

# PRODUCT MONOGRAPH

## <sup>Pr</sup>PRO-APIXABAN

Apixaban Tablets

2.5 mg and 5 mg

Anticoagulant

**PRO DOC LTÉE**  
2925 Boulevard Industriel  
Laval, Québec  
H7L 3W9

**Date of Initial Approval:**  
SEP 20, 2022

**Date of Revision:**  
APR 10, 2026

Submission Control No: 305778

## Table of Contents

|   |               |
|---|---------------|
| <b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b> | <b>3</b>      |
| SUMMARY PRODUCT INFORMATION.....                    | 3             |
| INDICATIONS AND CLINICAL USE .....                  | 3             |
| CONTRAINDICATIONS.....                              | 3             |
| WARNINGS AND PRECAUTIONS .....                      | 4             |
| ADVERSE REACTIONS.....                              | 11            |
| DRUG INTERACTIONS .....                             | 19            |
| DOSAGE AND ADMINISTRATION .....                     | 25            |
| OVERDOSAGE.....                                     | 32            |
| ACTION AND CLINICAL PHARMACOLOGY .....              | 33            |
| STORAGE AND STABILITY .....                         | 38            |
| SPECIAL HANDLING INSTRUCTIONS.....                  | 38            |
| DOSAGE FORMS, COMPOSITION AND PACKAGING.....        | 38            |
| <br><b>PART II: SCIENTIFIC INFORMATION .....</b>    | <br><b>40</b> |
| PHARMACEUTICAL INFORMATION.....                     | 40            |
| CLINICAL TRIALS .....                               | 41            |
| DETAILED PHARMACOLOGY .....                         | 72            |
| TOXICOLOGY.....                                     | 73            |
| REFERENCES.....                                     | 74            |
| <br><b>PART III: CONSUMER INFORMATION.....</b>      | <br><b>76</b> |

## Pr **PRO-APIXABAN**

### Apixaban Tablets

## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **SUMMARY PRODUCT INFORMATION**

| <b>Route of Administration</b> | <b>Dosage Form / Strength</b> | <b>Nonmedicinal Ingredients</b>  |
|--------------------------------|-------------------------------|--|
| Oral                           | Tablet, 2.5 mg and 5 mg       | Anhydrous lactose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, polyvinyl alcohol, talc, titanium dioxide, red ferric oxide (5 mg tablets) and yellow iron oxide (2.5 mg tablets). |

### **INDICATIONS AND CLINICAL USE**

PRO-APIXABAN (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 PRO-APIXABAN (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 PRO-APIXABAN, INCREASES THE RISK OF THROMBOTIC EVENTS.**

To reduce this risk, consider coverage with another anticoagulant if PRO-APIXABAN 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, PRO-APIXABAN (apixaban) should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with PRO-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 PRO-APIXABAN (see CONTRAINDICATIONS).

**Should severe bleeding occur, treatment with PRO-APIXABAN 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 <b>both</b> 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 PRO-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 PRO-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 PRO-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 PRO-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<sub>max</sub>. Therefore, the use of PRO-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 PRO-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***

PRO-APIXABAN is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see CONTRAINDICATIONS). PRO-APIXABAN is not recommended in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Hepatic Impairment). PRO-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  $\geq$  1.5 x ULN) were excluded in clinical trials. Therefore, PRO-APIXABAN should be used with caution in these patients.

## **Peri-Operative/Procedural Considerations**

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

### ***Pre-Operative Phase***

If an invasive procedure or surgical intervention is required, PRO-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 PRO-APIXABAN at least 48 hours before surgery, depending on clinical circumstances. PRO-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 PRO-APIXABAN. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of PRO-APIXABAN should be delayed for 24 hours.**

Patients who have undergone epidural puncture and who are receiving PRO-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 PRO-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 PRO-APIXABAN.

### ***Post-Procedural Period***

PRO-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 PRO-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 PRO-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 PRO-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 PRO-APIXABAN (see DOSAGE AND ADMINISTRATION).

PRO-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 to 30 mL/min, unless at least two (2) of the following criteria for dose reduction are met: age  $\geq$  80 years, body weight  $\leq$  60 kg, or patients with serum creatinine  $\geq$  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 to 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  $\sim$  30, C<sub>max</sub>  $\sim$  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 PRO-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, PRO-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 CLINICAL 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 ( $\geq$ 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 PRO-APIXABAN to elderly patients ( $\geq 75$  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 PRO-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 PRO-APIXABAN (see also DOSAGE AND ADMINISTRATION, Switching from PRO-APIXABAN to VKA, Considerations for INR Monitoring of VKA Activity during Concomitant PRO-APIXABAN Therapy). The INR is only calibrated and validated for vitamin K antagonists (VKA) and should not be used for any other anticoagulant, including PRO-APIXABAN.**

Apixaban demonstrates anti-FXa activity as evident by reduction in Factor-Xa enzyme activity in the Rotachrom<sup>®</sup> 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 PRO-APIXABAN during routine clinical practice, in certain infrequent situations such as overdose, 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  $\geq 12$  months for 9,375 patients, and  $\geq 24$  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 to 24 hours after surgery. Bleeding during the post-surgery treatment period only included events occurring after the first dose of study drug after surgery. Over half the occurrences of major bleeding in the apixaban group 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 to 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 <sup>a</sup>       | ADVANCE-3<br>Hip replacement surgery             |  | ADVANCE-2<br>Knee replacement surgery            |  | ADVANCE-1<br>Knee replacement surgery               |  |
|--------------------------------------|--|--|--|--|---|--|
|                                      | Apixaban<br>2.5 mg po<br>bid<br>35±3 days        | Enoxaparin<br>40 mg sc qd<br>35±3 days             | Apixaban<br>2.5 mg po<br>bid<br>12±2 days        | Enoxaparin<br>40 mg sc<br>qd<br>12±2 days          | Apixaban<br>2.5 mg po<br>bid<br>12±2 days           | Enoxaparin<br>30 mg sc<br>q12h<br>12±2 days      |
|                                      | First dose<br>12 to 24<br>hours post-<br>surgery | First dose<br>9 to 15 hours<br>prior to<br>surgery | First dose<br>12 to 24<br>hours post-<br>surgery | First dose<br>9 to 15<br>hours prior<br>to surgery | First dose<br>12 to 24<br>hours<br>post-<br>surgery | First dose<br>12 to 24<br>hours post-<br>surgery |
| All treated                          | n = 2673   | n = 2659   | n = 1501   | n = 1508   | n = 1596  | n = 1588   |
| <b>Treatment Period<sup>b</sup></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<br>+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%)                                       |
| <b>Post-surgery Treatment Period</b> |  |  |  |  |   |  |
| 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<br>+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%)                                       |

<sup>a</sup> All bleeding criteria included surgical site bleeding.

<sup>b</sup> 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**

|                           | <b>Apixaban<br/>N=9088<br/>n (%/year)</b> | <b>Warfarin<br/>N=9052<br/>n (%/year)</b> | <b>Hazard Ratio<br/>(95% CI)</b> | <b>p-value</b> |
|---------------------------|---|---|----------------------------------|----------------|
| <b>Major*</b>             | 327 (2.13)                                | 462 (3.09)                                | 0.69 (0.60, 0.80)                | < 0.0001       |
| <b>Fatal</b>              | 10 (0.06)                                 | 37 (0.24)                                 |                                  |                |
| <b>Intracranial</b>       | 52 (0.33)                                 | 122 (0.80)                                |                                  |                |
| <b>Major +<br/>CRNM**</b> | 613 (4.07)                                | 877 (6.01)                                | 0.68 (0.61, 0.75)                | < 0.0001       |
| <b>All</b>                | 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. PRO-APIXABAN, like other anticoagulants, should be used with caution in patients treated concomitantly with antiplatelet agents.

**Table 4 – Bleeding Events\* in the AVERROES Study**

|                       | <b>Apixaban<br/>N=2798<br/>n (%/year)</b> | <b>Aspirin<br/>N=2780<br/>n (%/year)</b> | <b>Hazard Ratio vs<br/>Aspirin<br/>(95%CI)</b> | <b>p-value</b> |
|-----------------------|---|--|--|----------------|
| <b>Major</b>          | 45 (1.41)                                 | 29 (0.92)                                | 1.54 (0.96, 2.45)                              | 0.0716         |
| <b>Fatal</b>          | 5 (0.16)                                  | 5 (0.16)                                 |  |                |
| <b>Intracranial</b>   | 11 (0.34)                                 | 11 (0.35)                                |  |                |
| <b>Major + CRNM**</b> | 140 (4.46)                                | 101 (3.24)                               | 1.38 (1.07, 1.78)                              | 0.0144         |
| <b>All</b>            | 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**

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

<sup>†</sup> 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**

|                   | <b>Apixaban<br/>2.5 mg<br/>(N=840)</b> | <b>Apixaban<br/>5.0 mg<br/>(N=811)<br/>n (%)</b> | <b>Placebo<br/>(N=826)</b> | <b>Relative Risk (95% CI)</b>              |  |
|-------------------|--|--|----------------------------|--|--|
|                   |  |  |                            | <b>Apixaban 2.5<br/>mg<br/>vs. Placebo</b> | <b>Apixaban 5.0<br/>mg<br/>vs. Placebo</b> |
| Major             | 2 (0.2)                                | 1 (0.1)  | 4 (0.5)                    | 0.49<br>(0.09, 2.64)                       | 0.25<br>(0.03, 2.24)                       |
| CRNM <sup>†</sup> | 25 (3.0)                               | 34 (4.2)*  | 19 (2.3)                   | 1.29<br>(0.72, 2.33)                       | 1.82<br>(1.05, 3.18)                       |
| Major + CRNM      | 27 (3.2)                               | 35 (4.3)   | 22 (2.7)                   | 1.20                                       | 1.62                                       |

|       | Apixaban<br>2.5 mg<br>(N=840) | Apixaban<br>5.0 mg<br>(N=811)<br>n (%) | Placebo<br>(N=826) | Relative Risk (95% CI)         |                                |
|-------|-------------------------------|--|--------------------|--------------------------------|--------------------------------|
|       |                               |  |                    | Apixaban 2.5 mg<br>vs. Placebo | Apixaban 5.0 mg<br>vs. Placebo |
|       |                               |  |                    | (0.69, 2.10)                   | (0.96, 2.73)                   |
| Minor | 75 (8.9)                      | 98 (12.1)*                             | 58 (7.0)           | 1.26<br>(0.91, 1.75)           | 1.70<br>(1.25, 2.31)           |
| All   | 94 (11.2)                     | 121 (14.9)*                            | 74 (9.0)           | 1.24<br>(0.93, 1.65)           | 1.65<br>(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  $\geq 1\%$  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  $\geq 1\%$  of Patients in Either Group Undergoing Hip or Knee Replacement Surgery**

|  | Apixaban<br>2.5 mg BID PO<br>n= 5924 (%) | Enoxaparin<br>40 mg SC OD or<br>30 mg SC q12h<br>n= 5904 (%) |
|--|--|--|
| <b>GASTROINTESTINAL DISORDERS</b>  |  |  |
| Nausea   | 153 (2.6)                                | 159 (2.7)  |
| <b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>  |  |  |
| Anemia (including post-operative and hemorrhagic anemia, and respective laboratory parameters) | 153 (2.6)                                | 178 (3.0)  |
| <b>VASCULAR DISORDERS</b>  |  |  |

|   | <b>Apixaban<br/>2.5 mg BID PO<br/>n= 5924 (%)</b> | <b>Enoxaparin<br/>40 mg SC OD or<br/>30 mg SC q12h<br/>n= 5904 (%)</b> |
|---|---|--|
| Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)  | 67 (1.1)  | 81 (1.4)   |
| <b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>   |   |  |
| 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)   |
| <b>HEPATOBIILIARY DISORDERS</b>   |   |  |
| 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  $\geq 1\%$  of Patients with Atrial Fibrillation in the ARISTOTLE and AVERROES Studies**

|  | <b>ARISTOTLE</b>                     |                                      | <b>AVERROES</b>                      |                                 |
|--|--------------------------------------|--------------------------------------|--------------------------------------|---------------------------------|
|  | <b>Apixaban<br/>N=9088<br/>n (%)</b> | <b>Warfarin<br/>N=9052<br/>n (%)</b> | <b>Apixaban<br/>N=2798<br/>n (%)</b> | <b>ASA<br/>N=2780<br/>n (%)</b> |
| <b>EYE DISORDERS</b>   |                                      |                                      |                                      |                                 |
| Eye hemorrhage (including conjunctival hemorrhage)             | 211 (2.3)                            | 326 (3.6)                            | 22 (0.8)                             | 11 (0.4)                        |
| <b>GASTROINTESTINAL DISORDERS</b>                              |                                      |                                      |                                      |                                 |
| 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)                         |
| <b>INJURY, POISONING, AND PROCEDURAL COMPLICATIONS</b>         |                                      |                                      |                                      |                                 |

|  | ARISTOTLE                   |                             | AVERROES                    |                        |
|--|-----------------------------|-----------------------------|-----------------------------|------------------------|
|  | Apixaban<br>N=9088<br>n (%) | Warfarin<br>N=9052<br>n (%) | Apixaban<br>N=2798<br>n (%) | ASA<br>N=2780<br>n (%) |
| Contusion  | 456 (5.0)                   | 745 (8.2)                   | 49 (1.8)                    | 61 (2.2)               |
| <b>RENAL AND URINARY DISORDERS</b>                     |                             |                             |                             |                        |
| Hematuria  | 340 (3.7)                   | 409 (4.5)                   | 31 (1.1)                    | 17 (0.6)               |
| <b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b> |                             |                             |                             |                        |
| Epistaxis  | 560 (6.2)                   | 685 (7.6)                   | 54 (1.9)                    | 52 (1.9)               |
| <b>VASCULAR DISORDERS</b>                              |                             |                             |                             |                        |
| 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 ( $\geq 1\%$ ) in VTE treatment patients are shown in Table 9, below

**Table 9 – Adverse Reactions Occurring in  $\geq 1\%$  of Patients in the AMPLIFY and AMPLIFY-EXT Studies**

|  | AMPLIFY                     |  | AMPLIFY-EXT                 |                           |
|--|-----------------------------|--|-----------------------------|---------------------------|
|  | Apixaban<br>N=2676<br>n (%) | Enoxaparin/<br>Warfarin<br>N=2689<br>n (%) | Apixaban<br>N=1651<br>n (%) | Placebo<br>N=826<br>n (%) |
| <b>GASTROINTESTINAL DISORDERS</b>                      |                             |  |                             |                           |
| 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)                   |
| <b>INJURY, POISONING, AND PROCEDURAL COMPLICATIONS</b> |                             |  |                             |                           |
| Contusion  | 49 (1.8)                    | 97 (3.6)                                   | 27 (1.6)                    | 13 (1.6)                  |
| <b>RENAL AND URINARY DISORDERS</b>                     |                             |  |                             |                           |
| Hematuria  | 46 (1.7)                    | 102 (3.8)                                  | 28 (1.7)                    | 9 (1.1)                   |
| <b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b> |                             |  |                             |                           |
| Epistaxis  | 77 (2.9)                    | 146 (5.4)                                  | 42 (2.5)                    | 9 (1.1)                   |
| Haemoptysis  | 32 (1.2)                    | 31 (1.2)                                   | (< 1.0)                     | (< 1.0)                   |
| <b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>        |                             |  |                             |                           |
| Menorrhagia  | 38 (1.4)                    | 30 (1.1)                                   | 16 (1.0)                    | 2 (0.2)                   |
| <b>VASCULAR DISORDERS</b>                              |                             |  |                             |                           |
| 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  $\geq 0.1\%$  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  $\geq 0.1\%$  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  $\geq 0.1\%$  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<sub>50</sub> >45 mM) and weak inhibitory effect on the activity of CYP 2C19 (IC<sub>50</sub> >20 mM) 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 mM.

#### ***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 PRO-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** CYP 3A4 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 PRO-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 <sub>max</sub> .  | The use of PRO-APIXABAN is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of <b>both</b> CYP 3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole and ritonavir (see 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 <sub>max</sub> .<br><br>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 <sub>max</sub> , respectively. A corresponding 63% increase in mean anti-Xa activity at 3 hours post-dose was observed when                                   | No dose adjustment for either agent is required. Use with caution.  |

| Proper Name                | Reference | Effect  | Clinical Comment   |
|----------------------------|-----------|---|--|
|                            |           | <p>apixaban was co-administered with naproxen.</p> <p>Apixaban had no effect on naproxen AUC or C<sub>max</sub>. No changes were observed in the usual effect of naproxen on (arachidonic acid-induced) platelet aggregation.</p> |  |
| 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 <sub>max</sub> 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 <sub>max</sub> , 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 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  | Concomitant use of ASA or dual antiplatelet therapy with either apixaban or warfarin increases the   |

| Proper Name          | Reference | Effect  | Clinical Comment  |
|----------------------|-----------|---|---|
|                      |           | the combination of clopidogrel 75 mg and acetylsalicylic acid 162 mg OD   | risk of major bleeding in patients with atrial fibrillation.<br><br>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 <sub>max</sub> 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 <sub>max</sub> .  | 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 <sub>max</sub> .   | 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 <b>not</b> 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   | May be useful in overdosage or accidental ingestion (see OVERDOSAGE).   |

| Proper Name  | Reference | Effect   | Clinical Comment   |
|--|-----------|--|--|
|  |           | mean 50% and 27% decrease in apixaban AUC, respectively.   |  |
| Selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs) | T, CT     | Serotonin release by platelets plays an important role in 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. | PRO-APIXABAN should be used with caution when co-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**

PRO-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 PRO-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 PRO-APIXABAN (apixaban), ensure that the patient understands and is prepared to accept adherence to NOAC therapy, as directed.*

PRO-APIXABAN (apixaban) can be taken with or without food.

**PRO-APIXABAN 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, PRO-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 PRO-APIXABAN, and monitor renal function during PRO-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 PRO-APIXABAN (see below, Renal Impairment).

Glomerular filtration rate may be estimated by calculating eCrCl, using the Cockcroft-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 PRO-APIXABAN 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 PRO-APIXABAN is 5 mg taken orally twice daily.

In patients fulfilling at least two (2) of the following criteria, a reduced dose of PRO-APIXABAN 2.5 mg twice daily is recommended: age  $\geq$  80 years, body weight  $\leq$  60 kg, or serum creatinine  $\geq$  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 PRO-APIXABAN 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 individualised 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, immobilisation) 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  $\geq$  30 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment).

Limited clinical data in patients with severe renal impairment (eCrCl 15 to 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**

| Indication   | Renal Impairment                       |                  |                  |   |  |
|--|--|------------------|------------------|---|--|
|  | Normal                                 | Mild             | Moderate         | Severe  |  |
| Creatinine Clearance (eCrCl)   | > 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 <sup>†</sup>                             |  |
| 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 <sup>†</sup> |  |
| Continued prevention of recurrent DVT and PE <sup>‡</sup>                          | 2.5 mg bid                             |                  |                  | 2.5 mg bid <sup>†</sup>                             |  |

<sup>†</sup> Must be used with caution due to potentially higher bleeding risks.

<sup>‡</sup> 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 to 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 to 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  |                |                |                |  |  |
|------------|---|---|----------------|----------------|----------------|--|--|
|            |   | Normal  | Mild           | Moderate       | Severe         |  |  |
| Indication | Creatinine Clearance (eCrCl)  | > 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       |                |                | No dosing recommendation due to very limited clinical data |  |
|            |   | Dose adjustment to 2.5 mg bid, if ≥2 of following criteria are met <sup>§</sup> :   |                |                |                |  |  |
|            |   | <ul style="list-style-type: none"> <li>• age ≥ 80 years</li> <li>• body weight ≤60 kg</li> <li>• serum creatinine ≥133 mcmol/L (1.5 mg/dL)</li> </ul> |                |                |                |  |  |

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

**Hepatic Impairment**

PRO-APIXABAN is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see CONTRAINDICATIONS).

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

PRO-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, PRO-APIXABAN should be used with caution in these patients.

**Concomitant Use of Antiplatelet Agents**

The concomitant use of PRO-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 PRO-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 PRO-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  $\geq$  80 years, body weight  $\leq$  60 kg, or serum creatinine  $\geq$  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 PRO-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 PRO-APIXABAN while being cardioverted (see ACTION AND CLINICAL PHARMACOLOGY, Cardioversion).

## **Switching from or to parenteral anticoagulants**

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

## **Switching from vitamin K antagonists (VKA) to PRO-APIXABAN**

When switching patients from a VKA, such as warfarin, to PRO-APIXABAN, discontinue warfarin or other VKA therapy, and start PRO-APIXABAN when the international normalized ration (INR) is below 2.0.

### **Switching from PRO-APIXABAN to VKA**

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

PRO-APIXABAN should be continued concurrently with the VKA until the INR is  $\geq 2.0$ . 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 PRO-APIXABAN Therapy). Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of PRO-APIXABAN, as appropriate. PRO-APIXABAN can be discontinued once the INR is  $> 2.0$ . Once PRO-APIXABAN is discontinued, INR testing may be done at least 12 hours after the last dose of PRO-APIXABAN, and should then reliably reflect the anticoagulant effect of the VKA.

### ***Considerations for INR Monitoring of VKA Activity during Concomitant PRO-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 to 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 PRO-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 PRO-APIXABAN. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including PRO-APIXABAN.

When switching patients from PRO-APIXABAN to a VKA, the INR should only be used to assess the anticoagulant effect of the VKA, and not that of PRO-APIXABAN. Therefore, while patients are concurrently receiving PRO-APIXABAN and VKA therapy, if the INR is to be tested, it should not be before 12 hours after the previous dose of PRO-APIXABAN, and should be just prior to the next dose of PRO-APIXABAN, since at this time the remaining PRO-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 PRO-APIXABAN, the reported INR will not reflect the anticoagulation effect of the VKA only, because PRO-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 PRO-APIXABAN 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 PRO-APIXABAN (apixaban) may lead to hemorrhagic complications, due to its pharmacologic properties.

A specific antidote for PRO-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 PRO-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 PRO-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 PRO-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<sup>®</sup> 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)**

|  | <b>Apixaban<br/>C<sub>max</sub></b> | <b>Apixaban<br/>C<sub>min</sub></b> | <b>Apixaban<br/>Anti-FXa<br/>Activity Max</b> | <b>Apixaban<br/>Anti-FXa<br/>Activity Min</b> |
|--|-------------------------------------|-------------------------------------|---|---|
|  | Median [5th, 95th Percentile]       |                                     |   |   |
| <i>Prevention of VTE: elective hip or knee replacement surgery</i> |                                     |                                     |   |   |
| 2.5 mg BID   | 77 [41, 146]                        | 51 [23, 109]                        | 1.3 [0.67, 2.4]                               | 0.84 [0.37, 1.8]                              |
| <i>Prevention of stroke and systemic embolism: NVAf</i>            |                                     |                                     |   |   |
| 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]                               |
| <i>Treatment of VTE</i>  |                                     |                                     |   |   |
| 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**

|  | <b>Oral Administration</b> | <b>IV Administration</b> |
|--|----------------------------|--------------------------|
|--|----------------------------|--------------------------|

|                           | <b>C<sub>max</sub></b><br><b>(ng/mL)</b> | <b>t<sub>½</sub></b><br><b>(h)</b> | <b>AUC<sub>0-12hrs</sub></b><br><b>(ng·h/mL)</b> | <b>Clearance</b><br><b>(L/h)</b> | <b>Volume of</b><br><b>distribution (L)</b> |
|---------------------------|--|------------------------------------|--|----------------------------------|---|
| <b>Healthy Volunteers</b> | 73                                       | 8.3                                | 530  | CL ~ 3.3<br>CLR ~0.9             | V <sub>ss</sub> ~ 21                        |
| <b>Patients</b>           | 77                                       | N/A                                | ~800   | N/A<br>(no IV data)              | N/A<br>(no IV data)                         |

N/A = Not available; C<sub>max</sub> = maximum plasma concentration; t<sub>½</sub> = terminal elimination half-life; AUC<sub>0-12</sub> = area under the plasma concentration-time curve from time 0 to 12 hours post dose; CL = total systemic clearance; CLR = renal clearance; V<sub>ss</sub> = 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<sub>max</sub>) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C<sub>max</sub> 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<sub>max</sub> 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 (V<sub>ss</sub>) 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, i.e. 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 PRO-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 to 80 mL/min), moderate (eCrCl 30 to 50 mL/min) and severe (eCrCl 15 to 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 to 29 mL/min) indicate that apixaban plasma concentrations are increased. In patients with atrial fibrillation having eCrCl 25 to 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 to 30% lower exposure, and body weight < 50 kg was associated with approximately 20 to 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°C to 30°C).

### ***SPECIAL HANDLING INSTRUCTIONS***

None.

### ***DOSAGE FORMS, COMPOSITION AND PACKAGING***

**Excipients:** Tablet core: Anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

Film coat: Polyethylene glycol 8000, polyvinyl alcohol, talc, titanium dioxide, red ferric oxide (5 mg) and yellow iron oxide (2.5 mg).

2.5mg: Yellow colored, round shaped, biconvex film-coated tablets engraved with “APO” on one side and “AP” over “2.5” on the other side.

5mg: Pink colored, oval shaped, biconvex film-coated tablets engraved with "APO" on one side and "AP5" on the other side.

PRO-APIXABAN (apixaban) 2.5 mg tablets are supplied in carton containing 60 (6 blister strips of 10) tablets and in bottles of 60 and 500 tablets.

PRO-APIXABAN (apixaban) 5 mg tablets are supplied in carton containing 60 (6 blister strips of 10) tablets and in bottles of 60, 180 and 500 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

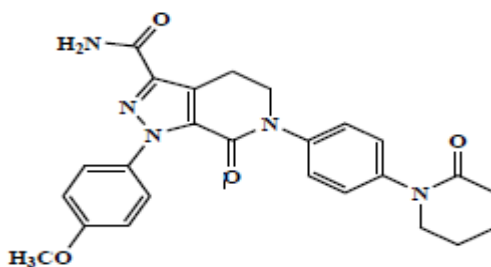
#### Drug Substance

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<sub>25</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>; 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.

PRO-APIXABAN 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: anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The film coating contains polyethylene glycol 8000, polyvinyl alcohol, talc, titanium dioxide, red ferric oxide (5 mg) and yellow iron oxide (2.5 mg).

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, single-dose, blinded, 2-way crossover comparative bioavailability study was conducted under fasting conditions, on healthy Asian male volunteers from 23 to 43 years of age (N=20). The rate and extent of absorption of apixaban was measured and compared following a single oral dose (1 x 5 mg tablet) of PRO-APIXABAN (apixaban) 5 mg (PRO DOC LTEE) and ELIQUIS® (apixaban) 5 mg tablet (Bristol-Myers Squibb Canada). The results from measured data in 19 subjects are summarized in the following table.

#### SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

| Apixaban<br>(1 x 5 mg)<br>From Measured Data  |                           |                           |                                  |                               |
|---|---------------------------|---------------------------|----------------------------------|-------------------------------|
| Geometric Mean<br>Arithmetic Mean (CV %)  |                           |                           |                                  |                               |
| Parameter   | Test*                     | Reference†                | % Ratio of<br>Geometric<br>Means | 90%<br>Confidence<br>Interval |
| AUC <sub>T</sub><br>(ng·h/mL)   | 1566.80<br>1591.00 (18.6) | 1435.96<br>1484.19 (26.1) | 109.1                            | 101.3-117.5                   |
| AUC <sub>I</sub><br>(ng·h/mL)   | 1583.28<br>1607.39 (18.4) | 1452.18<br>1500.24 (25.9) | 109.0                            | 101.4-117.2                   |
| C <sub>max</sub><br>(ng/mL)   | 174.30<br>178.47 (22.9)   | 161.30<br>166.58 (24.5)   | 108.1                            | 98.1-119.0                    |
| T <sub>max</sub> § (h)  | 3.16 (39.2)               | 3.16 (39.5)               |                                  |                               |
| T <sub>1/2</sub> § (h)  | 7.69 (26.9)               | 6.44 (18.6)               |                                  |                               |
| * PRO-APIXABAN (apixaban) 5 mg tablets (PRO DOC LTEE)                                     |                           |                           |                                  |                               |
| † ELIQUIS® (apixaban) 5 mg tablets (Bristol-Myers Squibb Canada) was purchased in Canada. |                           |                           |                                  |                               |
| § Expressed as the 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 Apixaban Dosed orally Versus ANtiCoagulation with injectable Enoxaparin) 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  $\geq 33$  kg/m<sup>2</sup>, 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  $\geq 1.5$ xULN); clinically significant renal impairment (Cr CL < 30 mL/min); thrombocytopenia; anemia (Hb < 10g/dl); platelet < 100,000/mm<sup>3</sup>; 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 to 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 to 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**

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

**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 (%) |
|-----------------------|---|--|-------------------------|------------------|------------------|
| CV185034<br>ADVANCE 1 | Randomized, double-blind, parallel group total knee replacement | Apixaban 2.5 mg BID PO                       | N=1599                  | 65.9 (26, 93)    | 38 / 62          |
|                       |   | Enoxaparin 30 mg q12h SC                     | N=1596                  | 65.7 (33, 89)    | 38 / 62          |

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<sup>a</sup>**

|  | ADVANCE-3 (hip)                          |   | ADVANCE-2 (knee)                         |   | ADVANCE-1 (knee)                            |   |
|--|--|---|--|---|---|---|
|  | Apixaban<br>2.5 mg po bid<br>35 ± 3 days | Enoxaparin<br>40 mg sc qd<br>35 ± 3<br>days | Apixaban<br>2.5 mg po bid<br>12 ± 2 days | Enoxaparin<br>40 mg sc<br>qd<br>12 ± 2 days | Apixaban<br>2.5 mg po<br>bid<br>12 ± 2 days | Enoxaparin<br>30 mg sc<br>q12h<br>12 ± 2 days |
| Events / N (Event Rate)  |  |   |  |   |   |   |
| <b>Total VTE/all-cause death (asymptomatic and symptomatic DVT, PE, and all-cause death)</b> |  |   |  |   |   |   |
|  | 27 / 1949<br>(1.39%)                     | 74 / 1917<br>(3.86%)                        | 147 / 976<br>(15.06%)                    | 243 / 997<br>(24.37%)                       | 104 / 1157<br>(8.99%)                       | 100 / 1130<br>(8.85%)                         |
| Relative Risk  | 0.36<br>0.22, 0.54                       |   | 0.62<br>0.51, 0.74                       |   | 1.02<br>0.78, 1.32                          |   |
| 95% CI   |  |   |  |   |   |   |
| P value  | < 0.0001                                 |   | < 0.0001                                 |   | NS  |   |
| <b>All cause death</b>   | 3 / 2708<br>(0.11 %)                     | 1 / 2699<br>(0.04 %)                        | 2 / 1528<br>(0.13 %)                     | 0 / 1529<br>(0.00%)                         | 3 / 1599<br>(0.19%)                         | 3 / 1596<br>(0.19%)                           |

|                                 | ADVANCE-3 (hip)                          |   | ADVANCE-2 (knee)                         |   | ADVANCE-1 (knee)                            |   |
|---------------------------------|--|---|--|---|---|---|
|                                 | Apixaban<br>2.5 mg po bid<br>35 ± 3 days | Enoxaparin<br>40 mg sc qd<br>35 ± 3<br>days | Apixaban<br>2.5 mg po bid<br>12 ± 2 days | Enoxaparin<br>40 mg sc<br>qd<br>12 ± 2 days | Apixaban<br>2.5 mg po<br>bid<br>12 ± 2 days | Enoxaparin<br>30 mg sc<br>q12h<br>12 ± 2 days |
| Events / N (Event Rate)         |  |   |  |   |   |   |
| <b>PE (Fatal or Non-Fatal)</b>  | 3 / 2708<br>(0.11 %)                     | 5 / 2699<br>(0.19 %)                        | 4 / 1528<br>(0.26%)                      | 0 / 1529<br>(0.00%)                         | 16 / 1599<br>(1.00 %)                       | 7 / 1596<br>(0.44 %)                          |
| <b>Symptomatic DVT</b>          | 1 / 2708<br>(0.04%)                      | 5 / 2699<br>(0.19%)                         | 3 / 1528<br>(0.20%)                      | 7 / 1529<br>(0.46%)                         | 3 / 1599<br>(0.19%)                         | 7 / 1596<br>(0.44%)                           |
| <b>Proximal DVT<sup>b</sup></b> | 7 / 2196<br>(0.32 %)                     | 20 / 2190<br>(0.91 %)                       | 9 / 1192<br>(0.76%)                      | 26 / 1199<br>(2.17%)                        | 9 / 1254<br>(0.72 %)                        | 11 / 1207<br>(0.91 %)                         |
| <b>Distal DVT<sup>b</sup></b>   | 20 / 1951<br>(1.03 %)                    | 57 / 1908<br>(2.99 %)                       | 142 / 978<br>(14.52%)                    | 239 / 1000<br>(23.90%)                      | 83 / 1146<br>(7.24 %)                       | 91 / 1133<br>(8.03 %)                         |

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

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

<sup>b</sup> 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**

| <b>Study</b>  | <b>ARISTOTLE</b>   | <b>AVERROES</b>  |
|---|--|--|
| <b>Trial design</b>                                       | Warfarin-controlled, randomized, double-blind, parallel arm, multi-national                  | Aspirin-controlled, randomized, double-blind, parallel arm, multi-national   |
| <b>Dosage, route of administration and duration</b>       | Apixaban 5 mg BID PO (2.5 mg BID in selected patients: 4.7%)<br>Warfarin: Target INR 2.0-3.0 | Apixaban 5 mg BID PO (2.5 mg BID in selected patients: 6.4%)<br>ASA 81 to 324 mg QD PO 81mg (64.3%)<br>162mg (26.2%) |
| <b>Randomized Subjects</b>                                | 18,201   | 5,598  |
| <b>Mean Age</b>   | 69.1   | 69.9   |
| <b>≥ 65 years</b>   | 69.9%  | 69.3%  |
| <b>≥ 75 years</b>   | 31.2%  | 33.8%  |
| <b>Gender</b>   |  |  |
| <b>Male</b>   | 64.7%  | 58.5%  |
| <b>Female</b>   | 35.3%  | 41.5%  |
| <b>Race</b>   |  |  |
| White/Caucasian   | 82.6%  | 78.6%  |
| Asian   | 14.5%  | 19.4%  |
| Black/African American                                    | 1.2%   | 0.6%   |
| <b>Prior stroke or TIA</b>                                | 18.6%  | 13.6%  |
| <b>Hypertension</b>                                       | 87.4%  | 86.4%  |
| <b>Diabetes</b>   | 25.0%  | 19.6%  |
| <b>Heart failure</b>                                      | 35.4% (LVEF ≤40%)  | 33.7% (LVEF ≤35%)  |
| <b>Valvular Disease (not meeting exclusion criteria)*</b> | 17.8%  | 22.7%  |
| <b>Mean CHADS<sub>2</sub> Score</b>                       | 2.1  | 2.0  |
| CHADS <sub>2</sub> ≤1                                     | 34.0%  | 38.3%  |
| CHADS <sub>2</sub> =2                                     | 35.8%  | 35.2%  |
| CHADS <sub>2</sub> ≥ 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 to 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  $\leq 30$  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  $\leq 5\%$ . 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**

|                                     | <b>Apixaban<br/>N=9120<br/>n (%/yr)</b> | <b>Warfarin<br/>N=9081<br/>n (%/yr)</b> | <b>Hazard Ratio<br/>(Apixaban vs.<br/>Warfarin)<br/>(95% CI)</b> | <b>P-Value,<br/>(superiority)</b> |
|-------------------------------------|---|---|--|-----------------------------------|
| <b>Stroke or systemic embolism*</b> | 212 (1.27)                              | 265 (1.60)                              | 0.79<br>(0.66, 0.95)   | 0.0114                            |
| <b>Stroke</b>                       |   |   |  |                                   |
| <b>Ischemic or unspecified</b>      | 162 (0.97)                              | 175 (1.05)                              | 0.92<br>(0.74, 1.13)   |                                   |
| <b>Hemorrhagic</b>                  | 40 (0.24)                               | 78 (0.47)                               | 0.51<br>(0.35, 0.75)   |                                   |
| <b>Systemic embolism</b>            | 15 (0.09)                               | 17 (0.10)                               | 0.87   |                                   |

|                           | <b>Apixaban<br/>N=9120<br/>n (%/yr)</b> | <b>Warfarin<br/>N=9081<br/>n (%/yr)</b> | <b>Hazard Ratio<br/>(Apixaban vs.<br/>Warfarin)<br/>(95% CI)</b> | <b>P-Value,<br/>(superiority)</b> |
|---------------------------|---|---|--|-----------------------------------|
|                           |   |   | (0.44, 1.75)   |                                   |
| <b>All-cause death**†</b> | 603 (3.52)                              | 669 (3.94)                              | 0.89<br>(0.80, 1.00)   | 0.047                             |

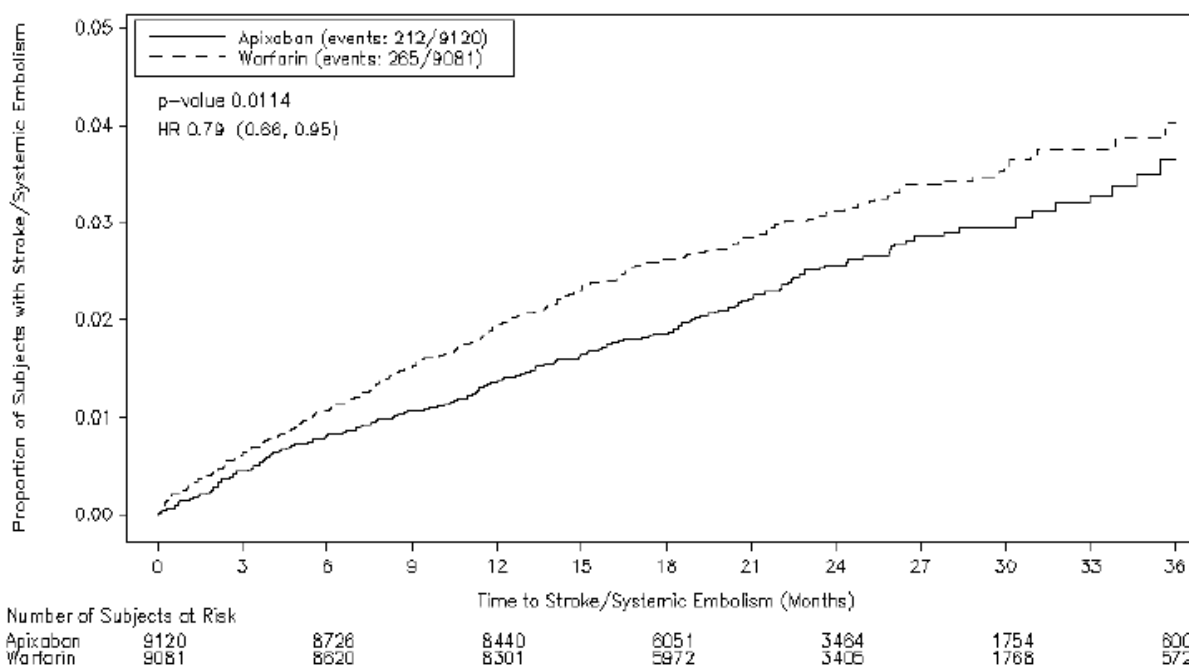
\* Assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

\*\* 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 |
| <b>Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 212 / 9120 | 1.27              | 265 / 9081 | 1.60              | 0.79<br>(0.66, 0.95)  | 0.0114  |
| < 65 years  | 51 / 2731  | 1.00              | 44 / 2740  | 0.86              | 1.16<br>(0.77, 1.73)  | -       |
| ≥ 65 to <75 years   | 82 / 3539  | 1.25              | 112 / 3513 | 1.73              | 0.72<br>(0.54, 0.96)  | -       |
| ≥ 75 years  | 79 / 2850  | 1.56              | 109 / 2828 | 2.19              | 0.71<br>(0.53, 0.95)  | -       |
| ≥ 80 years  | 33 / 1225  | 1.53              | 40 / 1211  | 1.90              | 0.81<br>(0.51, 1.29)  | -       |
| ≥ 85 years  | 6 / 322    | 1.14              | 18 / 345   | 3.25              | 0.35<br>(0.14, 0.89)  | -       |
| <b>Any Stroke</b>   |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 199 / 9120 | 1.19              | 250 / 9081 | 1.51              | 0.79<br>(0.65, 0.95)  | 0.0122  |
| < 65 years  | 49 / 2731  | 0.96              | 40 / 2740  | 0.78              | 1.22<br>(0.80, 1.85)  | -       |
| ≥ 65 to <75 years   | 74 / 3539  | 1.13              | 109 / 3513 | 1.69              | 0.67<br>(0.50, 0.90)  | -       |
| ≥ 75 years  | 76 / 2850  | 1.50              | 101 / 2828 | 2.03              | 0.74<br>(0.55, 1.00)  | -       |
| ≥ 80 years  | 33 / 1225  | 1.53              | 37 / 1211  | 1.76              | 0.88<br>(0.55, 1.40)  | -       |
| <b>Ischemic or Unspecified Stroke</b>                                     |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 162 / 9120 | 0.97              | 175 / 9081 | 1.05              | 0.92<br>(0.74, 1.13)  | 0.4220  |
| < 65 years  | 38 / 2731  | 0.74              | 27 / 2740  | 0.52              | 1.40<br>(0.86, 2.30)  | -       |
| ≥ 65 to <75 years   | 64 / 3539  | 0.97              | 79 / 3513  | 1.22              | 0.80<br>(0.58, 1.12)  | -       |
| ≥ 75 years  | 60 / 2850  | 1.18              | 69 / 2828  | 1.38              | 0.86<br>(0.61, 1.21)  | -       |
| ≥ 80 years  | 26 / 1225  | 1.21              | 27 / 1211  | 1.28              | 0.94<br>(0.55, 1.61)  | -       |
| <b>Hemorrhagic Stroke</b>   |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 40 / 9120  | 0.24              | 78 / 9081  | 0.47              | 0.51<br>(0.35, 0.75)  | 0.0006  |
| < 65 years  | 13 / 2731  | 0.25              | 13 / 2740  | 0.25              | 0.99<br>(0.46, 2.15)  | -       |
| ≥ 65 to <75 years   | 10 / 3539  | 0.15              | 33 / 3513  | 0.51              | 0.30<br>(0.15, 0.61)  | -       |
| ≥ 75 years  | 17 / 2850  | 0.33              | 32 / 2828  | 0.64              | 0.53<br>(0.29, 0.95)  | -       |
| ≥ 80 years  | 7 / 1225   | 0.32              | 10 / 1211  | 0.47              | 0.71<br>(0.27, 1.86)  | -       |

|                             | Apixaban   |                   | Warfarin   |                   | Apixaban vs Warfarin  |         |
|-----------------------------|------------|-------------------|------------|-------------------|-----------------------|---------|
|                             | n / N      | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
| <b>Cardiovascular Death</b> |            |                   |            |                   |                       |         |
| All Patients                | 308 / 9120 | 1.80              | 344 / 9081 | 2.02              | 0.89<br>(0.76, 1.04)  | 0.1384  |
| < 65 years                  | 87 / 2731  | 1.67              | 83 / 2740  | 1.58              | 1.04<br>(0.77, 1.41)  | -       |
| ≥ 65 to <75 years           | 86 / 3539  | 1.28              | 112 / 3513 | 1.69              | 0.76<br>(0.57, 1.01)  | -       |
| ≥ 75 years                  | 135 / 2850 | 2.60              | 149 / 2828 | 2.91              | 0.90<br>(0.71, 1.13)  | -       |
| ≥ 80 years                  | 64 / 1225  | 2.91              | 84 / 1211  | 3.86              | 0.76<br>(0.55, 1.05)  | -       |
| ≥ 85 years                  | 23 / 322   | 4.23              | 43 / 345   | 7.59              | 0.55<br>(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 |
| <b>ISTH Major Bleeding (Primary Outcome)</b>                  |            |                   |            |                   |                       |         |
| All Patients  | 327 / 9088 | 2.13              | 462 / 9052 | 3.09              | 0.69<br>(0.60, 0.80)  | <0.0001 |
| < 65 years  | 56 / 2723  | 1.17              | 72 / 2732  | 1.51              | 0.78<br>(0.55, 1.11)  | -       |
| ≥ 65 to <75 years   | 120 / 3529 | 1.99              | 166 / 3501 | 2.82              | 0.71<br>(0.56, 0.89)  | -       |
| ≥ 75 years  | 151 / 2836 | 3.33              | 224 / 2819 | 5.19              | 0.64<br>(0.52, 0.79)  | -       |
| ≥ 80 years  | 67 / 1217  | 3.55              | 96 / 1209  | 5.41              | 0.66<br>(0.48, 0.90)  | -       |
| ≥ 85 years  | 19 / 322   | 4.20              | 30 / 345   | 6.47              | 0.65<br>(0.36, 1.15)  | -       |
| <b>Major and Non-major Clinically Relevant Bleeding Event</b> |            |                   |            |                   |                       |         |
| All Patients  | 613 / 9088 | 4.07              | 877 / 9052 | 6.01              | 0.68<br>(0.61, 0.75)  | <0.0001 |
| < 65 years  | 122 / 2723 | 2.59              | 178 / 2732 | 3.82              | 0.68<br>(0.54, 0.86)  | -       |
| ≥ 65 to <75 years   | 234 / 3529 | 3.94              | 320 / 3501 | 5.57              | 0.71<br>(0.60, 0.84)  | -       |

|                                | Apixaban   |                   | Warfarin   |                   | Apixaban vs. Warfarin  |         |
|--------------------------------|------------|-------------------|------------|-------------------|------------------------|---------|
|                                | n / N      | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI)  | P-value |
| ≥ 75 years                     | 257 / 2836 | 5.81              | 379 / 2819 | 9.04              | 0.65<br>(0.55, 0.76)   | -       |
| ≥ 80 years                     | 110 / 1217 | 5.98              | 171 / 1209 | 9.93              | 0.61<br>(0.48, 0.77)   | -       |
| <b>Intracranial Hemorrhage</b> |            |                   |            |                   |                        |         |
| <b>All Patients</b>            | 52 / 9088  | 0.33              | 122 / 9052 | 0.80              | 0.42<br>(0.30, 0.58)   | <0.0001 |
| < 65 years                     | 15 / 2723  | 0.31              | 17 / 2732  | 0.35              | 0.87<br>(0.43, 1.74)   | -       |
| ≥ 65 to <75 years              | 17 / 3529  | 0.28              | 48 / 3501  | 0.81              | 0.35<br>(0.20, 0.60)   | -       |
| ≥ 75 years                     | 20 / 2836  | 0.43              | 57 / 2819  | 1.29              | 0.34<br>(0.20, 0.57)   | -       |
| ≥ 80 years                     | 9 / 1217   | 0.47              | 24 / 1209  | 1.32              | 0.36<br>(0.17, 0.77)   | -       |
| <b>Fatal Bleeding **</b>       |            |                   |            |                   |                        |         |
| <b>All Patients</b>            | 8 / 9088   | 0.05              | 11 / 9052  | 0.07              | 0.71<br>(0.25, 1.95)   | 0.6183  |
| < 65 years                     | 1 / 2723   | 0.02              | 2 / 2732   | 0.04              | 0.48<br>(0.04, 5.30)   | -       |
| ≥ 65 to <75 years              | 3 / 3529   | 0.05              | 4 / 3501   | 0.07              | 0.76<br>(0.17, 3.40)   | -       |
| ≥ 75 years                     | 4 / 2836   | 0.09              | 5 / 2819   | 0.11              | 0.79<br>(0.21, 2.93)   | -       |
| ≥ 80 years                     | 3 / 1217   | 0.16              | 1 / 1209   | 0.05              | 2.86<br>(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 |
| <b>Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 212 / 9120 | 1.27              | 265 / 9081 | 1.60              | 0.79                  | 0.0114  |

|                                       | Apixaban   |                   | Warfarin   |                   | Apixaban vs Warfarin  |         |
|---------------------------------------|------------|-------------------|------------|-------------------|-----------------------|---------|
|                                       | n / N      | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
|                                       |            |                   |            |                   | (0.66, 0.95)          |         |
| ≤ 30 mL/min                           | 6 / 137    | 2.79              | 10 / 133   | 5.06              | 0.55<br>(0.20, 1.53)  | -       |
| > 30 – ≤ 50 mL/min                    | 48 / 1365  | 2.05              | 59 / 1382  | 2.47              | 0.83<br>(0.57, 1.21)  | -       |
| > 50 – ≤ 80 mL/min                    | 87 / 3817  | 1.24              | 116 / 3770 | 1.69              | 0.74<br>(0.56, 0.97)  | -       |
| > 80 mL/min                           | 70 / 3761  | 0.99              | 79 / 3757  | 1.12              | 0.88<br>(0.64, 1.21)  | -       |
| <b>Any Stroke</b>                     |            |                   |            |                   |                       |         |
| <b>All Patients</b>                   | 199 / 9120 | 1.19              | 250 / 9081 | 1.51              | 0.79<br>(0.65, 0.95)  | 0.0122  |
| ≤ 30 mL/min                           | 6 / 137    | 2.79              | 10 / 133   | 5.06              | 0.55<br>(0.20, 1.53)  | -       |
| >30 – ≤ 50 mL/min                     | 45 / 1365  | 1.92              | 56 / 1382  | 2.34              | 0.82<br>(0.55, 1.21)  | -       |
| > 50 – ≤ 80 mL/min                    | 81 / 3817  | 1.16              | 108 / 3770 | 1.57              | 0.74<br>(0.55, 0.98)  | -       |
| > 80 mL/min                           | 66 / 3761  | 0.93              | 75 / 3757  | 1.06              | 0.87<br>(0.63, 1.21)  | -       |
| <b>Ischemic or Unspecified Stroke</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>                   | 162 / 9120 | 0.97              | 175 / 9081 | 1.05              | 0.92<br>(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<br>(0.70, 1.74)  | -       |
| > 50 – ≤ 80 mL/min                    | 65 / 3817  | 0.93              | 75 / 3770  | 1.09              | 0.85<br>(0.61, 1.19)  | -       |
| > 80 mL/min                           | 52 / 3761  | 0.73              | 56 / 3757  | 0.79              | 0.92<br>(0.63, 1.34)  | -       |
| <b>Hemorrhagic Stroke</b>             |            |                   |            |                   |                       |         |
| <b>All Patients</b>                   | 40 / 9120  | 0.24              | 78 / 9081  | 0.47              | 0.51<br>(0.35, 0.75)  | 0.0006  |
| ≤ 30 mL/min                           | 0 / 137    | 0                 | 3 / 133    | 1.48              | 0<br>§                | -       |
| >30 – ≤ 50 mL/min                     | 7 / 1365   | 0.29              | 20 / 1382  | 0.83              | 0.35<br>(0.15, 0.83)  | -       |
| > 50 – ≤ 80 mL/min                    | 16 / 3817  | 0.23              | 36 / 3770  | 0.52              | 0.44<br>(0.24, 0.79)  | -       |
| > 80 mL/min                           | 16 / 3761  | 0.22              | 19/3757    | 0.27              | 0.84<br>(0.43, 1.63)  | -       |
| <b>Cardiovascular Death</b>           |            |                   |            |                   |                       |         |
| <b>All Patients</b>                   | 308 / 9120 | 1.80              | 344 / 9081 | 2.02              | 0.89                  | 0.1384  |

|                    | Apixaban   |                   | Warfarin   |                   | Apixaban vs Warfarin  |         |
|--------------------|------------|-------------------|------------|-------------------|-----------------------|---------|
|                    | n / N      | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
|                    |            |                   |            |                   | (0.76, 1.04)          |         |
| ≤ 30 mL/min        | 15 / 137   | 6.85              | 14 / 133   | 6.68              | 1.03<br>(0.50, 2.15)  | -       |
| >30 – ≤ 50 mL/min  | 77 / 1365  | 3.18              | 97 / 1382  | 3.96              | 0.80<br>(0.60, 1.08)  | -       |
| > 50 – ≤ 80 mL/min | 126 / 3817 | 1.76              | 128 / 3770 | 1.81              | 0.97<br>(0.76, 1.25)  | -       |
| > 80 mL/min        | 88 / 3761  | 1.21              | 104 / 3757 | 1.44              | 0.84<br>(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 |
| <b>ISTH Major Bleeding (Principal Safety Endpoint)</b>        |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 327 / 9088 | 2.13              | 462 / 9052 | 3.09              | 0.69<br>(0.60, 0.80)  | <0.0001 |
| ≤ 30 mL/min   | 7 / 136    | 3.75              | 19 / 132   | 11.94             | 0.32<br>(0.13, 0.78)  | -       |
| >30 – ≤ 50 mL/min   | 66 / 1357  | 3.16              | 123 / 1380 | 6.01              | 0.53<br>(0.39, 0.71)  | -       |
| > 50 – ≤ 80 mL/min  | 157 / 3807 | 2.45              | 199 / 3758 | 3.21              | 0.76<br>(0.62, 0.94)  | -       |
| > 80 mL/min   | 96 / 3750  | 1.46              | 119 / 3746 | 1.84              | 0.79<br>(0.61, 1.04)  | -       |
| <b>Major and Non-Major Clinically Relevant Bleeding Event</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 613 / 9088 | 4.07              | 877 / 9052 | 6.01              | 0.68<br>(0.61, 0.75)  | <0.0001 |
| ≤ 30 mL/min   | 10 / 136   | 5.39              | 26 / 132   | 16.75             | 0.34<br>(0.16, 0.70)  | -       |
| >30 – ≤ 50 mL/min   | 113 / 1357 | 5.52              | 185 / 1380 | 9.17              | 0.60<br>(0.48, 0.76)  | -       |
| > 50 – ≤ 80 mL/min  | 281 / 3807 | 4.47              | 381 / 3758 | 6.31              | 0.71<br>(0.61, 0.83)  | -       |
| > 80 mL/min   | 206 / 3750 | 3.18              | 282 / 3746 | 4.46              | 0.71                  | -       |

|                                | Apixaban  |                   | Warfarin   |                   | Apixaban vs. Warfarin |         |
|--------------------------------|-----------|-------------------|------------|-------------------|-----------------------|---------|
|                                | n / N     | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
|                                |           |                   |            |                   | (0.60, 0.86)          |         |
| <b>Intracranial Hemorrhage</b> |           |                   |            |                   |                       |         |
| <b>All Patients</b>            | 52 / 9088 | 0.33              | 122 / 9052 | 0.80              | 0.42<br>(0.30, 0.58)  | <0.0001 |
| ≤ 30 mL/min                    | 0 / 136   | 0                 | 4 / 132    | 2.40              | 0<br>§                | -       |
| >30 – ≤ 50 mL/min              | 8 / 1357  | 0.38              | 36 / 1380  | 1.71              | 0.22<br>(0.10, 0.47)  | -       |
| > 50 – ≤ 80 mL/min             | 25 / 3807 | 0.38              | 52 / 3758  | 0.83              | 0.47<br>(0.29, 0.75)  | -       |
| > 80 mL/min                    | 18 / 3750 | 0.27              | 30 / 3746  | 0.46              | 0.59<br>(0.33, 1.05)  | -       |
| <b>Fatal Bleeding**</b>        |           |                   |            |                   |                       |         |
| <b>All Patients</b>            | 8 / 9088  | 0.05              | 11 / 9052  | 0.07              | 0.71<br>(0.25, 1.95)  | 0.6183  |
| ≤ 30 mL/min                    | 0 / 136   | 0                 | 1 / 132    | 0.60              | 0<br>(0.00, 32.57)    | -       |
| >30 – ≤ 50 mL/min              | 0 / 1357  | 0                 | 3 / 1380   | 0.14              | 0<br>(0.00, 2.38)     | -       |
| > 50 – ≤ 80 mL/min             | 7 / 3807  | 0.11              | 4 / 3758   | 0.06              | 1.70<br>(0.43, 7.94)  | -       |
| > 80 mL/min                    | 1 / 3750  | 0.01              | 3 / 3746   | 0.05              | 0.32<br>(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 (1.5 mg/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 |
| <b>Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)</b> |            |                   |            |                    |                       |         |
| <b>All Patients</b>   | 212 / 9120 | 1.27              | 265 / 9081 | 1.60               | 0.79<br>(0.66, 0.95)  | 0.0114  |

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

|   | Apixaban   |                   | Warfarin   |                   | Apixaban vs. Warfarin |         |
|---|------------|-------------------|------------|-------------------|-----------------------|---------|
|   | n / N      | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
| <b>All Patients</b>   | 327 / 9088 | 2.13              | 462 / 9052 | 3.09              | 0.69<br>(0.60, 0.80)  | <0.0001 |
| Apixaban 2.5 mg BID   | 20 / 424   | 3.29              | 37 / 402   | 6.71              | 0.50<br>(0.29, 0.86)  | -       |
| Apixaban 5 mg BID   | 307 / 8664 | 2.09              | 425 / 8650 | 2.95              | 0.71<br>(0.61, 0.82)  | -       |
| <b>Major and Non-Major Clinically Relevant Bleeding Event</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 613 / 9088 | 4.07              | 877 / 9052 | 6.01              | 0.68<br>(0.61, 0.75)  | <0.0001 |
| Apixaban 2.5 mg BID   | 30 / 424   | 4.97              | 53 / 402   | 9.80              | 0.52<br>(0.33, 0.81)  | -       |
| Apixaban 5 mg BID   | 583 / 8664 | 4.03              | 824 / 8650 | 5.86              | 0.69<br>(0.62, 0.77)  | -       |
| <b>Intracranial Hemorrhage</b>                                |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 52 / 9088  | 0.33              | 122 / 9052 | 0.80              | 0.42<br>(0.30, 0.58)  | <0.0001 |
| Apixaban 2.5 mg BID   | 2 / 424    | 0.32              | 9 / 402    | 1.59              | 0.21<br>(0.04, 0.96)  | -       |
| Apixaban 5 mg BID   | 50 / 8664  | 0.34              | 113 / 8650 | 0.77              | 0.43<br>(0.31, 0.61)  | -       |
| <b>Fatal Bleeding**</b>                                       |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 8 / 9088   | 0.05              | 11 / 9052  | 0.07              | 0.71<br>(0.25, 1.95)  | 0.6183  |
| Apixaban 2.5 mg BID   | 0 / 424    | 0                 | 1 / 402    | 0.18              | 0<br>§                | -       |
| Apixaban 5 mg BID   | 8 / 8664   | 0.05              | 10 / 8650  | 0.07              | 0.79<br>(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   |
|--|------------|------------|
| <b>Apixaban/Placebo 2.5 mg BID, N</b>      | 424        | 402        |
| Severe ( $\leq 30$ mL/min), n (%)          | 88 (20.8)  | 85 (21.1)  |
| Moderate ( $> 30 - \leq 50$ mL/min), n (%) | 294 (69.3) | 262 (65.2) |
| Mild ( $> 50 - \leq 80$ mL/min), n (%)     | 42 (9.9)   | 54 (13.4)  |

|   | <b>Apixaban</b> | <b>Warfarin</b> |
|---|-----------------|-----------------|
| Normal (> 80 mL/min), n (%)               | 0               | 1 (0.3)         |
| Not Reported, n (%)                       | 0               | 0               |
| <b>Apixaban/Placebo 5 mg BID, N</b>       | 8664            | 8650            |
| Severe ( $\leq 30$ mL/min), n (%)         | 48 (0.6)        | 47 (0.5)        |
| Moderate (> 30 - $\leq 50$ mL/min), n (%) | 1063 (12.3)     | 1118 (12.9)     |
| Mild (> 50 - $\leq 80$ 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  $\geq 80$  years, body weight  $\leq 60$  kg, or serum creatinine  $\geq 133$  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%), CHADS<sub>2</sub> 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  $\leq 5\%$ . 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**

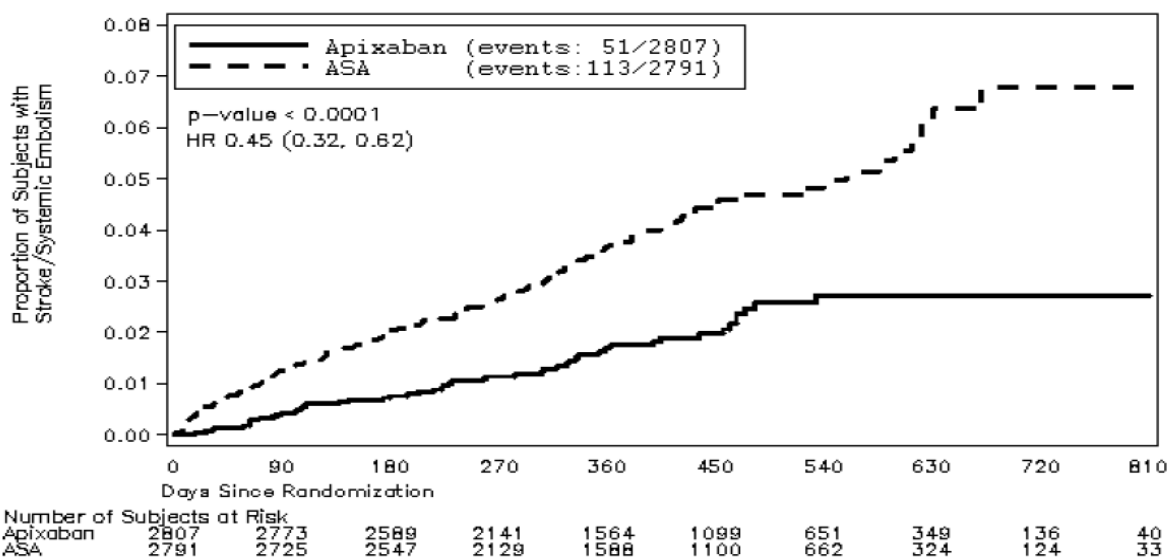
|  | <b>Apixaban<br/>N=2807<br/>n (% / year)</b> | <b>Aspirin<br/>N=2791<br/>n (% / year)</b> | <b>Hazard Ratio<br/>Apixaban vs.<br/>aspirin<br/>(95% CI)</b> | <b>P-Value<br/>(superiority)</b> |
|--|---|--|---|----------------------------------|
| <b>Stroke or systemic embolism*</b>                            | 51 (1.62)                                   | 113 (3.63)                                 | 0.45 (0.32, 0.62)   | < 0.0001                         |
| <b>Stroke</b>  |   |  |   |                                  |
| <b>Ischemic or undetermined</b>                                | 43 (1.37)                                   | 97 (3.11)                                  | 0.44 (0.31, 0.63)   |                                  |
| <b>Hemorrhagic</b>   | 6 (0.19)                                    | 9 (0.28)                                   | 0.67 (0.24, 1.88)   |                                  |
| <b>Systemic embolism</b>                                       | 2 (0.06)                                    | 13 (0.41)                                  | 0.15 (0.03, 0.68)   |                                  |
| <b>Stroke, systemic embolism,<br/>MI, or vascular death**†</b> | 132 (4.21)                                  | 197 (6.35)                                 | 0.66 (0.53, 0.83)   | 0.003                            |
| <b>Myocardial infarction</b>                                   | 24 (0.76)                                   | 28 (0.89)                                  | 0.86 (0.50, 1.48)   |                                  |
| <b>Vascular Death</b>  | 84 (2.65)                                   | 96 (3.03)                                  | 0.87 (0.65, 1.17)   |                                  |
| <b>All-cause death</b>   | 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 |
| <b>Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)</b> |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 51 / 2807 | 1.62              | 113 / 2791 | 3.63              | 0.45<br>(0.32, 0.62)  | <0.0001 |
| < 65 years  | 7 / 855   | 0.73              | 19 / 865   | 1.93              | 0.38<br>(0.16, 0.89)  | -       |
| ≥ 65 to <75 years   | 24 / 1049 | 2.02              | 29 / 938   | 2.78              | 0.73<br>(0.43, 1.25)  | -       |
| ≥ 75 years  | 20 / 903  | 2.00              | 65 / 988   | 6.00              | 0.34<br>(0.20, 0.56)  | -       |
| ≥ 80 years  | 8 / 455   | 1.60              | 38 / 499   | 7.06              | 0.23<br>(0.11, 0.49)  | -       |
| ≥ 85 years  | 2 / 180   | 1.02              | 15 / 186   | 7.53              | 0.14<br>(0.03, 0.60)  | -       |
| <b>Any Stroke</b>   |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 49 / 2807 | 1.56              | 105 / 2791 | 3.37              | 0.46<br>(0.33, 0.65)  | <0.0001 |
| < 65 years  | 7 / 855   | 0.73              | 17 / 865   | 1.72              | 0.42<br>(0.17, 1.01)  | -       |
| ≥ 65 to <75 years   | 23 / 1049 | 1.93              | 26 / 938   | 2.49              | 0.78<br>(0.45, 1.37)  | -       |
| ≥ 75 years  | 19 / 903  | 1.90              | 62 / 988   | 5.70              | 0.34<br>(0.20, 0.56)  | -       |
| ≥ 80 years  | 7 / 455   | 1.40              | 37 / 499   | 6.85              | 0.21<br>(0.09, 0.46)  | -       |
| <b>Ischemic or Unspecified Stroke</b>                                     |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 43 / 2807 | 1.37              | 97 / 2791  | 3.11              | 0.44<br>(0.31, 0.63)  | <0.0001 |
| < 65 years  | 7 / 855   | 0.73              | 15 / 865   | 1.52              | 0.48<br>(0.19, 1.17)  | -       |
| ≥ 65 to <75 years   | 18 / 1049 | 1.51              | 25 / 938   | 2.40              | 0.64<br>(0.35, 1.16)  | -       |
| ≥ 75 years  | 18 / 903  | 1.80              | 57 / 988   | 5.23              | 0.35<br>(0.20, 0.59)  | -       |
| ≥ 80 years  | 6 / 455   | 1.20              | 32 / 499   | 5.91              | 0.20<br>(0.09, 0.49)  | -       |
| <b>Hemorrhagic Stroke</b>   |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 6 / 2807  | 0.19              | 9 / 2791   | 0.28              | 0.67<br>(0.24, 1.88)  | 0.4471  |
| < 65 years  | 0 / 855   | 0.00              | 2 / 865    | 0.20              | 0                     | -       |

|                       | Apixaban  |                   | ASA       |                   | Apixaban vs ASA       |         |
|-----------------------|-----------|-------------------|-----------|-------------------|-----------------------|---------|
|                       | n / N     | Event rate (%/yr) | n / N     | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
|                       |           |                   |           |                   | §                     |         |
| ≥ 65 to <75 years     | 5 / 1049  | 0.42              | 1 / 938   | 0.09              | 4.44<br>(0.52, 38.01) | -       |
| ≥ 75 years            | 1 / 903   | 0.10              | 6 / 988   | 0.54              | 0.19<br>(0.02, 1.56)  | -       |
| ≥ 80 years            | 1 / 455   | 0.20              | 6 / 499   | 1.08              | 0.19<br>(0.02, 1.56)  | -       |
| <b>Vascular Death</b> |           |                   |           |                   |                       |         |
| <b>All Patients</b>   | 84 / 2807 | 2.65              | 96 / 2791 | 3.03              | 0.87<br>(0.65, 1.17)  | 0.3659  |
| < 65 years            | 21 / 855  | 2.18              | 10 / 865  | 1.00              | 2.17<br>(1.02, 4.60)  | -       |
| ≥ 65 to <75 years     | 24 / 1049 | 2.00              | 28 / 938  | 2.66              | 0.76<br>(0.44, 1.31)  | -       |
| ≥ 75 years            | 39 / 903  | 3.89              | 58 / 988  | 5.19              | 0.74<br>(0.49, 1.11)  | -       |
| ≥ 80 years            | 29 / 455  | 5.80              | 40 / 499  | 7.18              | 0.78<br>(0.48, 1.27)  | -       |
| ≥ 85 years            | 14 / 180  | 7.14              | 16 / 186  | 7.74              | 0.86<br>(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 |
| <b>ISTH Major Bleeding (Primary Safety Outcome)</b>           |           |                   |           |                   |                       |         |
| <b>All Patients</b>   | 45 / 2798 | 1.41              | 29 / 2780 | 0.92              | 1.54<br>(0.96, 2.45)  | 0.0716  |
| < 65 years  | 8 / 855   | 0.81              | 5 / 862   | 0.49              | 1.67<br>(0.55, 5.11)  | -       |
| ≥ 65 to <75 years   | 11 / 1044 | 0.90              | 6 / 935   | 0.56              | 1.61<br>(0.60, 4.36)  | -       |
| ≥ 75 years  | 26 / 899  | 2.65              | 18 / 983  | 1.70              | 1.57<br>(0.86, 2.86)  | -       |
| ≥ 80 years  | 19 / 454  | 3.94              | 13 / 498  | 2.53              | 1.57<br>(0.77, 3.17)  | -       |
| ≥ 85 years  | 9 / 179   | 4.77              | 6 / 185   | 3.31              | 1.44<br>(0.51, 4.06)  | -       |
| <b>Major and Non-major Clinically Relevant Bleeding Event</b> |           |                   |           |                   |                       |         |

|                                  | Apixaban   |                   | ASA        |                   | Apixaban vs ASA       |         |
|----------------------------------|------------|-------------------|------------|-------------------|-----------------------|---------|
|                                  | n / N      | Event rate (%/yr) | n / N      | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
| <b>All Patients</b>              | 140 / 2798 | 4.46              | 101 / 2780 | 3.24              | 1.38<br>(1.07, 1.78)  | 0.0144  |
| < 65 years                       | 32 / 855   | 3.26              | 26 / 862   | 2.58              | 1.26<br>(0.75, 2.12)  | -       |
| ≥ 65 to <75 years                | 45 / 1044  | 3.75              | 31 / 935   | 2.92              | 1.29<br>(0.82, 2.04)  | -       |
| ≥ 75 years                       | 63 / 899   | 6.59              | 44 / 983   | 4.20              | 1.56<br>(1.06, 2.30)  | -       |
| ≥ 80 years                       | 38 / 454   | 8.05              | 33 / 498   | 6.55              | 1.24<br>(0.78, 1.97)  | -       |
| <b>Intracranial Hemorrhage**</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>              | 11 / 2798  | 0.34              | 11 / 2780  | 0.35              | 0.99<br>(0.39, 2.51)  | 1.000   |
| < 65 years                       | 0 / 855    | 0                 | 2 / 862    | 0.20              | 0<br>§                | -       |
| ≥ 65 to <75 years                | 5 / 1044   | 0.41              | 1 / 935    | 0.09              | 4.42<br>(0.52, 37.86) | -       |
| ≥ 75 years                       | 6 / 899    | 0.61              | 8 / 983    | 0.75              | 0.81<br>(0.28, 2.35)  | -       |
| ≥ 80 years                       | 4 / 454    | 0.82              | 7 / 498    | 1.36              | 0.61<br>(0.18, 2.07)  | -       |
| <b>Fatal Bleeding**</b>          |            |                   |            |                   |                       |         |
| <b>All Patients</b>              | 5 / 2798   | 0.16              | 5 / 2780   | 0.16              | 0.99<br>(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<br>(0.38, 30.84) | -       |
| ≥ 75 years                       | 1 / 899    | 0.10              | 4 / 983    | 0.38              | 0.27<br>(0.03, 2.45)  | -       |
| ≥ 80 years                       | 1 / 454    | 0.21              | 2 / 498    | 0.39              | 0.54<br>(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 |
| <b>Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)</b> |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 51 / 2807 | 1.62              | 113 / 2791 | 3.63              | 0.45<br>(0.32, 0.62)  | <0.0001 |
| ≤ 30 mL/min   | 1 / 55    | 1.72              | 4 / 61     | 7.07              | 0.26<br>(0.03, 2.30)  | -       |
| >30 – ≤ 50 mL/min   | 12 / 490  | 2.31              | 28 / 478   | 5.45              | 0.42<br>(0.21, 0.83)  | -       |
| > 50 – ≤ 80 mL/min  | 22 / 1074 | 1.83              | 58 / 1075  | 4.95              | 0.37<br>(0.23, 0.61)  | -       |
| > 80 mL/min   | 12 / 955  | 1.09              | 16 / 923   | 1.48              | 0.74<br>(0.35, 1.57)  | -       |
| <b>Any Stroke</b>   |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 49 / 2807 | 1.56              | 105 / 2791 | 3.37              | 0.46<br>(0.33, 0.65)  | <0.0001 |
| ≤ 30 mL/min   | 1 / 55    | 1.72              | 4 / 61     | 7.07              | 0.26<br>(0.03, 2.30)  | -       |
| >30 – ≤ 50 mL/min   | 11 / 490  | 2.12              | 26 / 478   | 5.05              | 0.42<br>(0.21, 0.85)  | -       |
| > 50 – ≤ 80 mL/min  | 22 / 1074 | 1.83              | 54 / 1075  | 4.60              | 0.40<br>(0.24, 0.66)  | -       |
| > 80 mL/min   | 11 / 955  | 1.00              | 14 / 923   | 1.30              | 0.77<br>(0.35, 1.70)  | -       |
| <b>Ischemic or Unspecified Stroke</b>                                     |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 43 / 2807 | 1.37              | 97 / 2791  | 3.11              | 0.44<br>(0.31, 0.63)  | <0.0001 |
| ≤ 30 mL/min   | 1 / 55    | 1.72              | 4 / 61     | 7.07              | 0.26<br>(0.03, 2.30)  | -       |
| >30 – ≤ 50 mL/min   | 11 / 490  | 2.12              | 26 / 478   | 5.05              | 0.42<br>(0.21, 0.85)  | -       |
| > 50 – ≤ 80 mL/min  | 18 / 1074 | 1.50              | 48 / 1075  | 4.08              | 0.37<br>(0.21, 0.63)  | -       |
| > 80 mL/min   | 10 / 955  | 0.91              | 13 / 923   | 1.20              | 0.76<br>(0.33, 1.73)  | -       |
| <b>Hemorrhagic Stroke</b>   |           |                   |            |                   |                       |         |
| <b>All Patients</b>   | 6 / 2807  | 0.19              | 9 / 2791   | 0.28              | 0.67<br>(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<br>§                | -       |
| > 50 – ≤ 80 mL/min  | 4 / 1074  | 0.33              | 6 / 1075   | 0.50              | 0.66<br>(0.19, 2.35)  | -       |
| > 80 mL/min   | 1 / 955   | 0.09              | 1 / 923    | 0.09              | 0.97                  | -       |

|                       | Apixaban  |                   | ASA       |                   | Apixaban vs ASA       |         |
|-----------------------|-----------|-------------------|-----------|-------------------|-----------------------|---------|
|                       | n / N     | Event rate (%/yr) | n / N     | Event rate (%/yr) | Hazard Ratio (95% CI) | P-value |
|                       |           |                   |           |                   | (0.06, 15.53)         |         |
| <b>Vascular Death</b> |           |                   |           |                   |                       |         |
| <b>All Patients</b>   | 84 / 2807 | 2.65              | 96 / 2791 | 3.03              | 0.87<br>(0.65, 1.17)  | 0.3659  |
| ≤ 30 mL/min           | 8 / 55    | 13.74             | 8 / 61    | 14.02             | 0.99<br>(0.37, 2.63)  | -       |
| >30 – ≤ 50 mL/min     | 28 / 490  | 5.38              | 26 / 478  | 4.91              | 1.08<br>(0.63, 1.84)  | -       |
| > 50 – ≤ 80 mL/min    | 31 / 1074 | 2.56              | 42 / 1075 | 3.51              | 0.73<br>(0.46, 1.17)  | -       |
| > 80 mL/min           | 11 / 955  | 1.00              | 11 / 923  | 1.01              | 0.98<br>(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 |
| <b>ISTH Major Bleeding (Principal Safety Endpoint)</b>        |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 45 / 2798  | 1.41              | 29 / 2780  | 0.92              | 1.54<br>(0.96, 2.45)  | 0.0716  |
| ≤ 30 mL/min   | 3 / 55     | 5.26              | 2 / 61     | 3.40              | 1.71<br>(0.29, 10.22) | -       |
| >30 – ≤ 50 mL/min   | 17 / 489   | 3.35              | 7 / 475    | 1.39              | 2.43<br>(1.01, 5.85)  | -       |
| > 50 – ≤ 80 mL/min  | 12 / 1068  | 0.98              | 13 / 1072  | 1.09              | 0.90<br>(0.41, 1.98)  | -       |
| > 80 mL/min   | 8 / 953    | 0.71              | 4 / 919    | 0.36              | 2.01<br>(0.60, 6.67)  | -       |
| <b>Major and Non-Major Clinically Relevant Bleeding Event</b> |            |                   |            |                   |                       |         |
| <b>All Patients</b>   | 140 / 2798 | 4.46              | 101 / 2780 | 3.24              | 1.38<br>(1.07, 1.78)  | 0.0144  |
| ≤ 30 mL/min   | 4 / 55     | 7.16              | 6 / 61     | 10.47             | 0.73<br>(0.21, 2.59)  | -       |
| >30 – ≤ 50 mL/min   | 35 / 489   | 7.02              | 17 / 475   | 3.41              | 2.05<br>(1.15, 3.65)  | -       |
| > 50 – ≤ 80 mL/min  | 52 / 1068  | 4.34              | 40 / 1072  | 3.40              | 1.28<br>(0.85, 1.94)  | -       |
| > 80 mL/min   | 39 / 953   | 3.49              | 30 / 919   | 2.74              | 1.28<br>(0.79, 2.06)  | -       |

|                                  | Apixaban  |                   | ASA       |                   | Apixaban vs ASA       |         |
|----------------------------------|-----------|-------------------|-----------|-------------------|-----------------------|---------|
|                                  | n / N     | Event rate (%/yr) | n / N     | Event rate (%/yr) | Hazard Ratio (95% CI) | p-value |
| <b>Intracranial Hemorrhage**</b> |           |                   |           |                   |                       |         |
| All Patients                     | 11 / 2798 | 0.34              | 11 / 2780 | 0.35              | 0.99<br>(0.39, 2.51)  | 1.000   |
| ≤ 30 mL/min                      | 1 / 55    | 1.75              | 1 / 61    | 1.70              | 1.16<br>(0.07, 18.63) | -       |
| >30 – ≤ 50 mL/min                | 3 / 489   | 0.59              | 1 / 475   | 0.20              | 3.07<br>(0.32, 29.61) | -       |
| > 50 – ≤ 80 mL/min               | 4 / 1068  | 0.33              | 7 / 1072  | 0.59              | 0.56<br>(0.16, 1.90)  | -       |
| > 80 mL/min                      | 1 / 953   | 0.09              | 0 / 919   | 0.00              | §                     | -       |
| <b>Fatal Bleeding**</b>          |           |                   |           |                   |                       |         |
| All Patients                     | 5 / 2798  | 0.16              | 5 / 2780  | 0.16              | 0.99<br>(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<br>(0.15,7.46)   | -       |
| > 50 – ≤ 80 mL/min               | 1 / 1068  | 0.08              | 3 / 1072  | 0.25              | 0.33<br>(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 (1.5 mg/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 |
| <b>Adjudicated Stroke or Systemic Embolism (Primary Efficacy Outcome)</b> |           |                   |            |                     |                       |         |
| All Patients  | 51 / 2807 | 1.62              | 113 / 2791 | 3.63                | 0.45<br>(0.32, 0.62)  | <0.0001 |
| Apixaban 2.5 mg BID   | 3 / 179   | 1.63              | 12 / 182   | 6.24                | 0.26<br>(0.07, 0.93)  | -       |
| Apixaban 5 mg BID   | 48 / 2628 | 1.62              | 101 / 2609 | 3.46                | 0.47<br>(0.33, 0.66)  | -       |

|                                       | Apixaban  |                   | ASA        |                     | Apixaban vs ASA       |         |
|---------------------------------------|-----------|-------------------|------------|---------------------|-----------------------|---------|
|                                       | n / N     | Event rate (%/yr) | n / N      | Event rate (% / yr) | Hazard Ratio (95% CI) | P-value |
| <b>Any Stroke</b>                     |           |                   |            |                     |                       |         |
| All Patients                          | 49 / 2807 | 1.56              | 105 / 2791 | 3.37                | 0.46<br>(0.33, 0.65)  | <0.0001 |
| Apixaban 2.5 mg BID                   | 3 / 179   | 1.63              | 11 / 182   | 5.66                | 0.29<br>(0.08, 1.04)  | -       |
| Apixaban 5 mg BID                     | 46 / 2628 | 1.55              | 94 / 2609  | 3.21                | 0.48<br>(0.34, 0.69)  | -       |
| <b>Ischemic or Unspecified Stroke</b> |           |                   |            |                     |                       |         |
| All Patients                          | 43 / 2807 | 1.37              | 97 / 2791  | 3.11                | 0.44<br>(0.31, 0.63)  | <0.0001 |
| Apixaban 2.5 mg BID                   | 3 / 179   | 1.63              | 11 / 182   | 5.66                | 0.29<br>(0.08, 1.04)  | -       |
| Apixaban 5 mg BID                     | 40 / 2628 | 1.35              | 86 / 2609  | 2.94                | 0.46<br>(0.32, 0.67)  | -       |
| <b>Hemorrhagic Stroke</b>             |           |                   |            |                     |                       |         |
| All Patients                          | 6 / 2807  | 0.19              | 9 / 2791   | 0.28                | 0.67<br>(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<br>(0.24, 1.88)  | -       |
| <b>Vascular Death</b>                 |           |                   |            |                     |                       |         |
| All Patients                          | 84 / 2807 | 2.65              | 96 / 2791  | 3.03                | 0.87<br>(0.65, 1.17)  | 0.3659  |
| Apixaban 2.5 mg BID                   | 17 / 179  | 9.21              | 21 / 182   | 10.57               | 0.83<br>(0.43, 1.59)  | -       |
| Apixaban 5 mg BID                     | 67 / 2628 | 2.25              | 75 / 2609  | 2.52                | 0.89<br>(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 |
| <b>ISTH Major Bleeding (Principal Safety Endpoint)</b> |           |                     |           |                     |                       |         |
| All Patients   | 45 / 2798 | 1.41                | 29 / 2780 | 0.92                | 1.54<br>(0.96, 2.45)  | 0.0716  |
| Apixaban 2.5 mg BID                                    | 8 / 178   | 4.48                | 3 / 182   | 1.59                | 2.82<br>(0.75, 10.62) | -       |
| Apixaban 5 mg BID                                      | 37 / 2620 | 1.23                | 26 / 2598 | 0.88                | 1.40                  | -       |

|   | Apixaban   |                     | ASA        |                     | Apixaban vs ASA       |         |
|---|------------|---------------------|------------|---------------------|-----------------------|---------|
|   | n / N      | Event rate (% / yr) | n / N      | Event rate (% / yr) | Hazard Ratio (95% CI) | p-value |
|   |            |                     |            |                     | (0.85, 2.32)          |         |
| <b>Major and Non-Major Clinically Relevant Bleeding Event</b> |            |                     |            |                     |                       |         |
| <b>All Patients</b>   | 140 / 2798 | 4.46                | 101 / 2780 | 3.24                | 1.38<br>(1.07, 1.78)  | 0.0144  |
| Apixaban 2.5 mg BID   | 13 / 178   | 7.38                | 7 / 182    | 3.73                | 1.95<br>(0.78, 4.89)  | -       |
| Apixaban 5 mg BID   | 127 / 2620 | 4.29                | 94 / 2598  | 3.21                | 1.34<br>(1.02, 1.75)  | -       |
| <b>Intracranial Hemorrhage**</b>                              |            |                     |            |                     |                       |         |
| <b>All Patients</b>   | 11 / 2798  | 0.34                | 11 / 2780  | 0.35                | 0.99<br>(0.39, 2.51)  | 1.000   |
| Apixaban 2.5 mg BID   | 1 / 178    | 0.56                | 1 / 182    | 0.53                | 1.05<br>(0.07, 16.83) | -       |
| Apixaban 5 mg BID   | 10 / 2620  | 0.33                | 10 / 2598  | 0.34                | 0.98<br>(0.41, 2.36)  | -       |
| <b>Fatal Bleeding**</b>                                       |            |                     |            |                     |                       |         |
| <b>All Patients</b>   | 5 / 2798   | 0.16                | 5 / 2780   | 0.16                | 0.99<br>(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<br>(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         |
|--|-------------|-------------|
| <b>Apixaban/Placebo 2.5 mg BID, N</b>      | 178         | 182         |
| Severe ( $\leq 30$ mL/min), n (%)          | 39 (21.9)   | 41 (22.5)   |
| Moderate ( $> 30 - \leq 50$ mL/min), n (%) | 105 (59.0)  | 112 (61.5)  |
| Mild ( $> 50 - \leq 80$ 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)     |
| <b>Apixaban/Placebo 5 mg BID, N</b>        | 2620        | 2598        |
| Severe ( $\leq 30$ mL/min), n (%)          | 16 (0.6)    | 20 (0.8)    |
| Moderate ( $> 30 - \leq 50$ mL/min), n (%) | 384 (14.7)  | 363 (14.0)  |
| Mild ( $> 50 - \leq 80$ 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**

|  | <b>AMPLIFY</b> | <b>AMPLIFY-EXT</b> |
|--|----------------|--------------------|
| 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 to 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 to 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  $\leq 5\%$ . 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).

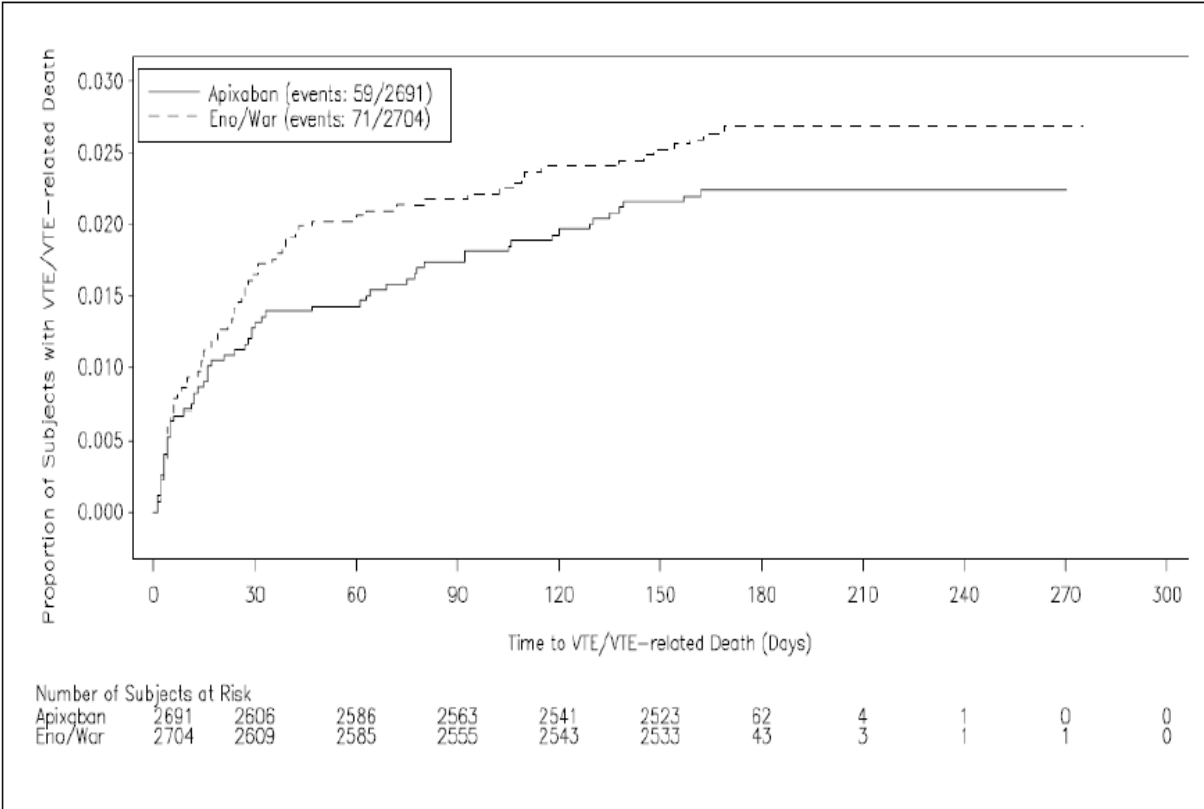
**Table 35 - Efficacy Results in the AMPLIFY Study**

|   | <b>Apixaban<br/>N=2609<br/>n(%)</b> | <b>Enoxaparin/Warfarin<br/>N=2635<br/>n(%)</b> | <b>Relative Risk<br/>(95% CI)</b> |
|---|-------------------------------------|--|-----------------------------------|
| VTE or VTE-related death*                 | 59 (2.3)                            | 71 (2.7)                                       | 0.84 (0.60,1.18)                  |
| Non-fatal DVT <sup>§</sup>                | 20 (0.7)                            | 33 (1.2)                                       |                                   |
| Non-fatal PE <sup>§</sup>                 | 27 (1.0)                            | 23 (0.9)                                       |                                   |
| VTE-related death <sup>§</sup>            | 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)

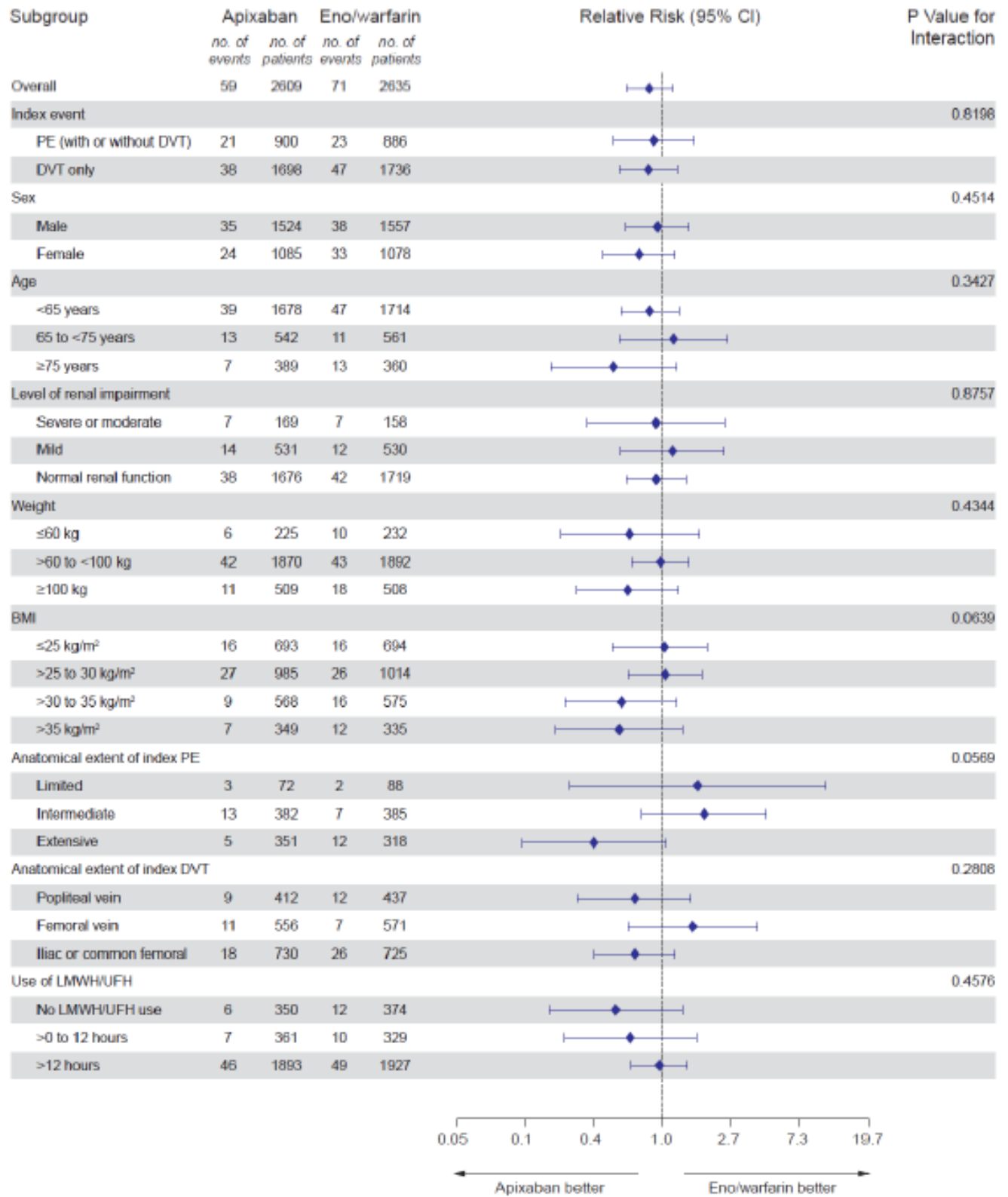
§ First event is the first primary event for each subject. Each subject is counted only once.

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 to 0.40) and 0.19 (95% CI: 0.11 to 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**

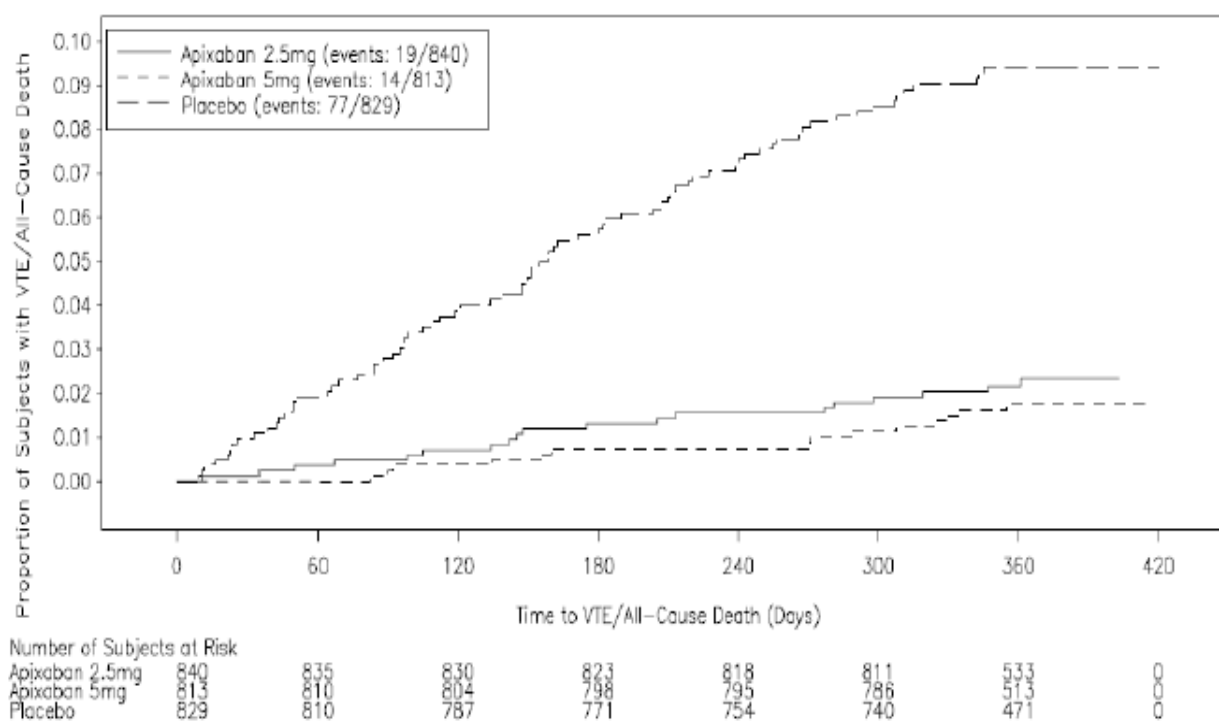
|  | Apixaban          | Apixaban          | Placebo  | Relative Risk (95% CI)     |                            | P-value |
|--|-------------------|-------------------|----------|----------------------------|----------------------------|---------|
|  | 2.5 mg<br>(N=840) | 5.0 mg<br>(N=813) | (N=829)  | Apix 2.5 mg<br>vs. Placebo | Apix 5.0 mg<br>vs. Placebo |         |
|  | n (%)             |                   |          |                            |                            |         |
| Recurrent VTE<br>or all-cause death      | 19 (2.3)          | 14 (1.7)          | 77 (9.3) | 0.24<br>(0.15, 0.40)       | 0.19<br>(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<br>or VTE-related<br>death | 14 (1.7)          | 14 (1.7)          | 73 (8.8) | 0.19<br>(0.11, 0.33)       | 0.20<br>(0.11, 0.34)       | <0.0001 |
| Recurrent<br>VTE or CV-<br>related death | 14 (1.7)          | 14 (1.7)          | 76 (9.2) | 0.18<br>(0.10, 0.32)       | 0.19<br>(0.11, 0.33)       | <0.0001 |
| Non-fatal DVT <sup>†</sup>               | 6 (0.7)           | 8 (1.0)           | 53 (6.4) | 0.11<br>(0.05, 0.26)       | 0.15<br>(0.07, 0.32)       | <0.0001 |
| Non-fatal PE <sup>†</sup>                | 8 (1.0)           | 4 (0.5)           | 15 (1.8) | 0.51                       | 0.27                       |         |

|                   | Apixaban          | Apixaban          | Placebo<br>(N=829) | Relative Risk (95% CI)                     |  | P-value |
|-------------------|-------------------|-------------------|--------------------|--|--|---------|
|                   | 2.5 mg<br>(N=840) | 5.0 mg<br>(N=813) |                    | Apix 2.5 mg<br>vs. Placebo<br>(0.22, 1.21) | Apix 5.0 mg<br>vs. Placebo<br>(0.09, 0.80) |         |
| VTE-related death | 2 (0.2)           | 3 (0.4)           | 7 (0.8)            | 0.28<br>(0.06, 1.37)                       | 0.45<br>(0.12, 1.71)                       |         |
| CV-related death  | 2 (0.2)           | 3 (0.4)           | 10 (1.2)           | 0.20<br>(0.04, 0.90)                       | 0.31<br>(0.09, 1.11)                       |         |
| All-cause death   | 7 (0.8)           | 4 (0.5)           | 14 (1.7)           | 0.49<br>(0.20, 1.21)                       | 0.29<br>(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.



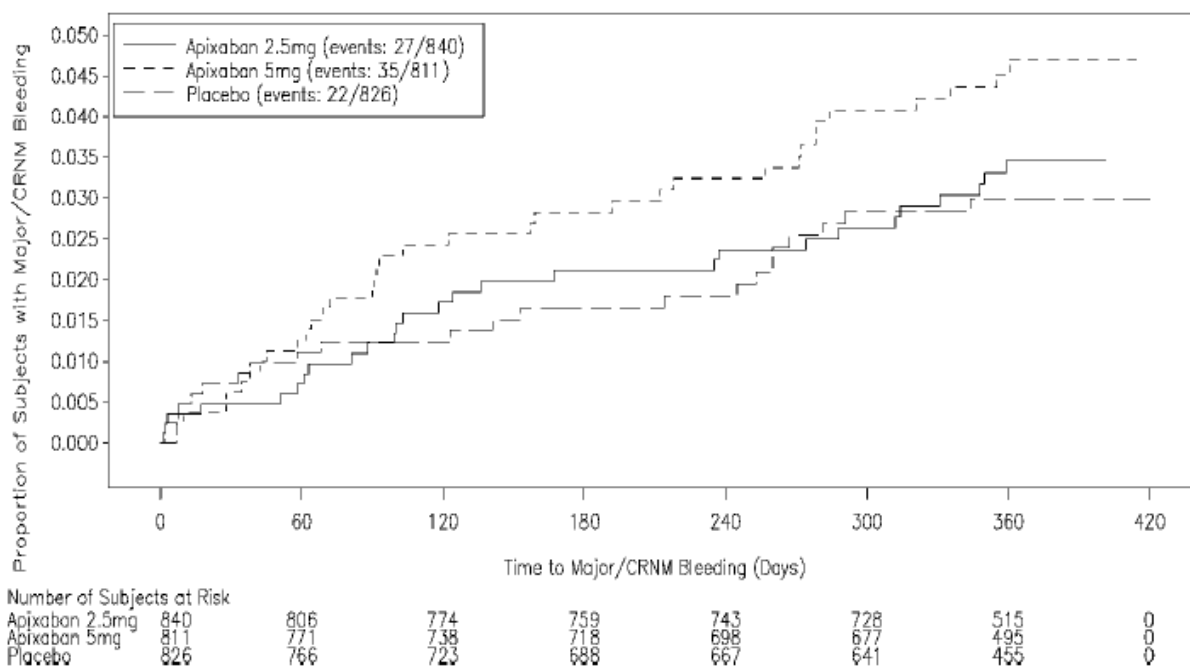
**Figure 5 – Kaplan-Meier Estimate of Time to First DVT or PE, or All-cause Death in the AMPLIFY-EXT Study (Intent-to-Treat Population)**

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 ( $K_i$ ) 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  $K_i$  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<sub>50</sub> 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 ( $\leq 1$  year) and rat ( $\leq 6$  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 $\times$  and 114 $\times$ , 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  $\leq 3000$  mg/kg/day or rats given  $\leq 600$  mg/kg/day for 2 years. Apixaban AUC multiples were  $\leq 30\times$  the RHD AUC value.

### **Reproductive Toxicology**

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

Apixaban administered to female rats at  $\leq 1000$  mg/kg/day during early gestation and throughout the lactation period, produced no findings in offspring (F<sub>1</sub> generation) at 25 mg/kg/day representing an AUC value 9.8 $\times$  the AUC at the RHD. Effects in the F<sub>1</sub>-generation females were limited to decreased mating and fertility indices at  $\geq 200$  mg/kg/day at AUC values  $\geq 36\times$  the AUC at the RHD. The lower F<sub>1</sub> 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.

## REFERENCES

1. Pinto DJP, Orwat MJ, Koch S, Rossi KA, Alexander RS, Smallwood A, et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation Factor-Xa. *J Med Chem* 2007; 50:5339–56.
2. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct Factor-Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost*. 2007; 5:2368–75.
3. Wong PC, Crain EJ, Xin B, Wexler RR, Lam PY, Pinto DJ, et al. Apixaban, an oral, direct and highly selective Factor-Xa inhibitor: *in vitro*, antithrombotic and antihemostatic studies. *J Thromb Haemost* 2008; 6(5):820-9.
4. Wong PC, Watson CA, Crain EJ. Arterial antithrombotic and bleeding time effects of apixaban, a direct Factor-Xa inhibitor, in combination with antiplatelet therapy in rabbits. *J Thromb Haemost* 2008; 6:1736-41.
5. Wong P, Crain EJ, Watson CA, Xin B. Favorable therapeutic index of the direct Factor-Xa inhibitors, apixaban and rivaroxaban, compared to the thrombin inhibitor dabigatran in rabbits. *J Thromb Haemost* 2009; 7:1313-20. Epub 2009 Jun 3.
6. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, et al. Apixaban metabolism and pharmacokinetics following oral administration to humans. *Drug Metab Dispos* 2009; 37(1):74-81.
7. Jiang X, Crain EJ, Luetzgen JM, Schumacher WA, Wong PC. Apixaban, an oral direct Factor-Xa inhibitor, inhibits human clot-bound Factor-Xa activity *in vitro*. *Thromb Haemost* 2009; 101(4):780-2.
8. Zhang D, He K, Raghavan N, Wang L, Mitroka J, Maxwell BD, et al. Comparative metabolism of C-14 Labeled apixaban in mice, rats, rabbits, dogs, and humans. *Drug Metab Dispos* 2009; 37(8):1738-48. Epub 2009 May 6.
9. Lassen MR, Raskob GE, Gallus A, Pineo G, Ansell JE, Chen D, et al. Randomized double-blind comparison of apixaban and enoxaparin for thromboprophylaxis after knee replacement: The ADVANCE-1 Trial. *N Engl J Med* 2009; 361:594-604.
10. Zhang D, He K, Raghavan N, Wang L, Crain EJ, He B, et al. Metabolism, pharmacokinetics and pharmacodynamics of the Factor-Xa inhibitor apixaban in rabbits. *J Thromb Thrombolysis* 2010; 29(1):70-80. Epub 2009 Oct 23.
11. Wang L, Zhang D, Raghavan N, Yao M, Ma L, Frost CA, et al. *In vitro* assessment of metabolic drug-drug interaction potential of apixaban through cytochrome P450

phenotyping, inhibition, and induction studies. *Drug Metab Dispos* 2010; 38(3):448-58. Epub 2009 Nov 25.

12. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, and the ADVANCE-2 Investigators. Randomised double-blind comparison of apixaban and once-daily enoxaparin for thromboprophylaxis after knee replacement: the ADVANCE-2 trial. *Lancet* 2010; 375:807-15.
13. Schumacher WA, Bostwick JS, Stewart AB, Steinbacher TE, Xin B, Wong PC. Effect of the direct Factor-Xa inhibitor apixaban in rat models of thrombosis and hemostasis. *J Cardiovasc Pharmacol*. Epub 2010 Mar 6.
14. Lassen MR, et al, for the ADVANCE-3 investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *New Engl J Med* 2010; 363:2487-2498.
15. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011 Sep 15;365(11):981-92.
16. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011 Mar 3;364(9):806-17.
17. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; 369:799-808.
18. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013, 368: 699-708.
19. Product Monograph - <sup>Pr</sup>ELIQUIS<sup>®</sup> (apixaban tablets) 2.5 mg and 5 mg. Pfizer Canada Inc. Control No.: 288960. Date of Revision: January 10, 2025.

**PART III: CONSUMER INFORMATION**

**PrPRO-APIXABAN  
Apixaban Tablets**

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

**ABOUT THIS MEDICATION**

**What the medication is used for:**

PRO-APIXABAN 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:**

PRO-APIXABAN 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 PRO-APIXABAN

- you are also taking prasugrel (EFFIENT®) or ticagrelor (BRILINTA®)
- PRO-APIXABAN 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. PRO-APIXABAN 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 PRO-APIXABAN) or any of the other ingredients of PRO-APIXABAN. 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:**

Anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

Coating ingredients: Polyethylene glycol 8000, polyvinyl alcohol, talc, titanium dioxide, red ferric oxide (5 mg) and yellow iron oxide (2.5 mg).

**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 PRO-APIXABAN without first talking with your doctor. If you stop taking PRO-APIXABAN, blood clots may cause a stroke or other complications. This can be fatal or lead to severe disability.**

BEFORE you use PRO-APIXABAN 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.

PRO-APIXABAN 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 apixaban on pregnancy and the unborn child are not known. You should not take PRO-APIXABAN if you are pregnant. **Contact your doctor immediately** if you become pregnant while taking PRO-APIXABAN.

It is not known if apixaban passes into human breast milk. Ask your doctor or pharmacist for advice before taking PRO-APIXABAN while breast-feeding.

#### **Anticoagulant-Related Nephropathy (ARN)**

Some cases were reported in patients taking PRO-APIXABAN. 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 PRO-APIXABAN. 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 PRO-APIXABAN and some may decrease its effects. Your

doctor will decide, if you should be treated with PRO-APIXABAN when taking these medicines and how closely you should be monitored.

#### **Drugs that may interact with PRO-APIXABAN include:**

##### Medicines that may increase the effects of PRO-APIXABAN:

You are at an increased risk for bleeding if you take PRO-APIXABAN 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 PRO-APIXABAN:

- **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**

#### **PRO-APIXABAN can be taken with or without food.**

PRO-APIXABAN 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 PRO-APIXABAN 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 PRO-APIXABAN 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 PRO-APIXABAN 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 PRO-APIXABAN 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 PRO-APIXABAN is appropriate for you, make sure you ask your doctor when and how best to switch and start taking PRO-APIXABAN.

If you have atrial fibrillation and stop taking PRO-APIXABAN 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 PRO-APIXABAN 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 PRO-APIXABAN until your doctor says otherwise.

**Overdose:**

**Tell your doctor immediately** if you have taken more than the prescribed dose of PRO-APIXABAN.

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

If you think you, or a person you are caring for, have taken too much PRO-APIXABAN, 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 PRO-APIXABAN; 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 PRO-APIXABAN.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, PRO-APIXABAN 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), PRO-APIXABAN 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.

| <b>SERIOUS SIDE EFFECTS,<br/>HOW OFTEN THEY HAPPEN<br/>AND WHAT TO DO ABOUT THEM</b> |   |                                     |              |  |
|--|---|-------------------------------------|--------------|--|
| Symptom / effect   |   | Talk with your doctor or pharmacist |              | Stop taking drug and seek immediate medical help |
|  |   | Only if severe                      | In all cases |  |
| <b>Common</b>  | <b>Anemia:</b><br>fatigue, loss of energy, weakness, shortness of breath  |                                     | ✓            |  |
|  | Blood in the urine (that stains the urine pink or red)  |                                     | ✓            |  |
|  | Bruising and swelling   |                                     | ✓            |  |
|  | Bleeding:<br>– in your eyes<br>– from your gums and blood in your spit when coughing<br>– from your rectum<br>– abnormally heavy or long menstrual bleeding |                                     | ✓            |  |

| <b>SERIOUS SIDE EFFECTS,<br/>HOW OFTEN THEY HAPPEN<br/>AND WHAT TO DO ABOUT THEM</b> |  |                                     |              |  |
|--|--|-------------------------------------|--------------|--|
| Symptom / effect   |  | Talk with your doctor or pharmacist |              | Stop taking drug and seek immediate medical help |
|  |  | Only if severe                      | In all cases |  |
| <b>Uncommon</b>  | Bleeding after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision          |                                     | ✓            |  |
|  | Bleeding in your stomach, bowel or blood in the stool  |                                     | ✓            |  |
|  | Bleeding from your nose  |                                     | ✓            |  |
|  | <b>Liver Disorder:</b><br>yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite          |                                     | ✓            |  |
|  | <b>Low Blood Pressure:</b><br>dizziness, fainting, lightheadedness<br>May occur when you go from lying or sitting to standing up | ✓                                   |              |  |
| <b>Rare</b>  | Bleeding:<br>– into a muscle   |                                     | ✓            |  |
| <b>Unknown frequency</b>   | <b>Allergic Reaction:</b><br>Rash, hives, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing      |                                     |              | ✓  |

| SERIOUS SIDE EFFECTS,<br>HOW OFTEN THEY HAPPEN<br>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 |  |
| 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 PRO-APIXABAN, contact your doctor or pharmacist.***

#### HOW TO STORE IT

Store at room temperature (15°C to 30°C).

Keep out of the reach and sight of children.

Do not use PRO-APIXABAN 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

##### If you want more information about PRO-APIXABAN:

- 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>). Or by contacting Pro Doc Ltée at 1-800-361-8559, <http://www.prodoc.qc.ca> or [medinfo@prodoc.qc.ca](mailto:medinfo@prodoc.qc.ca)

This leaflet was prepared by Pro Doc Ltée., Laval, Québec, H7L 3W9.

Last revised: APR 10, 2026