatinine (mcmol/L)}}$ or, $\frac{(140\text{-age}) \text{ (yrs)} \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/100 mL)}}$

Recommended Dose and Dosage Adjustment

Prevention of VTE following Elective Hip or Knee Replacement Surgery

The recommended dose of Sandoz Apixaban SDZ is 2.5 mg twice daily. The initial dose should be taken 12 to 24 hours after surgery, and after hemostasis has been obtained.

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.

Stroke Prevention in Patients with Atrial Fibrillation

The recommended dose of Sandoz Apixaban SDZ is 5 mg taken orally twice daily.

In patients fulfilling at least two (2) of the following criteria, a reduced dose of Sandoz Apixaban SDZ 2.5 mg twice daily is recommended: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromole/L (1.5 mg/dL). These patients have been determined to be at higher risk of bleeding.

Treatment of DVT and PE and Prevention of recurrent DVT and PE

The recommended dose of Sandoz Apixaban SDZ for the treatment of acute DVT or PE is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilization) and extended duration should be based on permanent risk factors or idiopathic DVT or PE.

Further to the course of a minimum of 6 months of treatment for DVT or PE, the recommended dose for the continued prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily.

Special Populations

Renal Impairment

Prevention of VTE following Elective Hip or Knee Replacement Surgery
Treatment of DVT and PE and Prevention of recurrent DVT and PE

No dose adjustment is necessary in patients with mild or moderate renal impairment (eCrCl ≥ 30 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment).

Limited clinical data in patients with severe renal impairment (eCrCl 15-29 mL/min) indicate that apixaban plasma concentrations are increased. Therefore, apixaban is to be used with caution in these patients because of potentially higher bleeding risk.

Because there is very limited clinical experience in patients with creatinine clearance < 15 ml/min, and there are no data in patients undergoing dialysis, apixaban is not recommended in these patients (see WARNINGS AND PRECAUTIONS, Renal Impairment, and ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment).

A summarized dosing table is presented in Table 11 below.

Table 11 – Dosage and Administration for Patients According to Renal Function

	Renal Impairment				
Creatinine Clearance (eCrCl) / Indication	Normal	Mild	Moderate	Severe	
	> 80 mL/min	>50 ≤80 mL/min	≥30-≤50 mL/min	≥15-<30 mL/min	<15 mL/min or patients undergoing dialysis
Prevention of VTE in adult patients after elective knee or hip replacement surgery	2.5 mg bid			2.5 mg bid†	Apixaban is not recommended
Treatment of VTE (DVT, PE)	10 mg bid 7 days, followed by 5 mg bid			10 mg bid 7 days, followed by 5 mg bid†	
Continued prevention of recurrent DVT and PE‡	2.5 mg bid			2.5 mg bid†	

† Must be used with caution due to potentially higher bleeding risks.
‡After a minimum of 6 months of treatment for DVT or PE.
bid = twice daily

Stroke Prevention in Patients with Atrial Fibrillation
No dose adjustment is necessary in patients with mild or moderate renal impairment, or in those with eCrCl 25 – 30 mL/min, unless at least two (2) of the following criteria for dose reduction are met: age ≥ 80 years, body weight ≤ 60 kg, or patients with serum creatinine ≥ 133 micromol/L (1.5 mg/dL). In this case, patients should receive a dose of apixaban 2.5 mg twice daily.

In patients with-eCrCl 15 - 24 mL/min, no dosing recommendation can be made as clinical data are very limited.

Because there are no data in patients with creatinine clearance < 15 ml/min, or in those undergoing dialysis, apixaban is not recommended in these patients (see ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment).

A summarized dosing table is presented in Table 12 below.

Table 12 – Dosage and Administration for Patients According to Renal Function

	Renal Impairment					
Creatinine Clearance (eCrCl) / Indication	Normal	Mild	Moderate	Severe		
	> 80 mL/min	>50 ≤80 mL/min	>30-≤50 mL/min	≥25-≤30 mL/min	≥15-≤24 mL/min	<15 mL/min or patients undergoing dialysis
Prevention of stroke and systemic embolism in patients with atrial fibrillation	5 mg bid Dose adjustment to 2.5 mg bid, if ≥2 of following criteria are met§: • age ≥ 80 years • body weight ≤60 kg • serum creatinine ≥133 mcmol/L (1.5 mg/dL)				No dosing recommendation due to very limited clinical data	Apixaban is not recommended

§ These patients have been determined to be at higher risk of bleeding.

Hepatic Impairment
Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see CONTRAINDICATIONS).

Apixaban is not recommended in patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS, Hepatic Impairment, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Apixaban 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 WARNINGS AND PRECAUTIONS, Hepatic Impairment, and ACTION AND CLINICAL PHARMACOLOGY, Hepatic Impairment).

Patients with elevated liver enzymes (ALT/AST > 2 x ULN, or total bilirubin ≥ 1.5 x ULN) were excluded in clinical trials. Therefore, apixaban should be used with caution in these patients.

Concomitant Use of Antiplatelet Agents

The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding (see WARNINGS AND PRECAUTIONS, Bleeding). If concomitant antiplatelet therapy is contemplated for indications related to coronary artery disease, a careful assessment of the potential risks should be made against potential benefits, weighing risk of increased bleeding against expected benefit (see ADVERSE REACTIONS, Bleeding, *Stroke Prevention in Patients with Atrial Fibrillation*, and DRUG INTERACTIONS, Drug Products Affecting Hemostasis).

Concomitant Use with CYP 3A4 and P-gp Inhibitors/Inducers

Inhibitors of Both CYP 3A4 and P-gp

The use of apixaban is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of **both** CYP 3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole, or posaconazole), and HIV protease inhibitors (e.g., ritonavir) (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Inhibitors of Both CYP 3A4 and P-gp).

Drugs moderately inhibiting the apixaban elimination pathways, CYP 3A4 and/or P-gp, would be expected to increase apixaban plasma concentrations to a lesser extent. For example, concomitant administration of diltiazem led to a 40% increase in apixaban AUC, while naproxen, an inhibitor of P-gp, led to a 50% increase in apixaban AUC and clarithromycin, an inhibitor of P-gp, led to a 60% increase in apixaban AUC. No dose adjustment for apixaban is required when co-administered with less potent inhibitors of CYP 3A4 and/or P-gp (see WARNINGS AND PRECAUTIONS, Bleeding and DRUG INTERACTIONS, Table 10).

Inducers of Both CYP 3A4 and P-gp

Co-administration of apixaban with rifampicin, a strong inducer of **both** CYP 3A4 and P-gp, led to an approximate 54% decrease in apixaban AUC. The concomitant use of apixaban with other strong inducers of **both** CYP 3A4 and P-gp (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. Combined use of apixaban with strong inducers of both CYP 3A4 and P-gp should generally be avoided since efficacy of apixaban may be compromised. (see WARNINGS AND PRECAUTIONS, Inducers of Both CYP 3A4 and P-gp).

Body Weight

Prevention of VTE following Elective Hip or Knee Replacement Surgery

No dose adjustment required.

Stroke Prevention in Patients with Atrial Fibrillation

No dose adjustment is generally required. However, patients fulfilling at least two (2) of the

following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromole/L (1.5 mg/dL), should receive a reduced dose of apixaban 2.5 mg twice daily.

Treatment of DVT and PE and Prevention of recurrent DVT and PE
No dose adjustment required

Gender
No dose adjustment required.

Ethnicity
No dose adjustment required.

Pediatrics (< *18* years of age)
The safety and effectiveness of apixaban in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ *65* years of age)
Prevention of VTE following Elective Hip or Knee Replacement Surgery
No dose adjustment required (see WARNINGS AND PRECAUTIONS, Geriatrics, and ACTION AND CLINICAL PHARMACOLOGY, Geriatrics).

Stroke Prevention in Patients with Atrial Fibrillation
No dose adjustment is generally required. However, patients fulfilling at least two (2) of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromole/L (1.5 mg/dL), should receive a reduced dose of apixaban 2.5 mg twice daily.

Treatment of DVT and PE and Prevention of recurrent DVT and PE
Although no dose adjustment required, caution is advised when prescribing apixaban to elderly patients (≥ 75 years of age (see WARNINGS AND PRECAUTIONS, Geriatrics, and ACTION AND CLINICAL PHARMACOLOGY, Geriatrics).

Cardioversion
Patients can be maintained on apixaban while being cardioverted (see ACTION AND CLINICAL PHARMACOLOGY, Cardioversion).

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

Switching from vitamin K antagonists (VKA) to apixaban
When switching patients from a VKA, such as warfarin, to apixaban, discontinue warfarin or other VKA therapy, and start apixaban when the international normalized ration (INR) is below 2.0.

Switching from apixaban to VKA

As with any short-acting anticoagulant, there is a potential for inadequate anticoagulation when transitioning from apixaban to a VKA. It is important to maintain an adequate level of anticoagulation when transitioning patients from one anticoagulant to another.

Apixaban should be continued concurrently with the VKA until the INR is ≥ 2.0. For the first 2 days of the conversion period, the VKA can be given in the usual starting doses without INR testing (see Considerations for INR Monitoring of VKA Activity during Concomitant apixaban Therapy). Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of apixaban, as appropriate. Apixaban can be discontinued once the INR is > 2.0. Once apixaban is discontinued, INR testing may be done at least 12 hours after the last dose of apixaban, and should then reliably reflect the anticoagulant effect of the VKA.

Considerations for INR Monitoring of VKA Activity during Concomitant Apixaban Therapy
In general, after starting VKA therapy, the initial anticoagulant effect is not readily apparent for at least 2 days, while the full therapeutic effect is achieved in 5-7 days. Consequently, INR monitoring in the first 2 days after starting a VKA is rarely necessary. Likewise, the INR may remain increased for a number of days after stopping VKA therapy.

Although apixaban therapy will lead to an elevated INR, depending on the timing of the measurement (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics), the INR is not a valid measure to assess the anticoagulant activity of apixaban. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including apixaban.

When switching patients from apixaban to a VKA, the INR should only be used to assess the anticoagulant effect of the VKA, and not that of apixaban. Therefore, while patients are concurrently receiving apixaban and VKA therapy, if the INR is to be tested, it should not be before 12 hours after the previous dose of apixaban, and should be just prior to the next dose of apixaban, since at this time the remaining apixaban concentration in the circulation is too low to have a clinically important effect on the INR. If INR testing is done earlier than just prior to the next dose of apixaban, the reported INR will not reflect the anticoagulation effect of the VKA only, because apixaban use may also affect the INR, leading to aberrant readings (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Missed Dose
If a dose is missed, the patient should take Sandoz Apixaban SDZ immediately and then continue with twice daily administration as before. A double dose should not be taken to make up for a missed tablet.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Overdose of apixaban may lead to hemorrhagic complications, due to its pharmacologic

properties.

A specific antidote for apixaban is not available. 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 to reduce absorption and systemic exposure of apixaban in the management of overdose or accidental ingestion.

Hemodialysis decreased apixaban AUC by 14% in subjects with end stage renal disease, when a single dose of apixaban 5 mg was administered orally. Apixaban protein binding has been shown to be over 90% in subjects with end-stage renal disease. Therefore, hemodialysis is unlikely to be an effective means of managing apixaban overdose (see ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment).

Management of Bleeding

In the event of hemorrhagic complications in a patient receiving apixaban, treatment must be discontinued, and the source of bleeding investigated. Appropriate standard treatment, e.g. surgical hemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or the transfusion of fresh frozen plasma.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

- activated prothrombin complex concentrate (APCC), e.g., FEIBA
- prothrombin complex concentrate (PCC)
- recombinant Factor-VIIa (rFVIIa)

Reversal of apixaban anticoagulant activity was evaluated by measuring endogenous thrombin potential (ETP) to assess thrombin generation using two different 4-factor PCC (prothrombin complex concentrate), one with and the other without heparin, in an open-label randomized, placebo-controlled study in 15 healthy adult subjects administered apixaban 10 mg twice daily. Reversal of the steady-state anticoagulant effect was observed 30 minutes after the start of a single infusion of either one of the PCC products indicating potential usefulness in the management of patients.

However, there are currently no clinical studies supporting the effectiveness of PCC in apixaban-treated patients.

Currently, there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban.

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 neither scientific rationale for benefit or experience with the systemic hemostatics, e.g., desmopressin and aprotinin in individuals receiving apixaban.

A calibrated quantitative anti-FXa assay may be useful to confirm excess apixaban exposure and help to inform clinical decisions in circumstances of clinical overdose (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). INR should **NOT** be used to assess the anticoagulant effect of apixaban (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

ACTION AND CLINICAL PHARMACOLOGY

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. Activation of Factor-X to Factor-Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. 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 hemostasis.

Pharmacodynamics

There is a clear correlation between plasma apixaban concentration and degree of anticoagulant effect. The maximum effect of apixaban on pharmacodynamic parameters occurs at the same time as C_{max}. The pharmacodynamic effects include the prolongation of clotting tests such as PT (including INR), and aPTT, as well as inhibition of FXa activity and *ex vivo* thrombin generation.

- The relationship between INR and apixaban plasma concentration was best described by a linear model, whereas that between aPTT and apixaban plasma concentration was best described by an E_{max} model. Both tests were subject to a high degree of variability and lacked sufficient sensitivity to gauge apixaban exposure. These tests are not recommended to assess the pharmacodynamic effects of apixaban.

- Anti-FXa activity, as measured by the Rotachrom® Heparin Anti-Xa assay and WHO LMWH standards, exhibits a close direct linear relationship with apixaban plasma concentration ($R^2 = .89$). The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban and subject populations. Precision of the Rotachrom assay is well within acceptable limits for use in a clinical laboratory. Thus, a calibrated quantitative anti-FXa assay may be useful in situations where knowledge of apixaban exposure may help to inform clinical decisions.

Table 13 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 nonvalvular 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 VTE or prevention of recurrence of VTE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

Table 13 – Predicted Apixaban Steady-state Exposure (ng/mL) and Anti-FXa Activity (IU/mL)

	Apixaban C_{max}	**Apixaban C_{min}**	**Apixaban Anti-FXa Activity Max**	**Apixaban Anti-FXa Activity Min**
	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]
Treatment of VTE				
2.5 mg BID	67 [30, 153]	32 [11, 90]	1.1 [0.47, 2.4]	0.51 [0.17, 1.4]
5 mg BID	132 [59, 302]	63 [22, 177]	2.1 [0.93, 4.8]	1.0 [0.35, 2.8]
10 mg BID	251 [111, 572]	120 [41, 335]	4.0 [1.8, 9.1]	1.9 [0.65, 5.3]

* Dose adjusted population based on 2 of 3 dose reduction criteria in the ARISTOTLE study.

Pharmacokinetics

Table 14 – Summary of Apixaban Pharmacokinetic Parameters After Repeated Oral Administration of 2.5 mg BID or Single IV Administration of Various Doses in Humans

	Oral Administration			**IV Administration**	
	C_{max} (ng/mL)	**$t_{½}$ (h)**	**$AUC_{0\text{-}12hrs}$ (ng·h/mL)**	**Clearance (L/h)**	**Volume of distribution (L)**
Healthy Volunteers	73	8.3	530	CL ~3.3 CLR ~0.9	Vss ~21
Patients	77	N/A	~800	N/A (no IV data)	N/A (no IV data)

N/A = Not available; C_{max} = maximum plasma concentration; $t^{½}$ = terminal elimination half-life; $AUC_{0\text{-}12}$ = area under the plasma concentration-time curve from time 0 to 12 hours post dose; CL = total systemic clearance; CLR = renal clearance; Vss = volume of distribution at steady state

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 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 intra-subject and inter-subject variability of ~20% CV (coefficient of variation) 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. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the C_{max} and AUC were 21% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets.

Distribution
Average plasma protein binding in humans is approximately 87% to 93%. The volume of distribution (Vss) is approximately 21 liters.

Metabolism
O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolized mainly via CYP 3A4/5 with minor contributions from CYP 1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites being present. Apixaban is a substrate of transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Excretion
Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in feces. 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.

After intravenous administration, apixaban has a systemic clearance of about 3.3 L/h and a half-life of approximately 12 hours.

Special Populations and Conditions
Pediatrics:
The efficacy and safety of apixaban in pediatric patients below age 18 years have not yet been established. Health Canada has not authorized an indication for pediatric use. Following the administration of apixaban oral solution, apixaban pharmacokinetics and pharmacodynamics were evaluated in a single-dose study in pediatric subjects at risk for venous or arterial thrombotic disorder. Data from 41 subjects between 28 days to <18 years of age were analyzed using a population pharmacokinetic modeling approach. A 2-compartment population pharmacokinetic model with first-order absorption and elimination described the pharmacokinetics of apixaban in pediatric subjects. The estimated apparent clearance increased with increasing age/body weight and reached adult levels in adolescent subjects (3.93 L/h in subjects 12 years to <18 years of age). Anti-FXa activity exhibited a direct linear relationship with apixaban plasma concentration, comparable to that in adults, with no apparent age-related differences.

Geriatrics
Elderly patients, ie. above 65 years of age, exhibited higher plasma concentrations than younger

patients, with mean AUC values being approximately 32% higher. No dose adjustment is required except as described in DOSAGE AND ADMINISTRATION, Geriatrics, *Stroke Reduction in Patients with Atrial Fibrillation.*

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

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. No dose adjustment is required.

Hepatic Impairment
Patients with severe hepatic impairment or active hepatobiliary disease have not been studied. Apixaban is not recommended in patients with severe hepatic impairment.

In a study comparing 16 subjects with mild and moderate hepatic impairment (classified as Child Pugh A and B, respectively) 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. 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 apixaban in this population (see WARNINGS AND PRECAUTIONS, Hepatic Impairment, and DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Renal Impairment
There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (eCrCl 51 – 80 mL/min), moderate (eCrCl 30 – 50 mL/min) and severe (eCrCl 15 - 29 mL/min) renal impairment, apixaban plasma concentrations, measured as AUC, were increased 16, 29, and 44%, respectively, compared to individuals with normal renal function. Renal impairment had no effect on the relationship between apixaban plasma concentration and anti-FXa activity. No dose adjustment is necessary in patients with mild or moderate renal impairment except as described in DOSAGE AND ADMINISTRATION, Renal Impairment, Stroke Prevention in Patients with Atrial Fibrillation.

Limited clinical data in patients with severe renal impairment (eCrCl 15 - 29 mL/min) indicate that apixaban plasma concentrations are increased. In patients with atrial fibrillation having eCrCl 25-29 mL/min at study entry, limited data exists in terms of clinical outcomes on stroke and major bleeding (see CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation, Tables 16, 17, 25 and 26).

There is very limited clinical experience in patients with creatinine clearance < 15 ml/min and no

data in patients undergoing dialysis. Therefore, apixaban is not recommended in these patients (see DOSAGE AND ADMINISTRATION, Renal Impairment).

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.

Body Weight
Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight >120 kg was associated with approximately 20-30% lower exposure, and body weight < 50 kg was associated with approximately 20-30% higher exposure. No dose adjustment is required, except as described in DOSAGE AND ADMINISTRATION, Body Weight, *Stroke Prevention in Patients with Atrial Fibrillation.*

Post-acute coronary syndrome patients
In a randomized, placebo-controlled trial of 7,392 post-acute coronary syndrome patients with elevated cardiovascular risk, addition of apixaban 5 mg bid to standard antiplatelet treatment caused a significant increased risk of major bleeding events. Major bleeding occurred in 1.1% of placebo-treated patients compared to 2.7% of apixaban-treated patients, without a significant reduction in recurrent ischemic events. All patients were treated with optimised medical treatment post-ACS, including antithrombotic therapy, with about 20 % taking ASA alone and 80% taking a dual antiplatelet regimen, consisting of ASA plus thienopyridine, generally clopidogrel (97.2%).

Acutely ill patients
In a randomized, active-controlled trial of 4,495 acutely ill patients with congestive heart failure, acute respiratory failure, infection or inflammatory diseases and requiring at least 3 days of hospitalisation, an extended course of thromboprophylaxis for 30 days with apixaban 2.5 mg bid was associated with significantly more major bleeding events, i.e., 0.5%, than was a 6- to 14-day course of treatment with enoxaparin 40 mg QD, i.e., 0.2%, while apixaban was not more efficacious.

Cardioversion
In the ARISTOTLE trial, a total of 577 (3.2%) patients underwent cardioversion, including 286, (49.6%) assigned to apixaban, and 291 (50.4%) assigned to warfarin. In the first 90 days following cardioversion, no patient in either group suffered a stroke or systemic embolism (see DOSAGE AND ADMINISTRATION, Cardioversion).

STORAGE AND STABILITY

Store at room temperature (15-30ºC).

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

Excipients: Lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, hypromellose, magnesium stearate, titanium dioxide, triacetin. Tartrazine aluminum lake, sunset yellow FCF aluminum lake, iron oxide yellow (2.5 mg tablets only), iron oxide red (5 mg tablets only).

2.5 mg tablet: yellow colored, round, biconvex film-coated tablets debossed with 'AX' on one side and '2.5' on other side.

5 mg tablet: pink colored, oval, biconvex film-coated tablets debossed with 'AX' on one side and '5' on other side.

Sandoz Apixaban SDZ (apixaban) 2.5 mg tablets product is available in bottles of 60 and 500 tablets and blisters of 60 tablets, and also approved in bottles of 180 tablets.

Sandoz Apixaban SDZ (apixaban) 5 mg tablets are supplied in bottles of 180 and 500 tablets and blisters of 60 tablets.

PART II: SCIENTIFIC INFORMATION

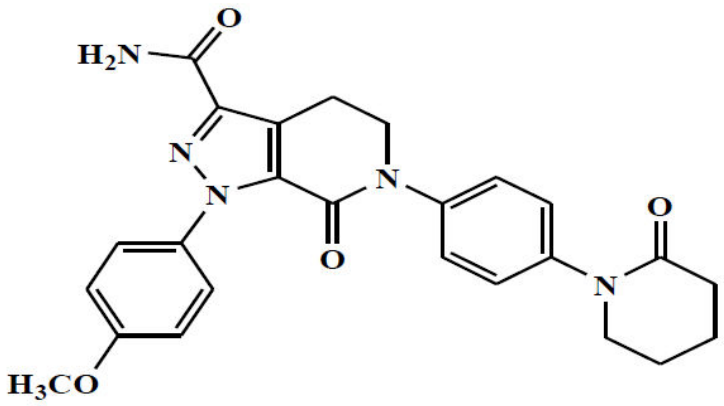
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: apixaban

Chemical name: 1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7- tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide

Molecular formula and molecular mass: $C_{25}H_{25}N_5O_4$; 459.5 g/moL
Structural formula:



Physicochemical properties:
Apixaban is a white to pale yellow powder. At physiological pH (1.2 - 6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

Sandoz Apixaban SDZ film-coated tablets are available for oral administration in the strength of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: Lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, hypromellose, magnesium stearate, titanium dioxide, triacetin. Tartrazine aluminum lake, sunset yellow FCF aluminum lake, iron oxide yellow (2.5 mg tablets only), iron oxide red (5 mg tablets only).

CLINICAL TRIALS

Comparative Bioavailability Studies

A blinded, single-dose, single center, randomized, two-period, two-sequence, crossover, comparative bioavailability study of Sandoz Apixaban SDZ (apixaban) 5 mg tablets (Sandoz Canada Inc.) and ELIQUIS® (apixaban) 5 mg tablets (Bristol-Myers Squibb Canada Co. and Pfizer Canada Inc.) was conducted with a 1 x 5 mg dose in 20 healthy, adult, male and female volunteers under fasting conditions. Bioavailability data were measured and the results from the 19 subjects (12 females and 7 males) who completed the study are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Apixaban (1 x 5 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	1713.85 1776.31 (24.8)	1725.55 1818.72 (25.7)	99.3	88.0 – 112.1
AUC_I (ng·h/mL)	1757.59 1822.22 (24.8)	1763.74 1861.68 (26.1)	99.7	88.3 – 112.5
C_{max} (ng/mL)	192.87 200.86 (26.2)	203.43 210.11 (23.4)	94.8	85.1 – 105.7
T_{max}§ (h)	2.33 (1.00, 5.00)	2.33 (1.00, 4.03)		
$T_{½}$‡ (h)	9.96 (31.9)	9.27 (27.8)		

* Sandoz Apixaban SDZ (apixaban) 5 mg film-coated tablets (Sandoz Canada Inc.)
† Eliquis® (apixaban) 5 mg film-coated tablets (Bristol-Myers Squibb Canada Co. and Pfizer Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
‡ Expressed as arithmetic mean (CV%) only

Prevention of VTE following Elective Hip or Knee Replacement Surgery

The clinical evidence for the effectiveness of apixaban is derived from the ADVANCE (Clinical Research trial to evaluate **A**pixaban **D**osed orally **V**ersus **AN**ti**C**oagulation with injectable **E**noxaparin) 1, 2 and 3 clinical trials program. The ADVANCE 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 surgery. A total of 11659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866

patients of age 75 or older, 1161 patients with low body weight (≤60 kg), 2528 patients with Body Mass Index ≥ 33 kg/m^2, 602 patients with moderate renal impairment, but only 23 patients with severe renal impairment.

Clinically significant exclusion criteria that were shared by the three ADVANCE studies were: active bleeding; brain, spinal or ophthalmologic major surgery or trauma < 90 days; contraindication to anticoagulant prophylaxis; need for ongoing anticoagulant or antiplatelet treatment; uncontrolled hypertension; active hepatobiliary disease (AST or ALT > 2xULN and/or total bilirubin ≥ 1.5xULN); clinically significant renal impairment (Cr CL < 30 ml/min); thrombocytopenia; anemia (Hb< 10g/dl); platelet < 100,000/mm^3; allergy to heparin; contraindication to (bilateral) venography.

In the ADVANCE-3 study, patients undergoing elective hip replacement surgery, were randomized to receive either apixaban 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily as recommended in many countries worldwide. The dose of enoxaparin sodium approved for use in thromboprophylaxis in conjunction with elective THR or TKR surgery in Canada is subcutaneous 30 mg twice daily with the first dose to be administered 12 to 24 hours postoperatively. The first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32-38 days. A total of 5407 patients were randomized in the ADVANCE-3 study.

In patients undergoing elective knee replacement surgery, apixaban 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1). In the ADVANCE-2 study, the first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both apixaban and enoxaparin were initiated 12 to 24 hours post-surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10-14 days. In the ADVANCE-2 and ADVANCE-1 studies, a total of 3057 and 3195 patients were randomized, respectively.

Table 15 - Summary of Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects n=number	Mean age (Range)	Gender M/F (%)
CV185035 ADVANCE 3	Randomized, double-blind, parallel group total hip replacement	Apixaban 2.5 mg BID PO Enoxaparin 40 mg QD SC	N=2708 N=2699	60.9 (19, 92) 60.6 (19, 93)	47/53 46/54
CV185047 ADVANCE 2	Randomized, double-blind, parallel group total knee replacement	Apixaban 2.5 mg BID PO Enoxaparin 40 mg QD SC	N=1528 N=1529	65.6 (22, 88) 65.9 (23, 89)	29/71 26/74
CV185034 ADVANCE 1	Randomized, double-blind, parallel group total knee	Apixaban 2.5 mg BID PO Enoxaparin 30 mg q12h SC	N=1599 N=1596	65.9 (26, 93) 65.7 (33, 89)	38/62 38/62

Study #	Trial design	Dosage, route of administration and duration	Study subjects n=number	Mean age (Range)	Gender M/F (%)
	replacement				

The efficacy data are provided in Table 16. In the ADVANCE-3 study, the rate of the primary endpoint, a composite of total VTE and all cause death (asymptomatic and symptomatic DVT, PE, and all-cause death), was 1.39% for apixaban and 3.86% for enoxaparin, relative risk reduction = 64%, p-value < 0.0001. In the ADVANCE-2 study, the rate of the primary endpoint, total VTE and all-cause death, was 15.06% for apixaban and 24.37% for enoxaparin, relative risk reduction = 38%, p-value < 0.0001. In the ADVANCE-1 study, the rate of the primary endpoint, total VTE and all-cause death, was 8.99% for apixaban and 8.85% for enoxaparin; relative risk 1.02, (95% CI 0.78, 1.32), p>0.05 for non-inferiority.

No clinically relevant differences were observed in the frequency of major bleeding, the composite of major and clinically relevant non-major (CRNM) bleeding and all bleeding in patients treated with apixaban 2.5 mg twice daily or enoxaparin 40 mg once daily and these endpoints were observed at a lower frequency with apixaban 2.5 mg twice daily compared with enoxaparin 30 mg every 12 hours (see ADVERSE REACTIONS, Adverse Drug Reaction Overview, Table 2). All the bleeding criteria included surgical site bleeding.

Table 16 – Efficacy of Apixaban in the Prevention of Venous Thromboembolic Events in Patients Undergoing Elective Hip or Knee Replacement Surgery[a]

	ADVANCE-3 (hip)		**ADVANCE-2 (knee)**		**ADVANCE-1 (knee)**	
	Apixaban 2.5 mg po bid 35 ± 3 days	Enoxaparin 40 mg sc qd 35 ± 3 days	Apixaban 2.5 mg po bid 12 ± 2 days	Enoxaparin 40 mg sc qd 12 ± 2 days	Apixaban 2.5 mg po bid 12 ± 2 days	Enoxaparin 30 mg sc q12h 12 ± 2 days
Events/N (Event Rate)						
Total VTE/all-cause death (asymptomatic and symptomatic DVT, PE, and all-cause death)						
	27/1949 (1.39%)	74/1917 (3.86%)	147/976 (15.06%)	243/997 (24.37%)	104/1157 (8.99%)	100/1130 (8.85%)
Relative Risk 95% CI	0.36 0.22, 0.54		0.62 0.51, 0.74		1.02 0.78, 1.32	
P value	< 0.0001		< 0.0001		NS	
All cause death	3/2708 (0.11 %)	1/2699 (0.04 %)	2/1528 (0.13 %)	0/1529 (0.00%)	3/1599 (0.19%)	3/1596 (0.19%)
PE (Fatal or Non-Fatal)	3/2708 (0.11 %)	5/2699 (0.19 %)	4/1528 (0.26%)	0/1529 (0.00%)	16/1599 (1.00 %)	7/1596 (0.44 %)
Symptomatic DVT	1/2708 (0.04%)	5/2699 (0.19%)	3/1528 (0.20%)	7/1529 (0.46%)	3/1599 (0.19%)	7/1596 (0.44%)
Proximal DVT[b]	7/2196 (0.32 %)	20/2190 (0.91 %)	9/1192 (0.76%)	26/1199 (2.17%)	9/1254 (0.72 %)	11/1207 (0.91 %)
Distal DVT[b]	20/1951 (1.03 %)	57/1908 (2.99 %)	142/978 (14.52%)	239/1000 (23.90%)	83/1146 (7.24 %)	91/1133 (8.03 %)

VTE: Venous Thrombembolic Events; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; NS: not significant

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

[b] Includes symptomatic and asymptomatic DVT.

Stroke Prevention in Patients with Atrial Fibrillation

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, as in the ARISTOTLE trial, and in patients unsuitable for VKA in the AVERROES trial. Both studies were active-controlled (against warfarin in ARISTOTLE, and against aspirin in AVERROES), randomized, double-blind, parallel-arm, multi-national trials in patients with persistent, paroxysmal, or permanent atrial fibrillation (AF) or atrial flutter, and one or more of the following additional risk factors:

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

Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were excluded from both the ARISTOTLE and AVERROES trials, and thus were not evaluated. These trial results do not apply to these patients, with or without atrial fibrillation (see WARNINGS AND PRECAUTIONS, Cardiovascular, Patients with Valvular Disease).

Table 17 – Study Demographics and Trial Design for the ARISTOTLE and AVERROES clinical trials

Study	ARISTOTLE	AVERROES
Trial design	Warfarin-controlled, randomized, double-blind, parallel arm, multi-national	Aspirin-controlled, randomized, double-blind, parallel arm, multi-national
Dosage, route of administration and duration	Apixaban 5 mg BID PO (2.5 mg BID in selected patients: 4.7%) Warfarin: Target INR 2.0-3.0	Apixaban 5 mg BID PO (2.5 mg BID in selected patients: 6.4%) ASA 81 to 324 mg QD PO 81mg (64.3%) 162mg (26.2%)
Randomized Subjects	18,201	5,598
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%

Study	ARISTOTLE	AVERROES
Heart failure	35.4% (LVEF ≤40%)	33.7% (LVEF ≤35%)
Valvular Disease (not meeting exclusion criteria) *	17.8%	22.7%
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%

*Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were excluded from both the ARISTOTLE and AVERROES trials

Study Results

The ARISTOTLE Study

Patients were randomized to treatment with apixaban 5 mg orally twice daily (apixaban 2.5 mg twice daily in selected patients) or dose-adjusted warfarin (INR 2.0-3.0). The apixaban 2.5 mg twice daily dose was assigned to patients with at least two (2) of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 micromole/L (1.5mg/dL). Overall, 43% were VKA naive, defined as not having previously received VKA, or having received ≤ 30 consecutive days of treatment with warfarin or another VKA.

Patients were treated for a median of 90 weeks for apixaban and 88 weeks for warfarin.

Coronary artery disease was present in 33% of patients at randomisation.

Patients with an eCrCl < 25 mL/min at study entry were excluded from this trial.

The median time in therapeutic range (TTR) for subjects randomized to warfarin, excluding the first 7 days of the study and excluding warfarin interruptions, was 66.0%.

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 non-inferior to warfarin for the prevention of total stroke (ischemic, hemorrhagic, or unspecified) or systemic embolism (SE).

The key study outcomes were pre-specified and tested in a sequential, hierarchical manner to preserve overall type 1 error (false-positive) at ≤ 5%. 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.

The results of the key efficacy outcomes are presented below in Table 18 and Figure 1.

To control the overall type I error, the pre-specified, hierarchical sequential testing approach was developed and finalized prior to the interim analysis and performed on the study's main endpoints. The intention-to-treat (ITT) population was used for efficacy outcome testing, the on-treatment population for safety outcomes. Testing demonstrated non-inferiority of apixaban to warfarin on the composite of stroke and SE, ($p<0.0001$). As non-inferiority was met, apixaban was tested for superiority on the composite of stroke and SE, with superiority over warfarin

demonstrated (HR 0.79, 95% CI 0.66 to 0.95, p = 0.01).

Table 18 – Key Efficacy Outcomes in the ARISTOTLE Study**

	Apixaban N=9120 n (%/yr)	Warfarin N=9081 n (%/yr)	Hazard Ratio (Apixaban vs. Warfarin) (95% CI)	P-Value, (superiority)
Stroke or systemic embolism*	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
Stroke				
Ischemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	
Hemorrhagic	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)	
All-cause death†**	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.047

* Assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.
** Intention-To-Treat analyses
† Secondary endpoint
Events for each endpoint were counted once per subject but subjects may have contributed events to more than one endpoint.

The rate of acute myocardial infarction was 0.53%/year in the apixaban and 0.61% in the warfarin treatment groups.

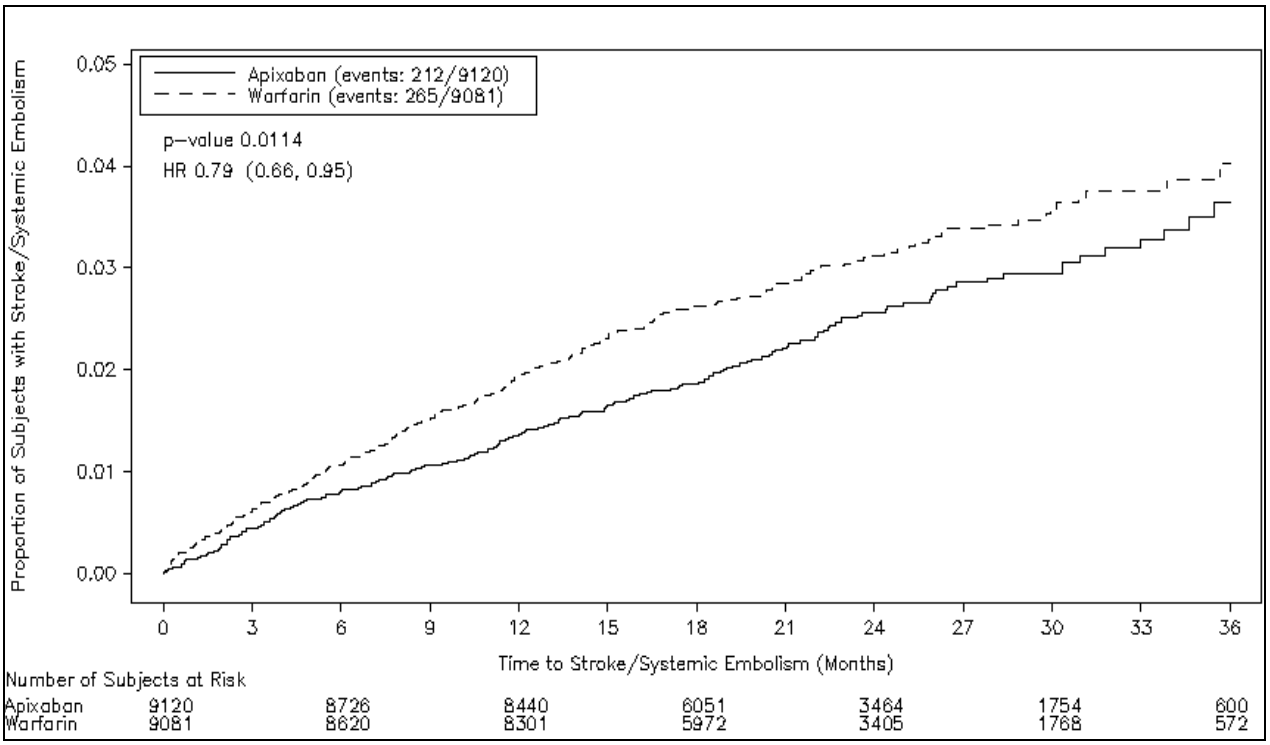


Figure 1 - Kaplan-Meier Curve Estimate of Time to Occurrence of First Stroke or Systemic Embolism in the ARISTOTLE Study

The incidence of clinically important bleeding is given in Table 3.

The event rates for efficacy and safety (bleeding) outcomes, stratified by age, are presented in Table 19 and Table 20, respectively.

Table 19 - – Efficacy Outcomes by Age Groups in the ARISTOTLE Trial - All Randomized Patients

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)						
All Patients	212/9120	1.27	265/9081	1.60	0.79 (0.66, 0.95)	0.0114
< 65 years	51/2731	1.00	44/2740	0.86	1.16 (0.77, 1.73)	-
≥ 65 to < 75 years	82/3539	1.25	112/3513	1.73	0.72 (0.54, 0.96)	-
≥ 75 years	79/2850	1.56	109/2828	2.19	0.71 (0.53, 0.95)	-
≥ 80 years	33/1225	1.53	40/1211	1.90	0.81 (0.51, 1.29)	-
≥ 85 years	6/322	1.14	18/345	3.25	0.35 (0.14, 0.89)	-
Any Stroke						
All Patients	199/9120	1.19	250/9081	1.51	0.79 (0.65, 0.95)	0.0122
< 65 years	49/2731	0.96	40/2740	0.78	1.22 (0.80, 1.85)	-
≥ 65 to < 75 years	74/3539	1.13	109/3513	1.69	0.67 (0.50, 0.90)	-
≥ 75 years	76/2850	1.50	101/2828	2.03	0.74 (0.55, 1.00)	-
≥ 80 years	33/1225	1.53	37/1211	1.76	0.88 (0.55, 1.40)	-
Ischemic or Unspecified Stroke						
All Patients	162/9120	0.97	175/9081	1.05	0.92 (0.74, 1.13)	0.4220
< 65 years	38/2731	0.74	27/2740	0.52	1.40 (0.86, 2.30)	-
≥ 65 to <75 years	64/3539	0.97	79/3513	1.22	0.80 (0.58, 1.12)	-
≥ 75 years	60/2850	1.18	69/2828	1.38	0.86 (0.61, 1.21)	-
≥ 80 years	26/1225	1.21	27/1211	1.28	0.94 (0.55, 1.61)	-
Hemorrhagic Stroke						
All Patients	40/9120	0.24	78/9081	0.47	0.51 (0.35, 0.75)	0.0006
< 65 years	13/2731	0.25	13/2740	0.25	0.99 (0.46, 2.15)	-
≥ 65 to < 75 years	10/3539	0.15	33/3513	0.51	0.30 (0.15, 0.61)	-
≥ 75 years	17/2850	0.33	32/2828	0.64	0.53 (0.29, 0.95)	-

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
≥ 80 years	7/1225	0.32	10/1211	0.47	0.71 (0.27, 1.86)	-
Cardiovascular Death						
All Patients	308/9120	1.80	344/9081	2.02	0.89 (0.76, 1.04)	0.1384
< 65 years	87/2731	1.67	83/2740	1.58	1.04 (0.77, 1.41)	-
≥ 65 to < 75 years	86/3539	1.28	112/3513	1.69	0.76 (0.57, 1.01)	-
≥ 75 years	135/2850	2.60	149/2828	2.91	0.90 (0.71, 1.13)	-
≥ 80 years	64/1225	2.91	84/1211	3.86	0.76 (0.55, 1.05)	-
≥ 85 years	23/322	4.23	43/345	7.59	0.55 (0.33, 0.91)	-

n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
Any Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and unspecified stroke.

Table 20 – Bleeding Endpoints by Age Groups in the ARISTOTLE Trial, While on Treatment – Treated Patients

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
ISTH Major Bleeding (Primary Outcome)						
All Patients	327/9088	2.13	462/9052	3.09	0.69 (0.60,0.80)	<0.0001
< 65 years	56/2723	1.17	72/2732	1.51	0.78 (0.55,1.11)	-
≥ 65 to < 75 years	120/3529	1.99	166/3501	2.82	0.71 (0.56,0.89)	-
≥ 75 years	151/2836	3.33	224/2819	5.19	0.64 (0.52,0.79)	-
≥ 80 years	67/1217	3.55	96/1209	5.41	0.66 (0.48,0.90)	-
≥ 85 years	19/322	4.20	30/345	6.47	0.65 (0.36, 1.15)	-
Major and Non-major Clinically Relevant Bleeding Event						
All Patients	613/9088	4.07	877/9052	6.01	0.68 (0.61,0.75)	<0.0001
< 65 years	122/2723	2.59	178/2732	3.82	0.68 (0.54,0.86)	-
≥ 65 to < 75 years	234/3529	3.94	320/3501	5.57	0.71 (0.60,0.84)	-
≥ 75 years	257/2836	5.81	379/2819	9.04	0.65 (0.55,0.76)	-
≥ 80 years	110/1217	5.98	171/1209	9.93	0.61 (0.48,0.77)	-
Intracranial Hemorrhage						

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
All Patients	52/9088	0.33	122/9052	0.80	0.42 (0.30,0.58)	<0.0001
< 65 years	15/2723	0.31	17/2732	0.35	0.87 (0.43,1.74)	-
≥ 65 to < 75 years	17/3529	0.28	48/3501	0.81	0.35 (0.20,0.60)	-
≥ 75 years	20/2836	0.43	57/2819	1.29	0.34 (0.20,0.57)	-
≥ 80 years	9/1217	0.47	24/1209	1.32	0.36 (0.17,0.77)	-
Fatal Bleeding **						
All Patients	8/9088	0.05	11/9052	0.07	0.71 (0.25, 1.95)	0.6183
< 65 years	1/2723	0.02	2/2732	0.04	0.48 (0.04, 5.30)	-
≥ 65 to < 75 years	3/3529	0.05	4/3501	0.07	0.76 (0.17, 3.40)	-
≥ 75 years	4/2836	0.09	5/2819	0.11	0.79 (0.21, 2.93)	-
≥ 80 years	3/1217	0.16	1/1209	0.05	2.86 (0.23, 150.09)	-

Treated patients analysis = adjudicated events while on treatment (up to last dose plus 2 days)
n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
**For fatal bleeding in all patients and in patients ≥ 80 years, risk ratios (95% CI) and p-values are from exact Poisson regression models with treatment group as a covariate.

The event rates for efficacy and safety (bleeding) outcomes, stratified by renal function, are presented in Table 21 and Table 22, respectively.

Table 21 – Efficacy Outcomes by Renal Function* at Baseline in the ARISTOTLE Trial, All Randomized Patients

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)						
All Patients	212/9120	1.27	265/9081	1.60	0.79 (0.66, 0.95)	0.0114
≤ 30 mL/min	6/137	2.79	10/133	5.06	0.55 (0.20, 1.53)	-
>30 – ≤ 50 mL/min	48/1365	2.05	59/1382	2.47	0.83 (0.57, 1.21)	-
> 50 – ≤ 80 mL/min	87/3817	1.24	116/3770	1.69	0.74 (0.56, 0.97)	-
> 80 mL/min	70/3761	0.99	79/3757	1.12	0.88 (0.64, 1.21)	-
Any Stroke						
All Patients	199/9120	1.19	250/9081	1.51	0.79 (0.65, 0.95)	0.0122

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
≤ 30 mL/min	6/137	2.79	10/133	5.06	0.55 (0.20, 1.53)	-
>30 – ≤ 50 mL/min	45/1365	1.92	56/1382	2.34	0.82 (0.55, 1.21)	-
> 50 – ≤ 80 mL/min	81/3817	1.16	108/3770	1.57	0.74 (0.55, 0.98)	-
> 80 mL/min	66/3761	0.93	75/3757	1.06	0.87 (0.63, 1.21)	-
Ischemic or Unspecified Stroke						
All Patients	162/9120	0.97	175/9081	1.05	0.92 (0.74, 1.13)	0.4220
≤ 30 mL/min	6/137	2.79	7/133	3.52	0.78 (0.26, 2.33)	-
>30 – ≤ 50 mL/min	39/1365	1.66	36/1382	1.50	1.11 (0.70, 1.74)	-
> 50 – ≤ 80 mL/min	65/3817	0.93	75/3770	1.09	0.85 (0.61, 1.19)	-
> 80 mL/min	52/3761	0.73	56/3757	0.79	0.92 (0.63, 1.34)	-
Hemorrhagic Stroke						
All Patients	40/9120	0.24	78/9081	0.47	0.51 (0.35, 0.75)	0.0006
≤ 30 mL/min	0/137	0	3/133	1.48	0 §	-
>30 – ≤ 50 mL/min	7/1365	0.29	20/1382	0.83	0.35 (0.15, 0.83)	-
> 50 – ≤ 80 mL/min	16/3817	0.23	36/3770	0.52	0.44 (0.24, 0.79)	-
> 80 mL/min	16/3761	0.22	19/3757	0.27	0.84 (0.43, 1.63)	-
Cardiovascular Death						
All Patients	308/9120	1.80	344/9081	2.02	0.89 (0.76, 1.04)	0.1384
≤ 30 mL/min	15/137	6.85	14/133	6.68	1.03 (0.50, 2.15)	-
>30 – ≤ 50 mL/min	77/1365	3.18	97/1382	3.96	0.80 (0.60, 1.08)	-
> 50 – ≤ 80 mL/min	126/3817	1.76	128/3770	1.81	0.97 (0.76, 1.25)	-
> 80 mL/min	88/3761	1.21	104/3757	1.44	0.84 (0.63, 1.11)	-

n=number of patients with an event, N=number of patients in each subgroup
*patients with eCrCl < 25 mL/min at baseline were excluded from this trial
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
Any Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and unspecified stroke.

Table 22 – Bleeding Endpoints by Renal Function* at Baseline in the ARISTOTLE Trial, While on Treatment – Treated Patients

	Apixaban	Warfarin	Apixaban vs Warfarin

	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
ISTH Major Bleeding (Principal Safety Endpoint)						
All Patients	327/9088	2.13	462/9052	3.09	0.69 (0.60,0.80)	<0.0001
≤ 30 mL/min	7/136	3.75	19/132	11.94	0.32 (0.13,0.78)	-
>30 – ≤ 50 mL/min	66/1357	3.16	123/1380	6.01	0.53 (0.39,0.71)	-
> 50 – ≤ 80 mL/min	157/3807	2.45	199/3758	3.21	0.76 (0.62,0.94)	-
> 80 mL/min	96/3750	1.46	119/3746	1.84	0.79 (0.61,1.04)	-
Major and Non-Major Clinically Relevant Bleeding Event						
All Patients	613/9088	4.07	877/9052	6.01	0.68 (0.61,0.75)	<0.0001
≤ 30 mL/min	10/136	5.39	26/132	16.75	0.34 (0.16,0.70)	-
>30 – ≤ 50 mL/min	113/1357	5.52	185/1380	9.17	0.60 (0.48,0.76)	-
> 50 – ≤ 80 mL/min	281/3807	4.47	381/3758	6.31	0.71 (0.61,0.83)	-
> 80 mL/min	206/3750	3.18	282/3746	4.46	0.71 (0.60, 0.86)	-
Intracranial Hemorrhage						
All Patients	52/9088	0.33	122/9052	0.80	0.42 (0.30, 0.58)	<0.0001
≤ 30 mL/min	0/136	0	4/132	2.40	0 §	-
>30 – ≤ 50 mL/min	8/1357	0.38	36/1380	1.71	0.22 (0.10, 0.47)	-
> 50 – ≤ 80 mL/min	25/3807	0.38	52/3758	0.83	0.47 (0.29, 0.75)	-
> 80 mL/min	18/3750	0.27	30/3746	0.46	0.59 (0.33, 1.05)	-
Fatal Bleeding**						
All Patients	8/9088	0.05	11/9052	0.07	0.71 (0.25, 1.95)	0.6183
≤ 30 mL/min	0/136	0	1/132	0.60	0 (0.00, 32.57)	-
>30 – ≤ 50 mL/min	0/1357	0	3/1380	0.14	0 (0.00, 2.38)	-
> 50 – ≤ 80 mL/min	7/3807	0.11	4/3758	0.06	1.70 (0.43, 7.94)	-
> 80 mL/min	1/3750	0.01	3/3746	0.05	0.32 (0.01, 3.97)	-

Treated patients analysis = adjudicated events while on treatment (up to last dose plus 2 days)
n=number of patients with an event, N=number of patients in each subgroup
*patients with eCrCl < 25 mL/min at baseline were excluded from this trial
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
**For fatal bleeding analyses, risk ratio (95% CI) and p-value are from an exact Poisson regression model with treatment as a covariate.

The event rates for efficacy and safety (bleeding) outcomes for those patients treated with apixaban 5 mg bid or apixaban 2.5 mg bid are presented in Table 23 and Table 24, respectively. Patients randomised to apixaban received a lower dose of apixaban 2.5 mg bid if they met at least two (2) of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 micromole/L (1.5mg/dL).

Table 23 – Efficacy Outcomes by Dose in the ARISTOTLE Trial, All Randomized Patients

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)						
All Patients	212/9120	1.27	265/9081	1.60	0.79 (0.66, 0.95)	0.0114
Apixaban 2.5 mg BID	12/428	1.70	22/403	3.33	0.50 (0.25, 1.02)	-
Apixaban 5 mg BID	200/8692	1.25	243/8678	1.53	0.82 (0.68, 0.98)	-
Any Stroke						
All Patients	199/9120	1.19	250/9081	1.51	0.79 (0.65, 0.95)	0.0122
Apixaban 2.5 mg BID	12/428	1.70	20/403	4.96	0.55 (0.27, 1.13)	-
Apixaban 5 mg BID	187/8692	1.17	230/8678	1.44	0.81 (0.66, 0.98)	-
Ischemic or Unspecified Stroke						
All Patients	162/9120	0.97	175/9081	1.05	0.92 (0.74, 1.13)	0.4220
Apixaban 2.5 mg BID	10/428	1.42	14/403	2.11	0.65 (0.29, 1.47)	-
Apixaban 5 mg BID	152/8692	0.95	161/8678	1.01	0.94 (0.75, 1.17)	-
Hemorrhagic Stroke						
All Patients	40/9120	0.24	78/9081	0.47	0.51 (0.35, 0.75)	0.0006
Apixaban 2.5 mg BID	2/428	0.28	6/403	0.89	0.32 (0.06, 1.57)	-
Apixaban 5 mg BID	38/8692	0.23	72/8678	0.45	0.52 (0.35, 0.78)	-
Cardiovascular Death						
All Patients	308/9120	1.80	344/9081	2.02	0.89 (0.76, 1.04)	0.1384
Apixaban 2.5 mg BID	33/428	4.54	44/403	6.38	0.73 (0.46, 1.15)	-
Apixaban 5 mg BID	275/8692	1.68	300/8678	1.84	0.91 (0.77, 1.07)	-

n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
Any Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and unspecified stroke.

Table 24 – Bleeding Endpoints by Dose in the ARISTOTLE Trial, While on Treatment – Treated Patients

	Apixaban		Warfarin		Apixaban vs Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
ISTH Major Bleeding (Principal Safety Endpoint)						
All Patients	327/9088	2.13	462/9052	3.09	0.69 (0.60,0.80)	<0.0001
Apixaban 2.5 mg BID	20/424	3.29	37/402	6.71	0.50 (0.29,0.86)	-
Apixaban 5 mg BID	307/8664	2.09	425/8650	2.95	0.71 (0.61,0.82)	-
Major and Non-Major Clinically Relevant Bleeding Event						
All Patients	613/9088	4.07	877/9052	6.01	0.68 (0.61,0.75)	<0.0001
Apixaban 2.5 mg BID	30/424	4.97	53/402	9.80	0.52 (0.33,0.81)	-
Apixaban 5 mg BID	583/8664	4.03	824/8650	5.86	0.69 (0.62,0.77)	-
Intracranial Hemorrhage						
All Patients	52/9088	0.33	122/9052	0.80	0.42 (0.30, 0.58)	<0.0001
Apixaban 2.5 mg BID	2/424	0.32	9/402	1.59	0.21 (0.04, 0.96)	-
Apixaban 5 mg BID	50/8664	0.34	113/8650	0.77	0.43 (0.31, 0.61)	-
Fatal Bleeding**						
All Patients	8/9088	0.05	11/9052	0.07	0.71 (0.25, 1.95)	0.6183
Apixaban 2.5 mg BID	0/424	0	1/402	0.18	0 §	-
Apixaban 5 mg BID	8/8664	0.05	10/8650	0.07	0.79 (0.31, 1.99)	-

Treated patients analysis = Adjudicated events while on treatment (up to last dose plus 2 days)
n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
**For fatal bleeding in all patients, risk ratio (95% CI) and p-value are from an exact Poisson regression model with treatment as a covariate and stratified by region and prior VKA status.

The number and percentage of patients who received apixaban by dose are provided below according to degree of renal function at baseline.

Table 25 – Number and percentage of patients who received apixaban by dose according to degree of renal function at baseline in the ARISTOTLE trial

	Apixaban	Warfarin
Apixaban/Placebo 2.5 mg BID, N	424	402
Severe (≤ 30 mL/min), n (%)	88 (20.8)	85 (21.1)
Moderate (> 30 - ≤ 50 mL/min), n (%)	294 (69.3)	262 (65.2)
Mild (> 50 - ≤ 80 mL/min), n (%)	42 (9.9)	54 (13.4)
Normal (> 80 mL/min), n (%)	0	1 (0.3)
Not Reported, n (%)	0	0
Apixaban/Placebo 5 mg BID, N	8664	8650

Severe (≤ 30 mL/min), n (%)	48 (0.6)	47 (0.5)
Moderate (> 30 - ≤ 50 mL/min), n (%)	1063 (12.3)	1118 (12.9)
Mild (> 50 - ≤ 80 mL/min), n (%)	3765 (43.5)	3704 (42.8)
Normal (> 80 mL/min), n (%)	3750 (43.3)	3745 (43.3)
Not Reported, n (%)	38 (0.4)	36 (0.4)

The denominator to calculate each percentage is the number of subjects treated in each of the apixaban dose groups and treatment group

The AVERROES Study

Patients were randomized to treatment with apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients), 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. The apixaban 2.5 mg twice daily dose was assigned to patients with at least two (2) of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 micromole/L (1.5mg/dL).

In the study, VKA therapy had been tried but discontinued in 40% of patients prior to enrollment. 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%), CHADS2 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%).

Patients were treated for a median of 58 weeks for apixaban, and 59 weeks for ASA.

Patients with an eCrCl < 25 mL/min at study entry were excluded from this trial.

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 to 324 mg QD) in the prevention of stroke or systemic embolism. Assessments of superiority of apixaban versus aspirin 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.

The key study outcomes were prespecified and tested in a sequential, hierarchical manner to preserve overall type 1 error (false-positive) at ≤ 5%. Apixaban was tested compared to aspirin for: (1) superiority on the composite endpoint of stroke and systemic embolism, (2) superiority on major vascular events (composite outcome of stroke, systemic embolism, myocardial infarction or vascular death), and (3) superiority on all-cause death.

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

The results of the key efficacy outcomes are presented below in Table 26 and Figure 2.

Table 26 - Key Efficacy Outcomes in the AVERROES Study**

	Apixaban N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio Apixaban vs. aspirin (95% CI)	P-Value (superiority)
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
Ischemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	
Hemorrhagic	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.
** Intent-To-Treat analyses
†Secondary endpoint
Events for each endpoint were counted once per subject but subjects may have contributed events to more than one endpoint.

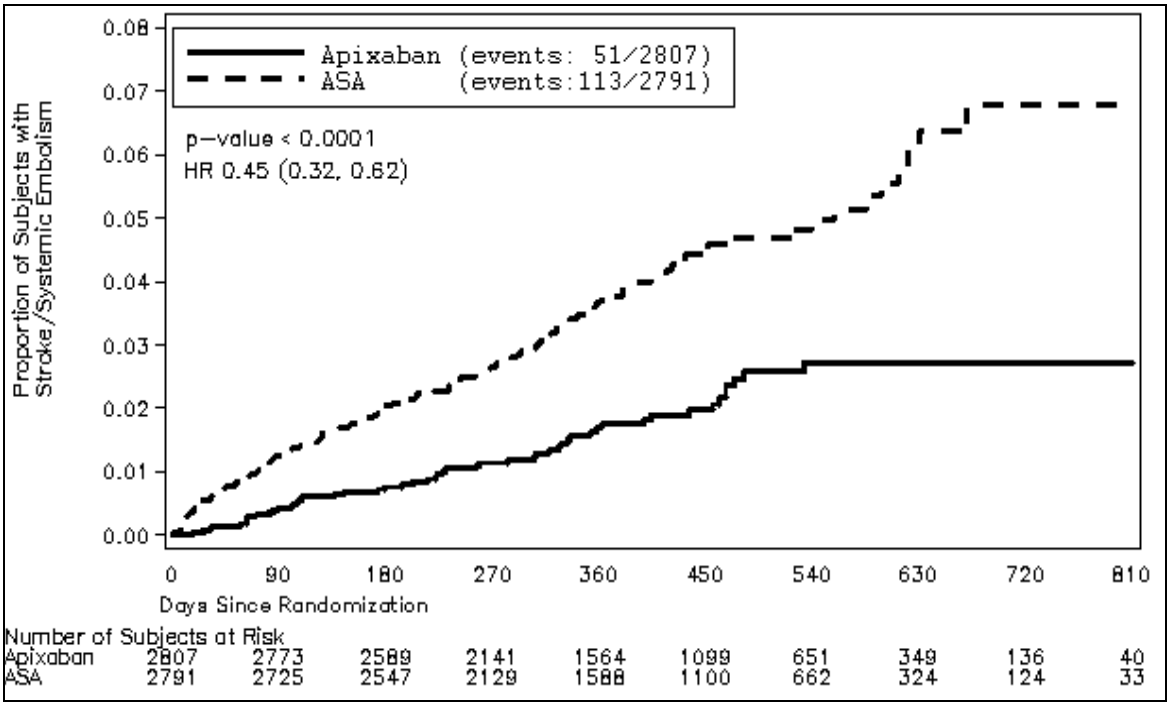


Figure 2 - Kaplan-Meier Curve Estimate of Time to First Occurrence of Stroke or Systemic Embolism in the AVERROES Study

The incidence of clinically important bleeding is given in Table 4.

The event rates for efficacy and safety (bleeding) outcomes, stratified by age, are presented in

Table 27 and Table 28, respectively.

Table 27 – Efficacy Outcomes by Age Groups in the AVERROES Trial - All Randomized Patients

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)						
All Patients	51/2807	1.62	113/2791	3.63	0.45 (0.32, 0.62)	<0.0001
< 65 years	7/855	0.73	19/865	1.93	0.38 (0.16, 0.89)	-
≥ 65 to < 75 years	24/1049	2.02	29/938	2.78	0.73 (0.43, 1.25)	-
≥ 75 years	20/903	2.00	65/988	6.00	0.34 (0.20, 0.56)	-
≥ 80 years	8/455	1.60	38/499	7.06	0.23 (0.11, 0.49)	-
≥ 85 years	2/180	1.02	15/186	7.53	0.14 (0.03, 0.60)	-
Any Stroke						
All Patients	49/2807	1.56	105/2791	3.37	0.46 (0.33, 0.65)	<0.0001
< 65 years	7/855	0.73	17/865	1.72	0.42 (0.17, 1.01)	-
≥ 65 to < 75 years	23/1049	1.93	26/938	2.49	0.78 (0.45, 1.37)	-
≥ 75 years	19/903	1.90	62/988	5.70	0.34 (0.20, 0.56)	-
≥ 80 years	7/455	1.40	37/499	6.85	0.21 (0.09, 0.46)	-
Ischemic or Unspecified Stroke						
All Patients	43/2807	1.37	97/2791	3.11	0.44 (0.31, 0.63)	<0.0001
< 65 years	7/855	0.73	15/865	1.52	0.48 (0.19, 1.17)	-
≥ 65 to <75 years	18/1049	1.51	25/938	2.40	0.64 (0.35, 1.16)	-
≥ 75 years	18/903	1.80	57/988	5.23	0.35 (0.20, 0.59)	-
≥ 80 years	6/455	1.20	32/499	5.91	0.20 (0.09, 0.49)	-
Hemorrhagic Stroke						
All Patients	6/2807	0.19	9/2791	0.28	0.67 (0.24, 1.88)	0.4471
< 65 years	0/855	0.00	2/865	0.20	0 §	-
≥ 65 to < 75 years	5/1049	0.42	1/938	0.09	4.44 (0.52, 38.01)	-
≥ 75 years	1/903	0.10	6/988	0.54	0.19 (0.02, 1.56)	-
≥ 80 years	1/455	0.20	6/499	1.08	0.19 (0.02, 1.56)	-

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Vascular Death						
All Patients	84/2807	2.65	96/2791	3.03	0.87 (0.65, 1.17)	0.3659
< 65 years	21/855	2.18	10/865	1.00	2.17 (1.02, 4.60)	-
≥ 65 to < 75 years	24/1049	2.00	28/938	2.66	0.76 (0.44, 1.31)	-
≥ 75 years	39/903	3.89	58/988	5.19	0.74 (0.49, 1.11)	-
≥ 80 years	29/455	5.80	40/499	7.18	0.78 (0.48, 1.27)	-
≥ 85 years	14/180	7.14	16/186	7.74	0.86 (0.41, 1.79)	-

n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
Any Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion and unspecified stroke

Table 28 – Bleeding Endpoints by Age Groups in the AVERROES Trial, While on Treatment – Treated Patients

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
ISTH Major Bleeding (Primary Safety Outcome)						
All Patients	45/2798	1.41	29/2780	0.92	1.54 (0.96, 2.45)	0.0716
< 65 years	8/855	0.81	5/862	0.49	1.67 (0.55, 5.11)	-
≥ 65 to < 75 years	11/1044	0.90	6/935	0.56	1.61 (0.60, 4.36)	-
≥ 75 years	26/899	2.65	18/983	1.70	1.57 (0.86, 2.86)	-
≥ 80 years	19/454	3.94	13/498	2.53	1.57 (0.77, 3.17)	-
≥ 85 years	9/179	4.77	6/185	3.31	1.44 (0.51, 4.06)	-
Major and Non-major Clinically Relevant Bleeding Event						
All Patients	140/2798	4.46	101/2780	3.24	1.38 (1.07, 1.78)	0.0144
< 65 years	32/855	3.26	26/862	2.58	1.26 (0.75, 2.12)	-
≥ 65 to < 75 years	45/1044	3.75	31/935	2.92	1.29 (0.82, 2.04)	-
≥ 75 years	63/899	6.59	44/983	4.20	1.56 (1.06, 2.30)	-
≥ 80 years	38/454	8.05	33/498	6.55	1.24 (0.78, 1.97)	-
Intracranial Hemorrhage**						
All Patients	11/2798	0.34	11/2780	0.35	0.99 (0.39, 2.51)	1.000

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
< 65 years	0/855	0	2/862	0.20	0 §	-
≥ 65 to <75 years	5/1044	0.41	1/935	0.09	4.42 (0.52, 37.86)	-
≥ 75 years	6/899	0.61	8/983	0.75	0.81 (0.28, 2.35)	-
≥ 80 years	4/454	0.82	7/498	1.36	0.61 (0.18, 2.07)	-
Fatal Bleeding**						
All Patients	5/2798	0.16	5/2780	0.16	0.99 (0.23, 4.29)	1.000
< 65 years	0/855	0.00	0/862	0.00	§	-
≥ 65 to < 75 years	4/1044	0.33	1/935	0.09	3.45 (0.38, 30.84)	-
≥ 75 years	1/899	0.10	4/983	0.38	0.27 (0.03, 2.45)	-
≥ 80 years	1/454	0.21	2/498	0.39	0.54 (0.05, 5.95)	-

Treated patients analysis = adjudicated events while on treatment (up to last dose, plus 2 days for patients who did not enter the open-label extension)
n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
**For fatal bleeding and intracranial bleeding in all patients, risk ratios (95% CI) and p-values are from exact Poisson regression models with treatment as a covariate.

The event rates for efficacy and safety (bleeding) outcomes, stratified by renal function, are presented in Table 29 and Table 30 respectively.

Table 29 – Efficacy Outcomes by Renal Function* at Baseline in the AVERROES Trial - All Randomized Patients

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)						
All Patients	51/2807	1.62	113/2791	3.63	0.45 (0.32, 0.62)	<0.0001
≤ 30 mL/min	1/55	1.72	4/61	7.07	0.26 (0.03, 2.30)	-
>30 – ≤ 50 mL/min	12/490	2.31	28/478	5.45	0.42 (0.21, 0.83)	-
> 50 – ≤ 80 mL/min	22/1074	1.83	58/1075	4.95	0.37 (0.23, 0.61)	-
> 80 mL/min	12/955	1.09	16/923	1.48	0.74 (0.35, 1.57)	-
Any Stroke						
All Patients	49/2807	1.56	105/2791	3.37	0.46 (0.33, 0.65)	<0.0001
≤ 30 mL/min	1/55	1.72	4/61	7.07	0.26 (0.03, 2.30)	-

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
>30 – ≤ 50 mL/min	11/490	2.12	26/478	5.05	0.42 (0.21, 0.85)	-
> 50 – ≤ 80 mL/min	22/1074	1.83	54/1075	4.60	0.40 (0.24, 0.66)	-
> 80 mL/min	11/955	1.00	14/923	1.30	0.77 (0.35, 1.70)	-
Ischemic or Unspecified Stroke						
All Patients	43/2807	1.37	97/2791	3.11	0.44 (0.31, 0.63)	<0.0001
≤ 30 mL/min	1/55	1.72	4/61	7.07	0.26 (0.03, 2.30)	-
>30 – ≤ 50 mL/min	11/490	2.12	26/478	5.05	0.42 (0.21, 0.85)	-
> 50 – ≤ 80 mL/min	18/1074	1.50	48/1075	4.08	0.37 (0.21, 0.63)	-
> 80 mL/min	10/955	0.91	13/923	1.20	0.76 (0.33, 1.73)	-
Hemorrhagic Stroke						
All Patients	6/2807	0.19	9/2791	0.28	0.67 (0.24, 1.88)	0.4471
≤ 30 mL/min	0/55	0.00	0/61	0.00	§	-
>30 – ≤ 50 mL/min	0/490	0.00	1/478	0.19	0 §	-
> 50 – ≤ 80 mL/min	4/1074	0.33	6/1075	0.50	0.66 (0.19, 2.35)	-
> 80 mL/min	1/955	0.09	1/923	0.09	0.97 (0.06, 15.53)	-
Vascular Death						
All Patients	84/2807	2.65	96/2791	3.03	0.87 (0.65, 1.17)	0.3659
≤ 30 mL/min	8/55	13.74	8/61	14.02	0.99 (0.37, 2.63)	-
>30 – ≤ 50 mL/min	28/490	5.38	26/478	4.91	1.08 (0.63, 1.84)	-
> 50 – ≤ 80 mL/min	31/1074	2.56	42/1075	3.51	0.73 (0.46, 1.17)	-
> 80 mL/min	11/955	1.00	11/923	1.01	0.98 (0.42, 2.26)	-

n=number of patients with an event, N=number of patients in each subgroup.
*patients with eCrCl < 25 mL/min at baseline were excluded from this trial
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
Any Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and unspecified stroke

Table 30 – Bleeding Endpoints by Renal Function* at Baseline in the AVERROES Trial, While on Treatment – Treated Patients

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
ISTH Major Bleeding (Principal Safety Endpoint)						

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
All Patients	45/2798	1.41	29/2780	0.92	1.54 (0.96, 2.45)	0.0716
≤ 30 mL/min	3/55	5.26	2/61	3.40	1.71 (0.29, 10.22)	-
>30 – ≤ 50 mL/min	17/489	3.35	7/475	1.39	2.43 (1.01, 5.85)	-
> 50 – ≤ 80 mL/min	12/1068	0.98	13/1072	1.09	0.90 (0.41, 1.98)	-
> 80 mL/min	8/953	0.71	4/919	0.36	2.01 (0.60, 6.67)	-
Major and Non-Major Clinically Relevant Bleeding Event						
All Patients	140/2798	4.46	101/2780	3.24	1.38 (1.07, 1.78)	0.0144
≤ 30 mL/min	4/55	7.16	6/61	10.47	0.73 (0.21, 2.59)	-
>30 – ≤ 50 mL/min	35/489	7.02	17/475	3.41	2.05 (1.15, 3.65)	-
> 50 – ≤ 80 mL/min	52/1068	4.34	40/1072	3.40	1.28 (0.85, 1.94)	-
> 80 mL/min	39/953	3.49	30/919	2.74	1.28 (0.79, 2.06)	-
Intracranial Hemorrhage**						
All Patients	11/2798	0.34	11/2780	0.35	0.99 (0.39, 2.51)	1.000
≤ 30 mL/min	1/55	1.75	1/61	1.70	1.16 (0.07, 18.63)	-
>30 – ≤ 50 mL/min	3/489	0.59	1/475	0.20	3.07 (0.32, 29.61)	-
> 50 – ≤ 80 mL/min	4/1068	0.33	7/1072	0.59	0.56 (0.16, 1.90)	-
> 80 mL/min	1/953	0.09	0/919	0.00	§	-
Fatal Bleeding**						
All Patients	5/2798	0.16	5/2780	0.16	0.99 (0.23, 4.29)	1.000
≤ 30 mL/min	0/55	0.00	0/61	0.00	§	-
>30 – ≤ 50 mL/min	2/489	0.39	2/475	0.40	1.05 (0.15, 7.46)	-
> 50 – ≤ 80 mL/min	1/1068	0.08	3/1072	0.25	0.33 (0.03, 3.13)	-
> 80 mL/min	1/953	0.09	0/919	0.00	§	-

Treated patients analysis = adjudicated events while on treatment (up to last dose, plus 2 days for patients who did not enter the open-label extension)
n=number of patients with an event, N=number of patients in each subgroup.
*patients with eCrCl < 25 mL/min at baseline were excluded from this trial
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
**For fatal bleeding and intracranial bleeding in all patients, risk ratios (95% CI) and p-values are from exact Poisson regression models with treatment as a covariate.

The event rates for efficacy and safety (bleeding) outcomes for those patients treated with apixaban 5 mg bid or apixaban 2.5 mg bid are presented in Table 31 and Table 32, respectively.

Patients randomised to apixaban received a lower dose of apixaban 2.5 mg bid if they met at least two (2) of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 micromole/L (1.5mg/dL).

Table 31 – Efficacy Outcomes by Dose in the AVERROES Trial - All Randomized Patients

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)						
All Patients	51/2807	1.62	113/2791	3.63	0.45 (0.32, 0.62)	<0.0001
Apixaban 2.5 mg BID	3/179	1.63	12/182	6.24	0.26 (0.07, 0.93)	-
Apixaban 5 mg BID	48/2628	1.62	101/2609	3.46	0.47 (0.33, 0.66)	-
Any Stroke						
All Patients	49/2807	1.56	105/2791	3.37	0.46 (0.33, 0.65)	<0.0001
Apixaban 2.5 mg BID	3/179	1.63	11/182	5.66	0.29 (0.08, 1.04)	-
Apixaban 5 mg BID	46/2628	1.55	94/2609	3.21	0.48 (0.34, 0.69)	-
Ischemic or Unspecified Stroke						
All Patients	43/2807	1.37	97/2791	3.11	0.44 (0.31, 0.63)	<0.0001
Apixaban 2.5 mg BID	3/179	1.63	11/182	5.66	0.29 (0.08, 1.04)	-
Apixaban 5 mg BID	40/2628	1.35	86/2609	2.94	0.46 (0.32, 0.67)	-
Hemorrhagic Stroke						
All Patients	6/2807	0.19	9/2791	0.28	0.67 (0.24, 1.88)	0.4471
Apixaban 2.5 mg BID	0/179	0.00	0/182	0.00	§	-
Apixaban 5 mg BID	6/2628	0.20	9/2609	0.30	0.67 (0.24, 1.88)	-
Vascular Death						
All Patients	84/2807	2.65	96/2791	3.03	0.87 (0.65, 1.17)	0.3659
Apixaban 2.5 mg BID	17/179	9.21	21/182	10.57	0.83 (0.43, 1.59)	-
Apixaban 5 mg BID	67/2628	2.25	75/2609	2.52	0.89 (0.64, 1.24)	-

n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
Any Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and unspecified stroke.

Table 32 – Bleeding Endpoints by Dose in the AVERROES Trial, While on Treatment – Treated Patients

	Apixaban		ASA		Apixaban vs ASA	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard Ratio (95% CI)	P-value
ISTH Major Bleeding (Principal Safety Endpoint)						
All Patients	45/2798	1.41	29/2780	0.92	1.54 (0.96, 2.45)	0.0716
Apixaban 2.5 mg BID	8/178	4.48	3/182	1.59	2.82 (0.75, 10.62)	-
Apixaban 5 mg BID	37/2620	1.23	26/2598	0.88	1.40 (0.85, 2.32)	-
Major and Non-Major Clinically Relevant Bleeding Event						
All Patients	140/2798	4.46	101/2780	3.24	1.38 (1.07, 1.78)	0.0144
Apixaban 2.5 mg BID	13/178	7.38	7/182	3.73	1.95 (0.78, 4.89)	-
Apixaban 5 mg BID	127/2620	4.29	94/2598	3.21	1.34 (1.02, 1.75)	-
Intracranial Hemorrhage**						
All Patients	11/2798	0.34	11/2780	0.35	0.99 (0.39, 2.51)	1.000
Apixaban 2.5 mg BID	1/178	0.56	1/182	0.53	1.05 (0.07, 16.83)	-
Apixaban 5 mg BID	10/2620	0.33	10/2598	0.34	0.98 (0.41, 2.36)	-
Fatal Bleeding**						
All Patients	5/2798	0.16	5/2780	0.16	0.99 (0.23, 4.29)	1.000
Apixaban 2.5 mg BID	0/178	0.00	0/182	0.00	§	-
Apixaban 5 mg BID	5/2620	0.17	5/2598	0.17	0.98 (0.28, 3.39)	-

Treated patients analysis = adjudicated events while on treatment (up to last dose, plus 2 days for patients who did not enter the open-label extension)
n=number of patients with an event, N=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value are from a Cox proportional hazards model with treatment group as a covariate.
**For fatal bleeding and intracranial bleeding in all patients, risk ratios (95% CI) and p-values are from exact Poisson regression models with treatment as a covariate.

The number and percentage of patients who received apixaban by dose are provided below according to degree of renal function at baseline.

Table 33 – Number and percentage of patients who received apixaban by dose according to degree of renal function at baseline in the AVERROES trial

	Apixaban	ASA
Apixaban/Placebo 2.5 mg BID, N	178	182
Severe (≤ 30 mL/min), n (%)	39 (21.9)	41 (22.5)
Moderate (> 30 - ≤ 50 mL/min), n (%)	105 (59.0)	112 (61.5)
Mild (> 50 - ≤ 80 mL/min), n (%)	22 (12.4)	20 (11.0)
Normal (> 80 mL/min), n (%)	1 (0.6)	1 (0.6)
Not Reported, n (%)	11 (6.2)	8 (4.4)
Apixaban/Placebo 5 mg BID, N	2620	2598

Severe (≤ 30 mL/min), n (%)	16 (0.6)	20 (0.8)
Moderate (> 30 - ≤ 50 mL/min), n (%)	384 (14.7)	363 (14.0)
Mild (> 50 - ≤ 80 mL/min), n (%)	1046 (39.9)	1052 (40.5)
Normal (> 80 mL/min), n (%)	952 (36.3)	918 (35.3)
Not Reported, n (%)	222 (8.5)	245 (9.4)

The denominator to calculate each percentage is the number of subjects treated in each of the apixaban dose groups and treatment group

Treatment of DVT and PE and Prevention of recurrent DVT and PE

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 34 – Patient baseline 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%
Body weight ≤ 60 kg	8.5%	6.6%
Race		
White/Caucasian	82.7%	85.3%
Black/African American	3.8%	3.2%
Asian	8.4%	4.8%
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 eCrCl > 80 mL/min	64.5%	70.1%
50< eCrCl ≤ 80 mL/min	20.3%	21.6%
30< eCrCl ≤ 50 mL/min	5.7%	5.3%
eCrCl ≤ 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 study. 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.

The key study outcomes were prespecified and tested in a sequential, hierarchical manner to preserve overall type 1 error (false-positive) at ≤ 5%. Apixaban was tested compared to enoxaparin/warfarin for: (1) non-inferiority on the composite endpoint of VTE/VTE-related death, (2) superiority on major bleeding, (3) superiority on the composite endpoint of VTE/VTE-related death, and (4) superiority on the composite of major/CRNM bleeding.

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 35).

Table 35 - 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)
Non-fatal DVT§	20 (0.7)	33 (1.2)	
Non-fatal 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)
All-cause death	41 (1.6)	52 (2.0)	0.79 (0.53, 1.19)
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)

§ First event is the first primary event for each subject. Each subject is counted only once.

Figure 3 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint in the two treatment groups in the AMPLIFY study.

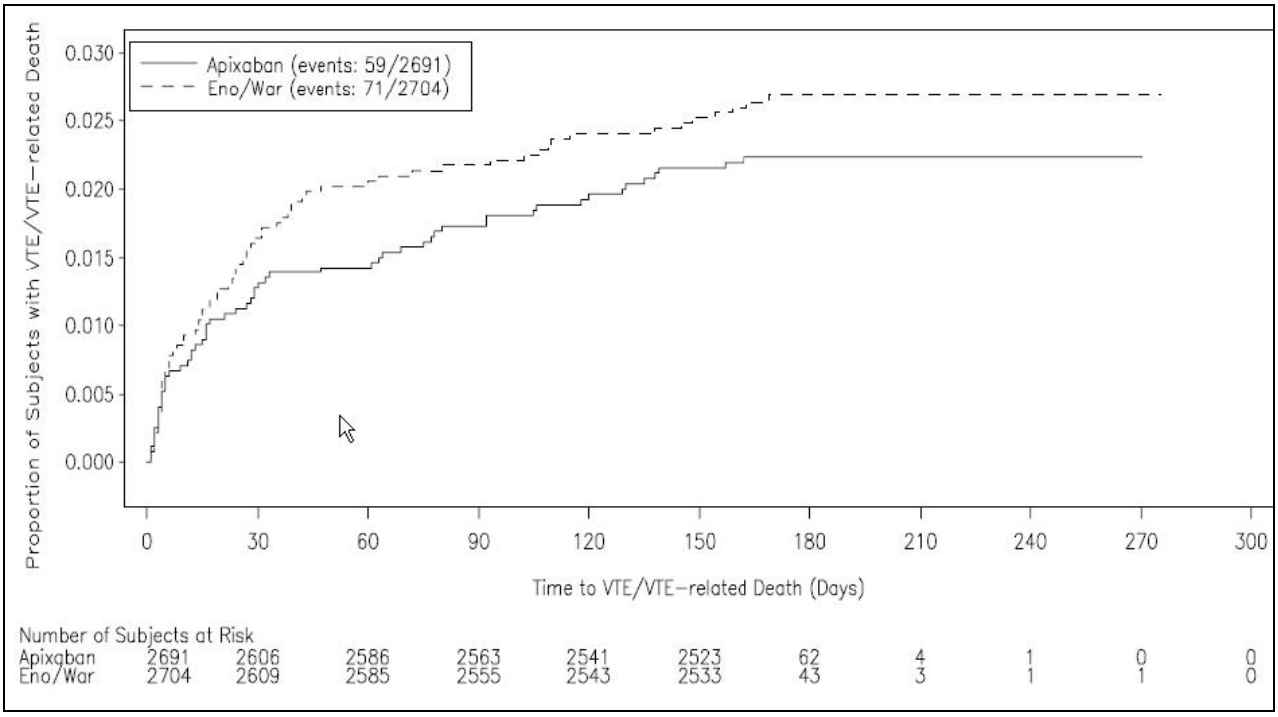


Figure 3 – Kaplan-Meier Estimate of Time to First DVT or PE, or VTE-related Death in the AMPLIFY Study (Intent-to-Treat Population)

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 of PE, location of DVT thrombus, and prior parenteral heparin use was generally consistent (see Figure 4).

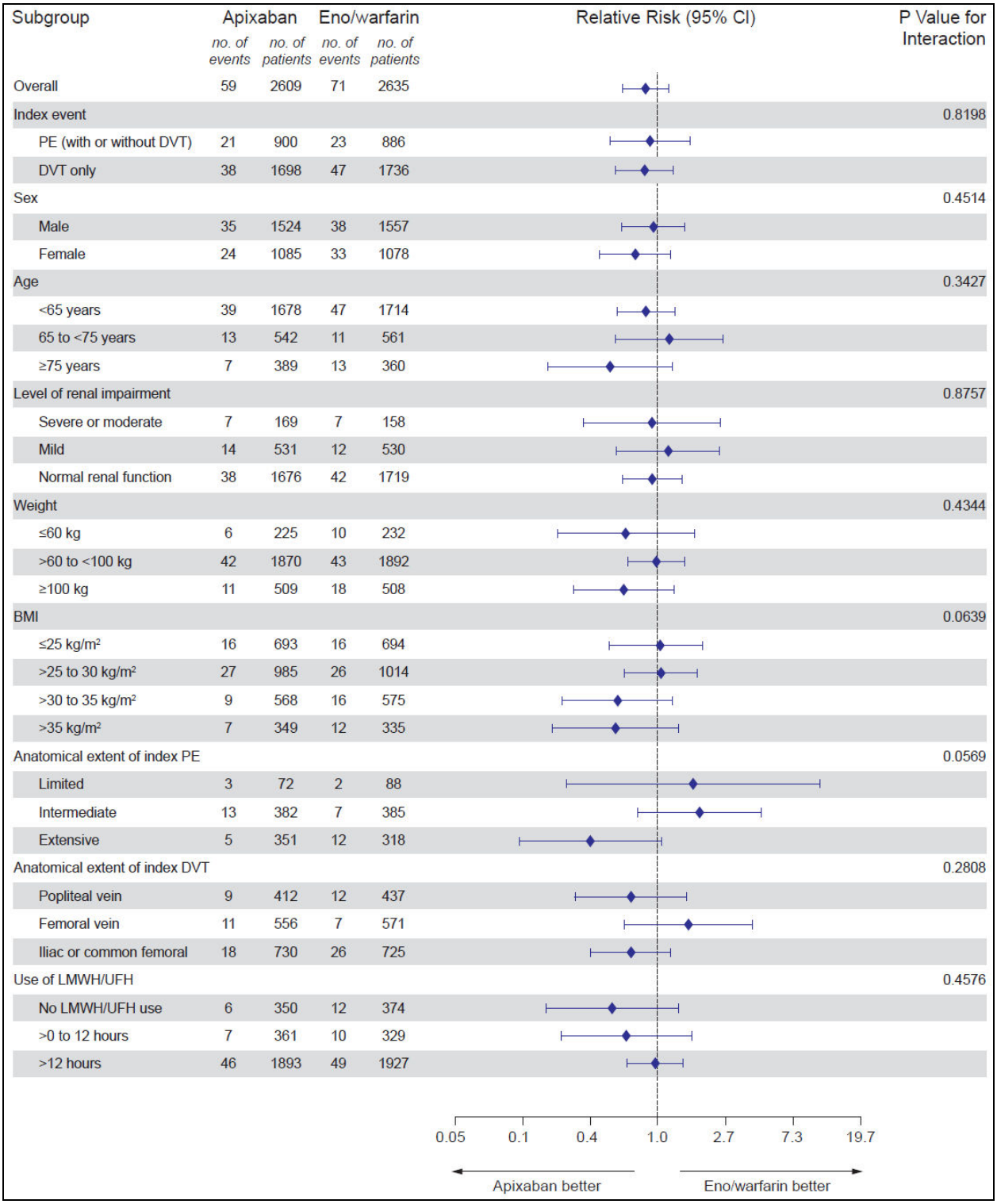


Figure 4 – Recurrent Symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related Death Relative Risk by Baseline Characteristics

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 5).

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.

Adjudicated myocardial infarction occurred in 4 (0.1%) apixaban-treated patients and 2 (0.1%) enoxaparin/warfarin-treated patients.

AMPLIFY-EXT Study: AMPLIFY-EXT study evaluated the benefit of continued treatment in patients for whom clinical uncertainty regarding the absolute risk-benefit of extended duration existed. 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, apixaban was superior to placebo for the primary efficacy endpoint with a relative risk of 0.24 (95% CI: 0.15 - 0.40) and 0.19 (95% CI: 0.11 - 0.33) for 2.5 mg and 5 mg apixaban, respectively (p<0.0001 for both) (see Table 36).

Table 36 – 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 (%)					
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)	<0.0001
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)	<0.0001
Non-fatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)	<0.0001
Non-fatal PE†	8 (1.0)	4 (0.5)	15 (1.8)	0.51 (0.22, 1.21)	0.27 (0.09, 0.80)	

	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 (%)					
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)	
All-cause death	7 (0.8)	4 (0.5)	14 (1.7)	0.49 (0.20, 1.21)	0.29 (0.10, 0.88)	

* For patients with more than one event contributing to the composite endpoint, only the first event was reported (eg, 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 5 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.

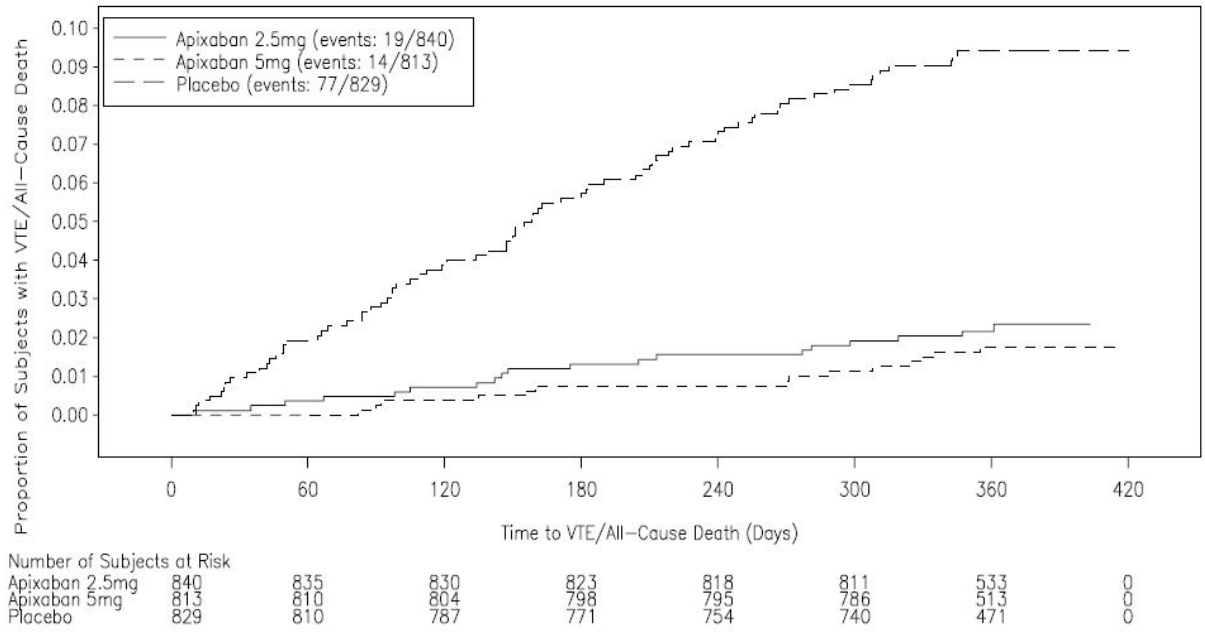


Figure 5 – Kaplan-Meier Estimate of Time to First DVT or PE, or All-cause Death in the AMPLIFY-EXT Study (Intent-to-Treat Population)

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 of 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 significantly higher than the placebo group. (See Table 6).

Figure 6 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.

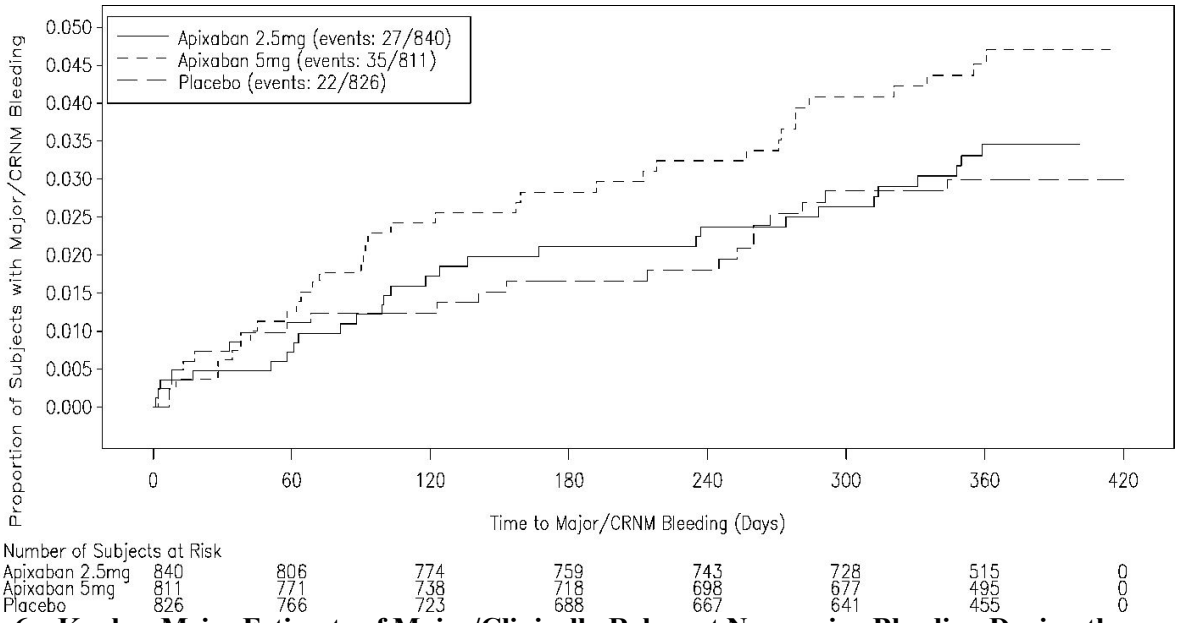


Figure 6 – Kaplan-Meier Estimate of Major/Clinically Relevant Non-major Bleeding During the Treatment Period in the AMPLIFY-EXT Study

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.

DETAILED PHARMACOLOGY

Apixaban is a potent, reversible, direct inhibitor of Factor-Xa (FXa) at the active site with an inhibitory constant (Ki) of 0.08 nM for human FXa and with greater than 30,000-fold selectivity over other human coagulation proteases. It does not require antithrombin III to inhibit FXa. It inhibits free, prothrombinase-bound as well as clot-bound FXa activity and reduces thrombin generation in vitro. Apixaban also inhibits FXa from rabbits, rats, and dogs, with Ki of 0.16, 1.4, and 1.8 nM, respectively, which parallels its antithrombotic potency in these species. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin derived from the upstream proteases in the blood coagulation cascade. In standard clotting assays, apixaban is more potent in the prolongation of PT than aPTT ex vivo in rats, rabbits and dogs.

Apixaban given prophylactically caused dose-dependent antithrombotic activity in multiple species, such as rats, rabbits and dogs, in models of arterial and venous thrombosis, and prevented the growth of a preexisting thrombus. Measurements of apixaban plasma concentrations in these experiments revealed EC_{50} values ranging from approximately 0.1 to 7.57 mcM for inhibition of thrombus formation and maintenance of blood flow. These concentrations

tended to be higher in species (rat and dog) for which the FXa affinity of apixaban was lower. Apixaban appeared to have a therapeutic window between the dose that inhibits thrombosis and the dose that increases provoked bleeding, which tended to be model and/or species dependent.

TOXICOLOGY

In chronic dog (≤1 year) and rat (≤6 months) toxicity studies, the principal findings were reversible pharmacological effects (minimally prolonged PT and aPTT values). At the highest doses tested (600 mg/kg/day in rats, 100 mg/kg/day in dogs), no target organs of toxicity, including liver were identified, there was no overt bleeding or hemorrhage and AUC values were 30× and 114×, respectively, the area under the plasma concentration-time curve (AUC) at the recommended human dose (RHD) of 5 mg (2.5 mg BID) for the indication of VTE prevention.

Carcinogenesis

Apixaban was not carcinogenic in mice given ≤3000 mg/kg/day or rats given ≤600 mg/kg/day for 2 years. Apixaban AUC multiples were ≤30× the RHD AUC value.

Reproductive Toxicology

Apixaban had no effects on male or female fertility in rats at doses ≤600 mg/kg and AUC values ≤30× the AUC at the RHD.

Apixaban administered to female rats at ≤1000 mg/kg/day during early gestation and throughout the lactation period, produced no findings in offspring (F1 generation) at 25 mg/kg/day representing an AUC value 9.8× the AUC at the RHD. Effects in the F1-generation females were limited to decreased mating and fertility indices at ≥ 200 mg/kg/day at AUC values ≥ 36× the AUC at the RHD. The lower F1 mating indices have limited clinical relevance because these effects were minimal and occurred only at AUC values well in excess of those at the RHD.

Mutagenesis

Apixaban was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay, not clastogenic *in vitro* (cytogenetics assay in Chinese hamster ovary cells) or *in vivo* (1-month *in vivo*/*in vitro* cytogenetics study in rat peripheral blood lymphocytes), and showed no evidence of genotoxicity in a micronucleus study in rats.

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PART III: CONSUMER INFORMATION

[Pr]Sandoz® Apixaban SDZ
Apixaban Tablets
2.5 mg and 5 mg

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Apixaban SDZ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sandoz Apixaban SDZ. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Sandoz Apixaban SDZ is used in adults for the following conditions:

- **Knee or hip replacement surgery:** To prevent blood clots from forming after knee or hip replacement surgery.
- **Atrial fibrillation:** To reduce the risk of stroke (damage to part of the brain caused by an interruption of its blood supply), and systemic embolism (the sudden blocking of a blood vessel by a blood clot) in people who have a heart condition called atrial fibrillation (irregular heart beat).
- **Blood clots:** To treat deep vein thrombosis (blood clots in the veins of your legs) and pulmonary embolism (blood clots in the blood vessels of your lungs) and reduce the risk of them occurring again.

What it does:
Sandoz Apixaban SDZ belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking one of the molecules that causes blood clotting (known as Factor-Xa).

When it should not be used:

- you are aware of body lesions at risk of bleeding, including bleeding in the brain (stroke)
- you have certain types of abnormal bleeding such as recent bleeding of a stomach ulcer
- you have active bleeding, especially if you are bleeding excessively
- you have a severe liver disease which leads to increased risk of bleeding (hepatic coagulopathy)
- you are already taking medicines to prevent blood clots, e.g.warfarin (COUMADIN®), heparin, rivaroxaban (XARELTO®), dabigatran (PRADAXA®), unless your physician has decided to switch you to Sandoz Apixaban SDZ
- you are also taking prasugrel (EFFIENT®) or ticagrelor (BRILINTA®)
- Sandoz Apixaban SDZ should not be used during pregnancy, since its effects on pregnancy and the unborn child are not known
- you are taking oral ketoconazole (a drug used to treat fungus infection)
- while epidural or spinal catheters are in place or within the first five hours after their removal. Your doctor will know what precautionary measures are required. Sandoz Apixaban SDZ is not recommended for patients receiving epidural pain control after surgery
- you have an artificial heart valve
- you are younger than 18 years old
- you are allergic (hypersensitive) to apixaban (active ingredient of Sandoz Apixaban SDZ) or any of the other ingredients of Sandoz Apixaban SDZ. The ingredients are listed in the "What the nonmedicinal ingredients are:" section of this leaflet

What the medicinal ingredient is:
Apixaban

What the nonmedicinal ingredients are:
Lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, hypromellose, magnesium stearate, titanium dioxide, triacetin. Tartrazine aluminum lake, sunset yellow FCF aluminum lake, iron oxide yellow (2.5 mg tablets only), iron oxide red (5 mg tablets only).

What dosage forms it comes in:
Film-coated tablets in yellow colour, 2.5 mg.
Film-coated tablets in pink colour, 5 mg.

WARNINGS AND PRECAUTIONS

Do not stop taking Sandoz Apixaban SDZ without first talking with your doctor. If you stop taking Sandoz Apixaban SDZ, blood clots may cause a stroke or other complications. This can be fatal or lead to severe disability.

BEFORE you use Sandoz Apixaban SDZ talk to your doctor or pharmacist if you have any of the following:

- an increased risk of bleeding, such as:
  - **bleeding disorders**
  - **an active or a recent ulcer** of your stomach or bowel
  - **infection of the heart** (bacterial endocarditis)
  - **recent bleeding in your brain** (hemorrhagic stroke)
  - **very high blood pressure,** not controlled by medical treatment
  - **a recent operation on your brain, spinal column or eye**

- severe kidney disease
- mild or moderate liver disease
- have antiphospholipid syndrome
- a tube (catheter) inserted in your back
- had **an injection into your spinal column within the previous 5 hours, such as an epidural,** for anaesthesia or pain relief.
- had an **operation for a hip fracture** because this medicine has not been studied for this condition.
- you are 75 years of age or older

Sandoz Apixaban SDZ is not recommended in children and adolescents under 18 years of age.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any

medicine.

The effects of Sandoz Apixaban SDZ on pregnancy and the unborn child are not known. You should not take Sandoz Apixaban SDZ if you are pregnant. **Contact your doctor immediately** if you become pregnant while taking Sandoz Apixaban SDZ.

It is not known if Sandoz Apixaban SDZ passes into human breast milk. Ask your doctor or pharmacist for advice before taking Sandoz Apixaban SDZ while breast-feeding.

Anticoagulant-Related Nephropathy (ARN)
Some cases were reported in patients taking Sandoz Apixaban SDZ. It is a type of serious kidney damage caused by anticoagulant medicines. ARN causes bleeding in the kidneys, sometimes with the presence of blood in the urine. This leads to the kidneys being unable to function properly. Your healthcare professional may monitor the health of your kidneys during your treatment with Sandoz Apixaban SDZ. If you are experiencing symptoms of ARN during your treatment, tell your healthcare professional right away.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal supplements.

Some medicines may increase the effects of Sandoz Apixaban SDZ and some may decrease its effects. Your doctor will decide, if you should be treated with Sandoz Apixaban SDZ when taking these medicines and how closely you should be monitored.

Drugs that may interact with Sandoz Apixaban SDZ include:

Medicines that may increase the effects of Sandoz Apixaban SDZ:
You are at an increased risk for bleeding if you take Sandoz Apixaban SDZ with one of these drugs:

- some **medicines for fungal infections** (e.g. ketoconazole, itraconazole, voriconazole and posaconazole)
- some **antiviral medicines for HIV / AIDS** (e.g. ritonavir)
- other **medicines that are used to reduce blood clotting** (e.g. enoxaparin, clopidogrel, prasugrel)
- **anti-inflammatory** or **pain medicines** (e.g. aspirin or naproxen)
- **medicines for high blood pressure or heart problems** (e.g. diltiazem)
- some **medicines for bacterial infections** (e.g. clarithromycin)
- **antidepressants/anti-anxiety** (SSRIs, SNRIs) (e.g. fluoxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxetine)

Medicines that may reduce the effects of Sandoz Apixaban SDZ:

- **medicines to treat tuberculosis** or **other infections** (e.g. rifampin, rifampicin)
- **medicines to prevent epilepsy or seizures** (e.g. phenytoin, carbamazepine, or phenobarbital)
- **St John's Wort** (a herbal supplement used for depression)

PROPER USE OF THIS MEDICATION

Sandoz Apixaban SDZ can be taken with or without food.

Sandoz Apixaban SDZ should be taken regularly, as prescribed, to ensure best results. All temporary discontinuations should be avoided, unless recommended by your physician.

Usual adult dose:
Knee or hip replacement surgery:
Take one 2.5 mg tablet twice daily, one in the morning and one in the evening. Take the tablet at the same time every day, preferably 12 hours apart. Swallow the tablet whole with a drink of water. DO NOT chew the tablet. DO NOT stop taking this medication without advice from the doctor.

Always take Sandoz Apixaban SDZ exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you have trouble swallowing the tablet(s)
Follow the steps below to crush the Sandoz Apixaban SDZ tablet(s). This will help make sure that all of the crushed tablet(s) will be taken.

Steps

- use a mortar and pestle or a similar device to crush the tablet (s)
- transfer the powder to a drinking glass or a small bowl
- when using water:
    - add a small amount of water (30 mL) to the mortar and pestle/device and stir
    - transfer the water to the drinking glass
    - mix the powder with the water and drink right away.
    - rinse the glass with a small amount of water and drink right away
- when using apple sauce:
    - mix the powder with a small amount of apple sauce (30 g) in a small bowl and eat with a spoon right away
    - add a small amount of water (30 mL) to the mortar and pestle/device and stir
    - transfer the water to the bowl and drink right away
    - rinse the bowl and the spoon with a small amount of water and drink right away.

Length of treatment
After major **hip** operation you will usually take the tablets for up to 38 days.

After major **knee** operation you will usually take the tablets for up to 14 days.

Do not stop taking Sandoz Apixaban SDZ without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early.

Atrial fibrillation (AF):
For most patients with AF, the recommended dose of Sandoz Apixaban SDZ is 5 mg taken orally twice daily.

Depending on your age, weight or kidney function, your doctor may prescribe 2.5 mg twice daily.

If you are currently taking warfarin (another oral anticoagulant) or receive anticoagulant treatment given by injection, and your doctor has decided Sandoz Apixaban SDZ is appropriate for you, make sure you ask your doctor when and how best to switch and start taking Sandoz Apixaban SDZ.

If you have atrial fibrillation and stop taking Sandoz Apixaban SDZ without talking to your doctor, you are at risk of suffering from a stroke or other complications due to blood clot formation, which can be fatal or lead to severe disability.

Treatment and prevention of blood clots in the veins of your legs or lungs:
Take 10 mg twice daily (two 5 mg tablets in the morning and two 5 mg tablets in the evening) for 7 days. For treatment after 7 days, take 5 mg twice daily (one 5 mg tablet in the morning and one 5 mg tablet in the evening).

After a minimum of 6 months of treatment, your doctor may prescribe Sandoz Apixaban SDZ 2.5 mg twice daily (one 2.5 mg tablet in the morning and one 2.5 mg tablet in the evening).

Length of treatment
This is long-term treatment and you should continue to take Sandoz Apixaban SDZ until your doctor says otherwise.

Overdose:
Tell your doctor immediately if you have taken more than the prescribed dose of Sandoz Apixaban SDZ.

You may have an increased risk of bleeding. If bleeding occurs, surgery or blood transfusions may be required.

If you think you have taken too much Sandoz Apixaban SDZ, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed a dose, take the medicine as soon as you remember and continue with your remaining daily dose of Sandoz Apixaban SDZ; then carry on taking one tablet, twice a day as normal.

Do not take a double dose to make up for a forgotten tablet of Sandoz Apixaban SDZ.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines Sandoz Apixaban SDZ can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist if you experience any of the following symptoms after taking this medicine.

Like other similar medicines (anticoagulants), Sandoz Apixaban SDZ may cause bleedings which could possibly lead to anemia (a low blood cell count which may cause tiredness or paleness). In some cases this bleeding may not be obvious. Nausea (feeling sick) is also a common side effect.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Anemia:** fatigue, loss of energy, weakness, shortness of breath		✓	
Common	Blood in the urine (that stains the urine pink or red)		✓	
Common	Bruising and swelling		✓	
Common	**Bleeding:** - in your eyes - from your gums and blood in your spit when coughing - from your rectum - abnormally heavy or long menstrual bleeding		✓	
Uncommon	Bleeding after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision		✓	
Uncommon	Bleeding in your stomach, bowel or blood in the stool		✓	
Uncommon	Bleeding from your nose		✓	
Uncommon	**Liver Disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Low Blood Pressure: dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up	✓		
Rare	Bleeding: – into a muscle		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek
Unknown frequency	**Allergic Reaction:** Rash, hives, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing			✓
	Anticoagulant-related nephropathy (serious kidney damage caused by anticoagulant medicines): bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly			✓

You should be aware that prescription medicines carry some risks and that all possible risks may not be known at this stage.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

This is not a complete list of side effects. For any unexpected effects while taking Sandoz Apixaban SDZ contact your doctor or pharmacist.

HOW TO STORE IT

Keep at room temperature (15-30ºC).

Keep out of the reach and sight of children.

Do not use Sandoz Apixaban SDZ after the expiry date which is stated on the carton, the blister, or on the bottle after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

If you want more information about Sandoz Apixaban SDZ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

or by written request at:
110 de Lauzon
Boucherville QC
J4B 1E6

Or by e-mail at :
medinfo@sandoz.com

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