AUSTRALIAN PI – APIXABAN-APX (APIXABAN)

1 NAME OF THE MEDICINE

Apixaban

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mg film-coated tablet contains 2.5 mg apixaban.

Each 5 mg film-coated tablet contains 5 mg apixaban.

List of excipients with known effect:

Contains sugars as lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

APIXABAN-APX containing 2.5 mg apixaban for oral administration is available as yellow round, biconvex, film-coated tablets debossed with “893” on one side and “2½” on the other side.

APIXABAN-APX containing 5 mg apixaban for oral administration is available as pink oval-shaped, biconvex, film-coated tablets debossed with “894” on one side and “5” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

APIXABAN-APX is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery.

APIXABAN-APX is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

APIXABAN-APX is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adult patients.

APIXABAN-APX is indicated for the prevention of recurrent DVT and PE in adult patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

APIXABAN-APX can be taken with or without food.

Missed Dose

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

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

The recommended dose of APIXABAN-APX is 2.5 mg taken twice daily. The initial dose should be taken 12 to 24 hours after surgery.

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

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

The dosage of 2.5 mg taken twice daily and the duration specified for each type of surgery should not be exceeded.

Anti-platelet agents other than acetylsalicylic acid (ASA) should be stopped prior to surgery and restarted after surgery as recommended in the anti-platelet product information documents. For patients on ASA therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The recommended dose of APIXABAN-APX is 5 mg taken twice daily.

The recommended dose of APIXABAN-APX is 2.5 mg taken twice daily in patients with at least two of the following characteristics:

- ≥80 years;
- body weight ≤60 kg;
- serum creatinine ≥133 μmol/L.

Treatment of DVT and PE

The recommended dose of APIXABAN-APX is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

Prevention of Recurrent DVT and PE

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

Use in Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment.

As there is no clinical experience in patients with renal impairment <15 mL/min or in patients undergoing dialysis APIXABAN-APX is contraindicated in these patients. There is limited experience in patients with renal impairment 15 mL to <25 mL/min with increased apixaban

exposure, therefore, APIXABAN-APX is also contraindicated in these patients (see section 4.3).

Dosage adjustment is needed in atrial fibrillation patients with at least two of the following criteria; serum creatinine ≥133 µmol/L, age ≥80 years, body weight ≤60 kg. See section 5.2 and section 4.4, Use in Renal Impairment.

Use in Hepatic Impairment

APIXABAN-APX may 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 section 4.4, Use in Hepatic Impairment and section 5.2.

Patients with elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore, APIXABAN-APX should be used cautiously in this population. Prior to initiating APIXABAN-APX, liver function testing should be performed (see section 4.4, Use in Hepatic Impairment).

APIXABAN-APX is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see section 4.3).

Body Weight

No dose adjustment is required (see section 5.2), except for atrial fibrillation patients with at least two of the following criteria; body weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation).

Gender

No dose adjustment required (see section 5.2).

Paediatric Use

The pharmacokinetics, efficacy and safety of APIXABAN-APX in children and adolescents below age 18 have not been established, therefore, the use of apixaban is not recommended in children and adolescents.

Use in the Elderly

Increasing age is associated with declining renal function (see section 5.1 Figure 1 and Figure 2).

No dose adjustment is required (see section 5.2), except for atrial fibrillation patients with at least two of the following criteria; age ≥80 years, weight ≤60 kg, serum creatinine ≥133 µmol/L an adjustment in dose is required (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation and section 4.4, Use in the Elderly and Use in Renal Impairment).

Converting From or To Parenteral Anticoagulants

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

Converting From or To Warfarin or Other Vitamin K Antagonists (VKA)

APIXABAN-APX affects international normalised ratio (INR), so that INR measurements during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin.

When converting patients from warfarin or other VKA therapy to APIXABAN-APX, discontinue warfarin or other VKA therapy and start APIXABAN-APX when the international normalised ratio (INR) is below 2.0.

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

After 2 days of co-administration of APIXABAN-APX with VKA therapy, obtain an INR prior to the next scheduled dose of APIXABAN-APX. Continue co-administration of APIXABAN-APX and VKA therapy until the INR is ≥2.0.

Surgery and Invasive Procedures

APIXABAN-APX should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. APIXABAN-APX should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where bleeding would be non-critical in location or easily controlled.

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

In non-valvular atrial fibrillation patients, bridging anticoagulation during the 24 to 48 hours after stopping APIXABAN-APX and prior to the intervention is not generally required. APIXABAN-APX could be restarted after the surgical or other procedure as soon as adequate haemostasis has been established. Clinicians need to evaluate the underlying risk of bleeding and thrombosis in individual patients based on their underlying disease and procedure to be undertaken.

<u>Cardioversion</u>

APIXABAN-APX can be initiated or continued in NVAF patients who may require cardioversion.

The initiation dosage information below was investigated in an exploratory study in 1,500 patients (see section 5.1 Pharmacodynamic Properties, Clinical Trials, Patients Undergoing Cardioversion).

For patients not previously treated with anticoagulants, at least 5 doses of APIXABAN-APX 5 mg twice daily [2.5 mg twice daily in patients who qualify for a dose reduction (see section 4.2 Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation)] should be given before cardioversion to ensure adequate anticoagulation.

If cardioversion is required before 5 doses of APIXABAN-APX can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction (see section 4.2 Prevention of Stroke and Systemic Embolism: Non-valvular

Atrial Fibrillation). The administration of the loading dose should be given at least 2 hours before cardioversion.

Confirmation should be sought prior to cardioversion that the patient has taken APIXABAN-APX as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Administration Options

For patients who are unable to swallow whole tablets, APIXABAN-APX tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally (see section 5.2, Absorption). Alternatively, APIXABAN-APX tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube (see section 5.2, Absorption).

Crushed APIXABAN-APX tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

4.3 CONTRAINDICATIONS

APIXABAN-APX is contraindicated in patients:

- with hypersensitivity to apixaban or to any of the excipients;
- with spontaneous or pharmacological impairment of haemostasis;
- with clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding);
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see section 5.2);
- with renal impairment creatinine clearance <25 mL/min (see section 5.2);
- receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir) (see section 4.5);
- with a lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under the circumstances of switching therapy to or from apixaban (see section 4.2) or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified Precautions

Haemorrhage Risk

As with all anticoagulants, APIXABAN-APX should be used with caution in circumstances associated with increased risk of bleeding. APIXABAN-APX increases the risk of bleeding and can cause serious, potentially fatal bleeding.

Patients taking APIXABAN-APX are to be carefully observed for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

APIXABAN-APX administration should be discontinued if severe haemorrhage occurs (see section 4.9).

Whilst APIXABAN-APX is contraindicated in a number of patients (see section 4.3), cautious use is recommended in patients with increased risk of haemorrhage such as:

- congenital or acquired bleeding disorders;
- bacterial endocarditis;
- thrombocytopenia;
- platelet disorders;
- history of haemorrhagic stroke;
- severe uncontrolled hypertension;
- age greater than 75 years;
- concomitant use of medications affecting haemostasis;
- bronchiectasis or history of pulmonary bleeding.

An increased risk of bleeding has been observed with increasing age (see section 4.4, Use in the Elderly) and with increased serum creatinine (see section 4.4, Use in Renal Impairment) when apixaban was used in these patients. Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to Accident and Emergency of the nearest hospital.

The anticoagulant effect of apixaban is expected to persist at least 24 hours after the last dose, i.e. for about two half-lives.

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

Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration (see section 4.9). Protamine sulphate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. Because of high plasma protein binding, apixaban is not expected to be dialysable (see section 5.2).

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate symptomatic treatments, e.g. surgical haemostasis, fluid replacement or the transfusion of fresh frozen plasma or blood products should be considered. If life-threatening bleeding cannot be controlled by the above measures,

administration of a reversal agent for factor Xa inhibitors, prothrombin complex concentrates (PCCs) (see section 5.2) or recombinant Factor VIIa may be considered. Currently, there is no experience with the use of recombinant Factor VIIa in individuals receiving apixaban. Re-dosing of recombinant Factor VIIa could be considered and titrated depending on improvement of bleeding.

There is no scientific experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no scientific rationale for reversal nor experience with systemic haemostastics (desmopressin, and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. These agents may be associated with a risk of thromboembolic complications.

Use of Thrombolytic Agents in the Treatment of Acute Ischaemic Stroke

There is very limited experience with the use of thrombolytic agents in the treatment of acute ischaemic stroke in patients administered apixaban.

Surgery and Invasive Procedures

See section 4.2, Surgery and Invasive Procedures.

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including APIXABAN-APX, in the absence of adequate alternative anticoagulation increases the risks of thrombotic events. An increased risk of stroke was observed during the transition from APIXABAN-APX to warfarin in clinical trials in atrial fibrillation patients. Discontinuation of apixaban prior to the onset of an effective antithrombotic effect of VKA could result in an increased risk of thrombosis. If anticoagulation with APIXABAN-APX must be discontinued for any reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant (see section 4.2, Converting from or to Warfarin or Other Vitamin K Antagonists (VKA)).

Patients with Valvular Disease

The safety and efficacy of APIXABAN-APX have not been studied in patients with prosthetic heart valves or those with haemodynamically significant rheumatic heart disease, especially mitral stenosis. As there are no data to support that APIXABAN-APX provides adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation, the use of APIXABAN-APX is not recommended in these patients.

Patients with Antiphospholipid Syndrome

Direct acting oral anticoagulants (DOACs), including APIXABAN-APX, are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS). In particular for patients who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy. The efficacy and safety of APIXABAN-APX in patients with APS have not been established.

Patients with Active Cancer

Efficacy and safety of apixaban in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established.

Acute Pulmonary Embolism in Haemodynamically Unstable Patients or Patients who require Thrombolysis or Pulmonary Embolectomy

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

Patients with Provoked VTE

Whilst patients with provoked VTE were not excluded from clinical studies there is limited experience in this sub-population.

Hip Fracture Surgery

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

Interaction with Other Medicines Affecting Haemostasis

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of APIXABAN-APX with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (ASA); selective serotonin reuptake inhibitors; and selective noradrenaline reuptake inhibitors because these medicines may impact haemostasis. Other platelet aggregation inhibitors or other antithrombotic agents are not recommended concomitantly with APIXABAN-APX following surgery.

In patients with atrial fibrillation and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with APIXABAN-APX. In a clinical trial of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of concomitant dual antiplatelet therapy with apixaban.

In a clinical study in patients with atrial fibrillation who had acute coronary syndrome (ACS) and/or underwent percutaneous coronary intervention (PCI), who are receiving anticoagulation (either apixaban or VKA) on top of P2Y12 inhibitor, concomitant use of ASA resulted in a near doubling of ISTH (International Society on Thrombosis and Hemostasis) major or CRNM (Clinically Relevant Non-Major) bleeding (see section 5.1, Pharmacodynamic properties).

An increased risk in bleeding was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with recent acute coronary syndrome, without atrial fibrillation (see section 4.5 and section 5.1, Clinical Trials).

Spinal/Epidural Anaesthesia or Puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic

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

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

Strong Inducers of both CYP3A4 and P-gp

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (see section 4.5 Interactions with other Medicines and Other Forms of Interaction, Effect of Other Medicines on Apixaban, Strong Inducers of CYP3A4 and P-gp):

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

Anticoagulant-related Nephropathy

There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following anticoagulant use, presenting as acute kidney injury.

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and haematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic).

Use in Hepatic Impairment

APIXABAN-APX is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see section 4.3).

APIXABAN-APX may be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B) (see section 4.2, Use in Hepatic Impairment and section 5.2).

Patients with elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore, APIXABAN-APX should be used cautiously in this population. Prior to initiating APIXABAN-APX, liver function testing should be performed.

Use in Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment.

As there is no clinical experience in patients with renal impairment <15 mL/min or in patients undergoing dialysis APIXABAN-APX is contraindicated in these patients. There is limited experience in patients with renal impairment 15 mL to <25 mL/min with increased apixaban exposure, therefore, APIXABAN-APX is also contraindicated in these patients (see section 4.3).

In patients with serum creatinine ≥133 µmol/L, the bleeding event rate of apixaban was 4.05%/years vs. warfarin 5.89%/years.

Dose adjustment is recommended in atrial fibrillation patients with at least two of the following criteria; serum creatinine ≥133 µmol/L, age ≥80 years, body weight ≤60 kg (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation, section 4.2, Use in Renal Impairment, and section 5.2).

Use in the Elderly

The co-administration of APIXABAN-APX with acetylsalicylic acid (ASA) in elderly patients should be used cautiously because of a potentially higher bleeding risk.

The event rate of stroke in patients >75 years old was greater than those <75 years old. Increasing age, >75 years old, is associated with a greater risk of bleeding (all, major and CRNM) including ocular and gastrointestinal bleeding. The event rate of bleeding in patients >80 years old with apixaban was 3.62%/year vs. warfarin 4.89%/year.

The benefit of apixaban in this age group was preserved for stroke, systemic embolism and risk of bleeding when compared to warfarin.

It should be taken into consideration that increasing age may be associated with declining renal function.

Consideration should be made to re-evaluating the risk of stroke versus bleeding at regular intervals in elderly patients.

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of apixaban, 50% were 65 and older, while 16% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The efficacy and safety results in elderly patients (including those ≥75 years) in both studies were consistent with the overall population (see section 5.1, Clinical Trials). In subjects ≥75 years of age in the pivotal study (ARISTOTLE) the Hazard Ratio for the primary efficacy endpoint of stroke and systemic embolus was 0.71 (95% CI 0.53, 0.95) in favour of apixaban compared with warfarin and the Hazard Ratio for the primary safety endpoint of ISTH Major

Bleeding was 0.64 (95% CI 0.52, 0.79) also in favour of apixaban. No dose adjustment is required, except for patients with at least two of the following criteria; age ≥80 years, body weight ≤60 kg, serum creatinine ≥133 μmol/L (see section 4.2, Use in the Elderly).

Treatment and Prevention of DVT and PE

No dose adjustment is necessary in elderly patients. Of the total number of subjects in the AMPLIFY and AMPLIFY-EXT studies of apixaban, 35% were 65 and older, while 14% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Paediatric Use

The pharmacokinetics, efficacy and safety of APIXABAN-APX in children and adolescents below age 18 have not been established, therefore the use of apixaban is not recommended in children and adolescents.

Effects on Laboratory Tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Apixaban is eliminated by renal and non-renal pathways, including metabolism and biliary excretion. Metabolism occurs mainly via CYP3A4/5. Apixaban is a substrate of efflux transport proteins; P-gp and BCRP (see section 5.2).

Effect of Other Medicines on Apixaban

Strong Inhibitors of CYP3A4 and P-gp

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

Two-fold increases in apixaban plasma concentrations may lead to an increased bleeding risk and, therefore, apixaban is contraindicated in patients who are receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as systemic treatment with azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole or posaconazole) or HIV protease inhibitors (e.g. ritonavir) (see section 4.3).

Other Inhibitors of CYP3A4 and P-gp

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

Clarithromycin (500 mg, twice a day), an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean apixaban AUC and $C_{max,}$ respectively.

Strong Inducers of CYP3A4 and P-gp

Co-administration of apixaban with rifampin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and C_{max}, respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations.

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

No dose adjustment for apixaban is required during concomitant therapy with such agents, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp, apixaban should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke or systemic embolism in nonvalvular atrial fibrillation patients and for the prevention of recurrent DVT and PE (see section 4.4, Strong Inducers of both CYP3A4 and P-gp**)**.

Increased stroke rates have been noted in atrial fibrillation patients taking these medicines with either apixaban or warfarin.

Anticoagulants, Platelet Aggregation Inhibitors and NSAIDs

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

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

Pharmacokinetic or pharmacodynamic interactions were not evident in healthy subjects when apixaban was co-administered with ASA 325 mg once a day.

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

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

Despite these findings, APIXABAN-APX should be used with caution when co-administered with NSAIDs, ASA or P2Y12 inhibitors, because these medicinal products typically increase the bleeding risk. In a clinical study in patients with atrial fibrillation who had ACS and/or underwent PCI, who are receiving anticoagulation (either apixaban or VKA) on top of P2Y12 inhibitor, concomitant use of ASA resulted in a near doubling of ISTH major or CRNM

bleeding (see section 4.4, Interaction with Other Medicines Affecting Haemostasis and section 5.1, Pharmacological Properties).

A significant increase in bleeding risk was reported in a clinical study in patients with ACS without atrial fibrillation with the triple combination of apixaban, ASA and clopidogrel compared to placebo, ASA and clopidogrel.

Other agents associated with serious bleeding are not recommended concomitantly with APIXABAN-APX, such as: thrombolytic agents, GPIIb/IIIa receptor antagonists, dipyridamole, and dextran. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section 4.4, Interaction with Other Medicines Affecting Haemostasis).

In patients with atrial fibrillation and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with APIXABAN-APX (see section 4.4, Interaction with Other Medicines Affecting Haemostasis).

Other Concomitant Therapies

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

Concomitant Therapies Affecting Bleeding

Patients taking apixaban may be at increased risk of bleeding when taking certain concomitant medications i.e. NSAIDs, Platelet Aggregation Inhibitors, diltiazem, amiodarone, verapamil, clarithromycin and quinidine.

Paediatric Population

Interaction studies have only been performed in adults.

Effect of Apixaban on Other Medicines

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

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

<u>Digoxin</u>

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

Naproxen

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

Atenolol

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies in adult rats dosed with apixaban at up to 600 mg/kg/day (up to 10 times the clinical exposure at 2.5 mg twice daily, or 3 times at 5 mg twice daily, based on free fraction AUC) showed no effect on fertility. In the offspring of rats treated with apixaban from gestation day 6 to lactation day 20, there were decreases in female mating and fertility at ≥200 mg/kg/day (12 times at 2.5 mg twice daily, or 4 times at 5 mg twice daily of the human exposure based on free fraction AUC). Fertility of the female offspring was unaffected at the maternal dose of 25 mg/kg/day (3 times at 2.5 mg twice daily, or 1.2 times at 5 mg twice daily of the human exposure). There were no effects on mating or fertility of male offspring at ≥1,000 mg/kg/day (13 times at 2.5 mg twice daily, or 5 times at 5 mg twice daily of the human exposure based on free fraction AUC). Plasma apixaban concentrations in the offspring were not measured, but high apixaban concentrations (30 times the maternal plasma AUC) were detected in milk.

Use in Pregnancy

Category C

There are limited data for the use of apixaban in pregnant women. As such apixaban is not recommended during pregnancy. In the event that a patient becomes pregnant while taking apixaban, a benefit risk assessment should be undertaken to determine whether or not to continue apixaban treatment.

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss. However, animal studies with apixaban do not indicate direct or indirect harmful effects with respect to embryo-fetal development,

Embryo-fetal development studies at oral doses up to 1500, 3000 and 1500 mg/kg/day in mice, rats and rabbits, respectively, and IV doses up to 5 mg/kg/day in rabbits showed no evidence of effects on embryo-fetal development in the 3 animal species tested. Maternal exposures to apixaban in the animal studies were 20 times (mouse), 4 times (rat) and 0.3 times (rabbit) the human exposure at 5 mg twice daily, based on free fraction AUC. Very low exposure to apixaban was detected in the fetus (8-11% of the maternal plasma concentration in mice, 7% in rats and <1% in rabbits).

Use in Lactation

There are no human data on the excretion of apixaban in milk. Apixaban is a substrate of BCRP, an active transporter expressed in tissues including mammary gland alveolar epithelium. Available data in animals have shown excretion of apixaban in rat milk

(milk/plasma ratio: 30). Apixaban may be excreted in human milk and may present a bleeding risk to newborns and infants. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

In a pre/postnatal study in rats dosed from gestation day 6 to postnatal day 20, mating and fertility of female offspring were reduced (see section 4.6, Effects on Fertility). Otherwise, postnatal development was unaffected at maternal doses up to 1000 mg/kg/day, with exposures up to 5 times the human exposure at 5 mg twice daily based on free fraction AUC.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

APIXABAN-APX has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

The safety of apixaban has been evaluated in one phase II and three phase III studies including 5,924 patients exposed to apixaban 2.5 mg twice daily undergoing major orthopaedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days. Of these, 2,673 patients undergoing hip replacement were treated for a mean duration of 34 days and 3,251 patients undergoing knee replacement were treated for a mean duration of 10 and 12 days in the phase II and III studies, respectively.

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. Bleeding may occur during apixaban therapy in the presence of associated risk factors such as organic lesions liable to bleed. Common adverse reactions were anaemia, haemorrhage, contusion and nausea. The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g. alanine aminotransferase levels) were similar between treatment groups in the phase II and phase III studies in elective hip and knee replacement surgery. The adverse reactions should be interpreted within the surgical setting.

The use of APIXABAN-APX may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms and severity will vary according to the location and degree or extent of the bleeding (see section 4.4, Haemorrhage Risk and section 5.1, Clinical Trials). Bleeding was assessed as a safety endpoint in the clinical trials. Similar rates were seen for major bleeding, the composite of major and clinically relevant non-major bleeding, and all bleeding in patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see section 5.1, Clinical Trials, Table 8).

Adverse events from the pivotal phase III studies (ADVANCE-2 and ADVANCE-3) are listed in Table 1 by system organ classification (MedDRA) and by frequency.

Table 1: Common adverse events occurring in ≥1% of patients in either group undergoing hip or knee replacement surgery, regardless of causality

System Organ Classification / Preferred Term	Apixaban 2.5 mg po twice daily n (%)	Enoxaparin 40 mg sc once daily n (%)
Number treated	4174 (100)	4167 (100)
Gastrointestinal disorders		
Nausea	587 (14.1)	649 (15.6)

System Organ Classification / Preferred Term	Apixaban 2.5 mg po twice daily n (%)	Enoxaparin 40 mg sc once daily n (%)
Constipation	392 (9.4)	441 (10.6)
Vomiting	288 (6.9)	350 (8.4)
Diarrhoea	96 (2.3)	110 (2.6)
Dyspepsia	48 (1.2)	60 (1.4)
Injury, poisoning and procedural complications		
Procedural pain	431 (10.3)	433 (10.4)
Anaemia postoperative	194 (4.6)	196 (4.7)
Contusion	63 (1.5)	86 (2.1)
Procedural hypotension	62 (1.5)	58 (1.4)
Wound secretion	58 (1.4)	54 (1.3)
General disorders and administration site conditions		
Pyrexia	307 (7.4)	313 (7.5)
Oedema peripheral	222 (5.3)	201 (4.8)
Pain	93 (2.2)	96 (2.3)
Chest pain	46 (1.1)	40 (1.0)
Vascular disorders		
Hypotension	299 (7.2)	296 (7.1)
Deep vein thrombosis	144 (3.5)	217 (5.2)
Hypertension	70 (1.7)	71 (1.7)
Thrombosis	70 (1.7)	71 (1.7)
Haematoma	58 (1.4)	66 (1.6)
Investigations		
Haemoglobin decreased	142 (3.4)	171 (4.1)
Blood creatine phosphokinase increased	102 (2.4)	104 (2.5)
Body temperature increased	85 (2.0)	88 (2.1)
Aspartate aminotransferase increased	56 (1.3)	78 (1.9)
Alanine aminotransferase increased	50 (1.2)	77 (1.8)
Gamma-glutamyltransferase increased	41 (1.0)	72 (1.7)
Nervous system disorders		
Dizziness	207 (5.0)	176 (4.2)
Headache	87 (2.1)	90 (2.2)
Somnolence	33 (0.8)	47 (1.1)
Skin and subcutaneous tissue disorders		
Pruritus	145 (3.5)	137 (3.3)
Rash	65 (1.6)	67 (1.6)
Erythema	49 (1.2)	46 (1.1)
Blister	44 (1.1)	42 (1.0)

System Organ Classification / Preferred Term	Apixaban 2.5 mg po twice daily n (%)	Enoxaparin 40 mg sc once daily n (%)
Musculoskeletal and connective tissue disorders		
Arthralgia	108 (2.6)	87 (2.1)
Pain in extremity	100 (2.4)	79 (1.9)
Muscle spasms	82 (2.0)	85 (2.0)
Renal and urinary disorders		
Urinary retention	184 (4.4)	169 (4.1)
Haematuria	51 (1.2)	58 (1.4)
Psychiatric disorders		
Insomnia	167 (4.0)	163 (3.9)
Anxiety	30 (0.7)	44 (1.1)
Infections and infestations		
Urinary tract infection	80 (1.9)	82 (2.0)
Cardiac disorders		
Tachycardia	135 (3.2)	147 (3.5)
Bradycardia	49 (1.2)	48 (1.2)
Respiratory, thoracic and mediastinal disorders		
Cough	45 (1.1)	41 (1.0)
Dyspnoea	33 (0.8)	43 (1.0)
Blood and lymphatic system disorders		
Anaemia	110 (2.6)	131 (3.1)
Metabolism and nutrition disorders		
Hypokalaemia	50 (1.2)	52 (1.2)

Common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥1% to <10% (≥1/100 to <1/10):

Blood and lymphatic system disorders: anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)

Vascular disorders: haemorrhage (including haematoma, and vaginal and urethral haemorrhage)

Gastrointestinal disorders: nausea

Injury, poisoning and procedural complications: contusion

Uncommon adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1% (≥1/1,000 to <1/100):

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal haemorrhage (including haematemesis and melaena), haematochezia

Hepatobiliary disorders: transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal), aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: haematuria (including respective laboratory parameters)

Injury, poisoning and procedural complications: post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage

Rare or very rare adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1% (<1/1,000):

Gingival bleeding, haemoptysis, hypersensitivity, muscle haemorrhage, ocular haemorrhage (including conjunctival haemorrhage), rectal haemorrhage.

In the knee replacement surgery study during the intended treatment period, in the apixaban arm 4 cases of PE were diagnosed against no cases in the enoxaparin arm. No explanation can be given to this higher incidence of PE. In the hip replacement surgery study during the intended treatment period, in the apixaban arm 3 cases of PE were diagnosed against 5 cases in the enoxaparin arm (see section 5.1, Clinical Trials, Table 7).

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The safety of apixaban has been evaluated in the ARISTOTLE and AVERROES phase III studies, including 11,284 patients exposed to apixaban 5 mg twice daily and 602 patients to 2.5 mg twice daily. The apixaban exposures were ≥ 12 months for 9,375 patients and ≥ 24 months for 3,369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89.2 weeks on apixaban and 87.5 weeks on warfarin; total patient-years for exposure was 15,534 on apixaban and 15,184 on warfarin. In AVERROES, the mean duration of exposure was approximately 59 weeks in both treatment groups; total patient-years for exposure was 3,193 on apixaban and 3,150 on ASA.

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

Bleeding

Bleeding was assessed as a safety endpoint in the clinical trials. Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in haemoglobin of 1.24 mmol/L or more; transfusion of 2 or more units of packed blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome,

retroperitoneal; or bleeding that was fatal. Intracranial haemorrhage included intracerebral (haemorrhagic stroke), subarachnoid, and subdural bleeds (see section 5.1 Clinical Trials).

ARISTOTLE Study

There was a statistically superior reduction in the incidence of ISTH major bleeding in the apixaban treatment group compared to the warfarin treatment group. There was also a significant reduction in the incidence of ISTH major+CRNM and all bleeding.

Table 2: Bleeding events in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N=9088 n (%/year)	**Warfarin N=9052 n (%/year)**	**Hazard Ratio (95% CI)**	**P-Value**
Major*	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Fatal[#]	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	
Intraocular[+]	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	
Gastrointestinal (GI)[‡]	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	
Major + CRNM	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	<0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	<0.0001

*Assessed by sequential testing strategy for superiority designed to control the overall Type I error in the trial.
Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal and extracranial bleeds and fatal haemorrhagic stroke.
+ Intraocular bleed is within the corpus of the eye (a conjunctival bleed in not an intraocular bleed).
‡ GI bleed includes upper GI, lower GI, and rectal bleeding.
Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

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

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

AVERROES Study

There was an increase in the incidence of major bleeding in the apixaban treatment group compared to the ASA treatment group, which was not statistically significant. Furthermore, there was a significant increase in the Major + CRNM and all bleeding events in the subjects treated with apixaban compared with ASA. The frequency of fatal and intracranial bleeding was similar in the two treatment groups.

Table 3: Bleeding events in patients with atrial fibrillation in the AVERROES study

	Apixaban N=2798 n (%/year)	**ASA N=2780 n (%/year)**	**Hazard Ratio (95%CI)**	**p-value**
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716

Fatal	5 (0.16)	5 (0.16)		
Intracranial	11 (0.34)	11 (0.35)		
Major + CRNM	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

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

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

Adverse events from the ARISTOTLE and AVERROES studies are listed by system organ classification (MedDRA) and by frequency, in Table 4.

Table 4: Common adverse events occurring in ≥1% of patients in the ARISTOTLE and AVERROES studies, regardless of causality

	ARISTOTLE CV185030		**AVERROES CV185048**	
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Warfarin n (%)**	**Apixaban n (%)**	**ASA n (%)**
Number treated	9,088	9,052	2,798	2,780
Infections and infestations				
Nasopharyngitis	763 (8.4)	779 (8.6)	89 (3.2)	80 (2.9)
Urinary tract infection	512 (5.6)	532 (5.9)	71 (2.5)	57 (2.1)
Bronchitis	503 (5.5)	516 (5.7)	80 (2.9)	68 (2.4)
Upper respiratory tract infection	436 (4.8)	456 (5.0)	57 (2.0)	55 (2.0)
Influenza	362 (4.0)	333 (3.7)	59 (2.1)	56 (2.0)
Pneumonia	324 (3.6)	385 (4.3)	61 (2.2)	79 (2.8)
Sinusitis	180 (2.0)	161 (1.8)		
Gastroenteritis	145 (1.6)	157 (1.7)		
Cellulitis	139 (1.5)	179 (2.0)	28 (1.0)	18 (0.6)
Lower respiratory tract infection	126 (1.4)	118 (1.3)		
Respiratory tract infection	95 (1.0)	101 (1.1)		
Herpes zoster	81 (0.9)	91 (1.0)		
Gastrointestinal Disorders				
Diarrhoea	585 (6.4)	584 (6.5)	77 (2.8)	80 (2.9)
Nausea	282 (3.1)	286 (3.2)	42 (1.5)	48 (1.7)
Constipation	207 (2.3)	225 (2.5)	35 (1.3)	64 (2.3)
Vomiting	197 (2.2)	163 (1.8)	21 (0.8)	31 (1.1)
Abdominal pain upper	176 (1.9)	177 (2.0)	50 (1.8)	56 (2.0)
Abdominal pain	172 (1.9)	192 (2.1)	39 (1.4)	30 (1.1)

	ARISTOTLE CV185030		AVERROES CV185048	
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Warfarin n (%)**	**Apixaban n (%)**	**ASA n (%)**
Dyspepsia	152 (1.7)	164 (1.8)	26 (0.9)	44 (1.6)
Gastritis	144 (1.6)	159 (1.8)	46 (1.6)	35 (1.3)
Toothache	134 (1.5)	121 (1.3)		
Rectal haemorrhage	125 (1.4)	142 (1.6)		
Gingival bleeding	113 (1.2)	223 (2.5)		
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	605 (6.7)	649 (7.2)	109 (3.9)	141 (5.1)
Epistaxis	560 (6.2)	685 (7.6)	54 (1.9)	52 (1.9)
Cough	495 (5.4)	505 (5.6)	85 (3.0)	97 (3.5)
Chronic obstructive pulmonary disease	145 (1.6)	140 (1.5)		
Dyspnoea exertional	104 (1.1)	103 (1.1)		
Haemoptysis	85 (0.9)	119 (1.3)		
Cardiac Disorders				
Atrial fibrillation	496 (5.5)	473 (5.2)	131 (4.7)	128 (4.6)
Cardiac failure	481 (5.3)	453 (5.0)	89 (3.2)	112 (4.0)
Cardiac failure congestive	233 (2.6)	245 (2.7)	57 (2.0)	41 (1.5)
Palpitations	198 (2.2)	196 (2.2)	56 (2.0)	60 (2.2)
Angina pectoris	145 (1.6)	133 (1.5)	31 (1.1)	33 (1.2)
Bradycardia	132 (1.5)	125 (1.4)		
Angina unstable	127 (1.4)	98 (1.1)		
Tachycardia	99 (1.1)	83 (0.9)		
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	447 (4.9)	463 (5.1)	69 (2.5)	68 (2.4)
Back pain	433 (4.8)	506 (5.6)	70 (2.5)	64 (2.3)
Pain in extremity	320 (3.5)	325 (3.6)	40 (1.4)	47 (1.7)
Osteoarthritis	235 (2.6)	227 (2.5)	35 (1.3)	24 (0.9)
Muscle spasms	171 (1.9)	151 (1.7)	12 (0.4)	30 (1.1)
Musculoskeletal pain	161 (1.8)	219 (2.4)	23 (0.8)	28 (1.0)
Myalgia	132 (1.5)	126 (1.4)		
Arthritis	115 (1.3)	116 (1.3)		
Joint swelling	77 (0.8)	92 (1.0)		
Nervous System Disorders				

	ARISTOTLE CV185030		AVERROES CV185048	
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Warfarin n (%)**	**Apixaban n (%)**	**ASA n (%)**
Dizziness	663 (7.3)	709 (7.8)	109 (3.9)	144 (5.2)
Headache	482 (5.3)	485 (5.4)	98 (3.5)	91 (3.3)
Syncope	186 (2.0)	150 (1.7)	29 (1.0)	37 (1.3)
Ischaemic stroke	94 (1.0)	81 (0.9)	19 (0.7)	47 (1.7)
Cerebrovascular accident			17 (0.6)	43 (1.5)
Transient ischaemic attack			11 (0.4)	36 (1.3)
General Disorders and Administration Site Conditions				
Oedema peripheral	611 (6.7)	663 (7.3)	87 (3.1)	106 (3.8)
Fatigue	392 (4.3)	381 (4.2)	74 (2.6)	68 (2.4)
Chest pain	347 (3.8)	357 (3.9)	72 (2.6)	78 (2.8)
Asthenia	217 (2.4)	202 (2.2)	41 (1.5)	39 (1.4)
Pyrexia	155 (1.7)	136 (1.5)		
Chest discomfort	96 (1.1)	101 (1.1)	19 (0.7)	29 (1.0)
Injury, Poisoning and Procedural Complications				
Fall	321 (3.5)	395 (4.4)	55 (2.0)	62 (2.2)
Contusion	301 (3.3)	482 (5.3)	35 (1.3)	48 (1.7)
Laceration	160 (1.8)	178 (2.0)		
Investigations				
Blood glucose increased	143 (1.6)	123 (1.4)		
Blood pressure increased	134 (1.5)	138 (1.5)	32 (1.1)	19 (0.7)
Blood creatinine increased	132 (1.5)	143 (1.6)		
Blood creatine phosphokinase increased	100 (1.1)	123 (1.4)	22 (0.8)	28 (1.0)
Gamma-glutamyltransferase increased	98 (1.1)	111 (1.2)		
Vascular Disorders				
Hypertension	386 (4.2)	409 (4.5)	80 (2.9)	104 (3.7)
Haematoma	224 (2.5)	424 (4.7)		
Hypotension	196 (2.2)	169 (1.9)	32 (1.1)	28 (1.0)
Haemorrhage	106 (1.2)	122 (1.3)		
Metabolism and Nutrition Disorders				
Gout	210 (2.3)	222 (2.5)	33 (1.2)	27 (1.0)
Diabetes mellitus	179 (2.0)	191 (2.1)	32 (1.1)	24 (0.9)
Hyperglycaemia	119 (1.3)	100 (1.1)		

	ARISTOTLE CV185030		AVERROES CV185048	
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Warfarin n (%)**	**Apixaban n (%)**	**ASA n (%)**
Decreased appetite	106 (1.2)	88 (1.0)	28 (1.0)	25 (0.9)
Hypokalaemia	105 (1.2)	106 (1.2)		
Skin and Subcutaneous Tissue Disorders				
Rash	185 (2.0)	194 (2.1)	39 (1.4)	28 (1.0)
Pruritis	184 (2.0)	139 (1.5)	37 (1.3)	29 (1.0)
Ecchymosis	140 (1.5)	228 (2.5)		
Renal and Urinary Disorders				
Haematuria	338 (3.7)	408 (4.5)	30 (1.1)	17 (0.6)
Renal failure	107 (1.2)	103 (1.1)		
Eye Disorders				
Cataract	180 (2.0)	184 (2.0)		
Conjunctival haemorrhage	103 (1.1)	206 (2.3)		
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)				
Basal cell carcinoma	79 (0.9)	95 (1.0)		
Psychiatric Disorders				
Insomnia	160 (1.8)	159 (1.8)	32 (1.1)	35 (1.3)
Depression	119 (1.3)	95 (1.0)	23 (0.8)	32 (1.2)
Blood and Lymphatic System Disorders				
Anaemia	270 (3.0)	265 (2.9)	41 (1.5)	44 (1.6)
Ear and Labyrinth Disorders				
Vertigo	174 (1.9)	182 (2.0)	38 (1.4)	35 (1.3)
Surgical and Medical Procedures				
Tooth extraction			29 (1.0)	30 (1.1)

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

Common adverse reactions in apixaban-treated patients with AF occurring at a frequency of ≥1% to <10% (≥1/100 to <1/10):

Eye disorders: eye haemorrhage (including conjunctival haemorrhage)

Vascular disorders: other haemorrhage, haematoma

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal haemorrhage (including haematemesis and melaena), rectal haemorrhage, gingival bleeding

Renal and urinary disorders: haematuria

Injury, poisoning and procedural complications: contusion

Uncommon adverse reactions in apixaban-treated patients with AF occurring at a frequency of ≥0.1% to <1% (≥1/1,000 to <1/100):

Immune system disorders: hypersensitivity (including drug hypersensitivity such as skin rash and anaphylactic reaction such as allergic oedema)

Nervous system disorders: brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)

Vascular disorders: intra-abdominal haemorrhage

Respiratory, thoracic and mediastinal disorders: haemoptysis

Gastrointestinal disorders: haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage

Reproductive system and breast disorders: abnormal vaginal haemorrhage, urogenital haemorrhage

General disorders and administration site conditions: application site bleeding

Investigations: occult blood positive

Injury, poisoning and procedural complications: traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage

Rare adverse reactions in apixaban-treated patients with AF occurring at a frequency of ≥0.01% to <0.1% (≥1/10,000 to <1/1,000):

Respiratory, thoracic and mediastinal disorders: respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage, and pharyngeal haemorrhage)

Gastrointestinal disorders: retroperitoneal haemorrhage.

Treatment VTE

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

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

In the AMPLIFY-EXT study, adverse reactions related to bleeding occurred in 219 (13.3%) of apixaban-treated patients compared to 72 (8.7%) of placebo-treated patients. The

discontinuation rate due to bleeding events was approximately 1% in the apixaban -treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Common adverse reactions (≥1**%)** were gingival bleeding, epistaxis, contusion, haematuria, haematoma, and menorrhagia.

Adverse events regardless of causality occurring in ≥1% of patients in the AMPLIFY and AMPLIFY-EXT studies are listed in Table 5 by system organ classification (MedDRA).

Table 5: Common adverse events occurring in ≥1% of patients in the AMPLIFY and AMPLIFY-EXT studies, regardless of causality

	AMPLIFY CV185056		**AMPLIFY-EXT CV185057**		
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Enoxaparin /Warfarin n (%)**	**Apixaban 2.5 mg n (%)**	**Apixaban 5 mg n (%)**	**Placebo n (%)**
Number treated	2,676	2,689	840	811	826
Infections and Infestations					
Nasopharyngitis	104 (3.9)	98 (3.6)	41 (4.9)	31 (3.8)	40 (4.8)
Urinary tract infection	95 (3.6)	85 (3.2)	29 (3.5)	31 (3.8)	35 (4.2)
Bronchitis	55 (2.1)	57 (2.1)	25 (3.0)	32 (3.9)	14 (1.7)
Upper respiratory tract infection	51 (1.9)	51 (1.9)	19 (2.3)	18 (2.2)	18 (2.2)
Influenza	37 (1.4)	37 (1.4)	18 (2.1)	20 (2.5)	20 (2.4)
Pneumonia	30 (1.1)	29 (1.1)	9 (1.1)	8 (1.0)	5 (0.6)
Sinusitis	17 (0.6)	27 (1.0)	7 (0.8)	13 (1.6)	12 (1.5)
Rhinitis			5 (0.6)	9 (1.1)	4 (0.5)
Gastroenteritis			11 (1.3)	7 (0.9)	7 (0.8)
Lower respiratory tract infection			14 (1.7)	5 (0.6)	6 (0.7)
Pharyngitis			8 (1.0)	2 (0.2)	9 (1.1)
Gastrointestinal Disorders					
Diarrhoea	100 (3.7)	106 (3.9)	37 (4.4)	24 (3.0)	24 (2.9)
Nausea	81 (3.0)	107 (4.0)	20 (2.4)	18 (2.2)	20 (2.4)
Constipation	74 (2.8)	87 (3.2)	18 (2.1)	12 (1.5)	14 (1.7)
Vomiting	50 (1.9)	70 (2.6)	12 (1.4)	10 (1.2)	11 (1.3)
Dyspepsia	40 (1.5)	34 (1.3)	13 (1.5)	9 (1.1)	11 (1.3)
Abdominal pain upper	39 (1.5)	32 (1.2)	6 (0.7)	10 (1.2)	10 (1.2)
Abdominal pain	33 (1.2)	42 (1.6)	7 (0.8)	10 (1.2)	8 (1.0)
Gingival bleeding	26 (1.0)	50 (1.9)	12 (1.4)	9 (1.1)	3 (0.4)

	AMPLIFY CV185056		AMPLIFY-EXT CV185057		
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Enoxaparin /Warfarin n (%)**	**Apixaban 2.5 mg n (%)**	**Apixaban 5 mg n (%)**	**Placebo n (%)**
Number treated	2,676	2,689	840	811	826
Rectal haemorrhage	26 (1.0)	39 (1.5)			
Gastritis	25 (0.9)	31 (1.2)			
Toothache			6 (0.7)	9 (1.1)	8 (1.0)
Respiratory, Thoracic and Mediastinal Disorders					
Epistaxis	77 (2.9)	146 (5.4)	13 (1.5)	29 (3.6)	9 (1.1)
Dyspnoea	72 (2.7)	77 (2.9)	18 (2.1)	15 (1.8)	19 (2.3)
Cough	61 (2.3)	58 (2.2)	21 (2.5)	21 (2.6)	18 (2.2)
Pulmonary embolism	44 (1.6)	56 (2.1)	7 (0.8)	4 (0.5)	24 (2.9)
Haemoptysis	32 (1.2)	31 (1.2)			
Oropharyngeal pain			12 (1.4)	12 (1.5)	11 (1.3)
Musculoskeletal and Connective Tissue Disorders					
Pain in extremity	122 (4.6)	131 (4.9)	43 (5.1)	52 (6.4)	54 (6.5)
Back pain	80 (3.0)	88 (3.3)	27 (3.2)	45 (5.5)	24 (2.9)
Arthralgia	75 (2.8)	86 (3.2)	33 (3.9)	22 (2.7)	23 (2.8)
Musculoskeletal chest pain	58 (2.2)	50 (1.9)	8 (1.0)	10 (1.2)	16 (1.9)
Muscle spasms	36 (1.3)	38 (1.4)	21 (2.5)	16 (2.0)	13 (1.6)
Musculoskeletal pain	30 (1.1)	29 (1.1)	8 (1.0)	5 (0.6)	10 (1.2)
Osteoarthritis			15 (1.8)	17 (2.1)	18 (2.2)
Myalgia			16 (1.9)	12 (1.5)	14 (1.7)
Nervous System Disorders					
Headache	169 (6.3)	168 (6.2)	44 (5.2)	42 (5.2)	42 (5.1)
Dizziness	66 (2.5)	69 (2.6)	20 (2.4)	18 (2.2)	15 (1.8)
Paraesthesia	20 (0.7)	40 (1.5)	9 (1.1)	4 (0.5)	10 (1.2)
Sciatica			6 (0.7)	9 (1.1)	4 (0.5)
General Disorders and Administration Site Conditions					
Oedema peripheral	96 (3.6)	113 (4.2)	28 (3.3)	25 (3.1)	34 (4.1)
Fatigue	58 (2.2)	50 (1.9)	17 (2.0)	14 (1.7)	11 (1.3)
Pyrexia	56 (2.1)	57 (2.1)	6 (0.7)	12 (1.5)	6 (0.7)
Non-cardiac chest pain	36 (1.3)	25 (0.9)	11 (1.3)	8 (1.0)	12 (1.5)

	AMPLIFY CV185056		AMPLIFY-EXT CV185057		
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Enoxaparin /Warfarin n (%)**	**Apixaban 2.5 mg n (%)**	**Apixaban 5 mg n (%)**	**Placebo n (%)**
Number treated	2,676	2,689	840	811	826
Asthenia	30 (1.1)	43 (1.6)	10 (1.2)	4 (0.5)	10 (1.2)
Injection site haematoma	8 (0.3)	39 (1.5)			
Chest pain			4 (0.5)	4 (0.5)	9 (1.1)
Reproductive System and Breast Disorders					
Menorrhagia	38 (1.4)	30 (1.1)	6 (0.7)	10 (1.2)	2 (0.2)
Hepatobiliary Disorders					
Hepatic steatosis	36 (1.3)	32 (1.2)			
Injury, Poisoning and Procedural Complications					
Contusion	49 (1.8)	97 (3.6)	12 (1.4)	15 (1.8)	13 (1.6)
Investigations					
Gamma-glutamyltransferase increased	38 (1.4)	57 (2.1)	9 (1.1)	12 (1.5)	4 (0.5)
Blood creatine phosphokinase increased	33 (1.2)	78 (2.9)	26 (3.1)	20 (2.5)	21 (2.5)
Alanine aminotransferase increased	31 (1.2)	105 (3.9)	13 (1.5)	4 (0.5)	10 (1.2)
Aspartate aminotransferase increased	17 (0.6)	34 (1.3)	5 (0.6)	8 (1.0)	5 (0.6)
Liver function test abnormal	12 (0.4)	38 (1.4)	31 (3.7)	24 (3.0)	27 (3.3)
Vascular Disorders					
Hypertension	71 (2.7)	69 (2.6)	34 (4.0)	19 (2.3)	14 (1.7)
Deep vein thrombosis	42 (1.6)	66 (2.5)	15 (1.8)	17 (2.1)	61 (7.4)
Haematoma	35 (1.3)	76 (2.8)	12 (1.4)	15 (1.8)	10 (1.2)
Metabolism and Nutrition Disorders					
Hypercholesterolaemia	28 (1.0)	55 (2.0)	14 (1.7)	11 (1.4)	11 (1.3)
Skin and Subcutaneous Tissue Disorders					
Rash	47 (1.8)	46 (1.7)	18 (2.1)	8 (1.0)	12 (1.5)

	AMPLIFY CV185056		AMPLIFY-EXT CV185057		
System Organ Classification / Preferred Term	**Apixaban n (%)**	**Enoxaparin /Warfarin n (%)**	**Apixaban 2.5 mg n (%)**	**Apixaban 5 mg n (%)**	**Placebo n (%)**
Number treated	2,676	2,689	840	811	826
Pruritis	31 (1.2)	42 (1.6)	8 (1.0)	10 (1.2)	7 (0.8)
Ecchymosis	12 (0.4)	27 (1.0)			
Renal and Urinary Disorders					
Haematuria	46 (1.7)	102 (3.8)	11 (1.3)	17 (2.1)	9 (1.1)
Renal cyst	33 (1.2)	34 (1.3)			
Eye Disorders					
Conjunctival haemorrhage	9 (0.3)	38 (1.4)			
Psychiatric Disorders					
Insomnia	48 (1.8)	49 (1.8)	9 (1.1)	11 (1.4)	8 (1.0)
Anxiety	39 (1.5)	38 (1.4)	6 (0.7)	10 (1.2)	5 (0.6)
Depression	29 (1.1)	18 (0.7)	7 (0.8)	14 (1.7)	11 (1.3)
Blood and Lymphatic System Disorders					
Anaemia	43 (1.6)	43 (1.6)	12 (1.4)	10 (1.2)	9 (1.1)
Ear and Labyrinth Disorders					
Vertigo	28 (1.0)	18 (0.7)	9 (1.1)	4 (0.5)	12 (1.5)

Adverse reactions in the AMPLIFY and AMPLIFY-EXT studies are listed below by system organ classification (MedDRA) and by frequency. Common adverse reactions in apixaban-treated patients occurring at a frequency of ≥1% to <10% (≥1/100 to <1/10):

Vascular disorders: haematoma

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: gingival bleeding

Renal and urinary disorders: haematuria

Reproductive system and breast disorders: menorrhagia

Injury, poisoning, and procedural complications: contusion

Uncommon adverse reactions in apixaban-treated patients occurring at a frequency of ≥0.1% to <1% (≥1/1,000 to <1/100):

Eye disorders: conjunctival haemorrhage

Respiratory, thoracic and mediastinal disorders: haemoptysis

Gastrointestinal disorders: rectal haemorrhage, haematochezia, haemorrhoidal haemorrhage, gastrointestinal haemorrhage, haematemesis

Skin and subcutaneous tissue disorders: ecchymosis, skin haemorrhage

Reproductive system and breast disorders: vaginal haemorrhage, metrorrhagia

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

Investigations: blood urine present, occult blood positive

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

Rare adverse reactions in apixaban-treated patients occurring at a frequency of ≥0.01% to <0.1% (≥1/10,000 to <1/1,000):

Blood and lymphatic system disorders: haemorrhagic anaemia, haemorrhagic diathesis, spontaneous haematoma

Nervous system disorders: cerebral haemorrhage, haemorrhagic stroke

Eye disorders: eye haemorrhage, retinal haemorrhage, scleral haemorrhage, vitreous haemorrhage

Ear and labyrinth disorders: ear haemorrhage

Cardiac disorders: pericardial haemorrhage

Vascular disorders: haemorrhage, intra-abdominal haematoma, shock haemorrhagic

Respiratory, thoracic and mediastinal disorders: pulmonary alveolar haemorrhage

Gastrointestinal disorders: melaena, anal haemorrhage, gastric ulcer haemorrhage, mouth haemorrhage, abdominal wall haematoma, Mallory-Weiss syndrome, gastric haemorrhage, peptic ulcer haemorrhage, small intestine haemorrhage

Skin and subcutaneous tissue disorders: petechiae, purpura, increased tendency to bleed, blood blister, skin ulcer haemorrhage

Musculoskeletal and connective tissue disorders: muscle haemorrhage

Renal and urinary disorders: haemorrhage urinary tract

Reproductive system and breast disorders: menometrorrhagia, uterine haemorrhage, genital haemorrhage, breast haematoma, haematospermia, postmenopausal haemorrhage

General disorders and administration site conditions: injection site haemorrhage, infusion site haematoma

Investigations: occult blood, red blood cells urine positive

Injury, poisoning, and procedural complications: periorbital haematoma, vascular pseudoaneurysm, subcutaneous haematoma, procedural haematoma, post procedural

haematoma, post procedural haematuria, extradural haematoma, renal haematoma, subdural haemorrhage

Post-marketing Experience

System organ class	Adverse effect	Frequency
Renal and urinary disorders	Anticoagulant-related nephropathy (see section 4.4)	Not known
	Haematuria	Not known

Reporting Suspected Adverse Events

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available (see section 4.4, Haemorrhage Risk).

Overdose of APIXABAN-APX may result in a higher risk of bleeding. In the event of haemorrhagic complications, the source of bleeding needs to be investigated and appropriate symptomatic treatment initiated (see section 4.4, Haemorrhage Risk).

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

Administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected, given the high incidence of gastrointestinal side effects, such as vomiting, associated with activated charcoal. Healthcare professionals are encouraged to review the activated charcoal product information for further information pertaining to the administration of activated charcoal.

A nonclinical study in dogs demonstrated that oral administration of activated charcoal suspended in water up to 3 hours after apixaban administration reduced apixaban exposure.

Eighteen healthy subjects were enrolled in a study to assess the effect of activated charcoal with sorbitol on the pharmacokinetics of a single 20 mg dose of apixaban. This was a three treatment, three period, randomised, cross over study where the subjects received a dose of apixaban alone, or followed by the administration of activated charcoal with sorbitol 2 and 6 hours after ingestion of the apixaban dose. The administration of activated charcoal with sorbitol 2 and 6 hours after 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 with sorbitol was administered 2 and 6 hours after apixaban.

Haemodialysis decreased apixaban AUC by 14% in subjects with end stage renal disease, when a single dose of apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose (see section 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment).

Management of Bleeding

In the event of hemorrhagic complications in a patient receiving APIXABAN-APX, 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.

For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available. Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered.

Re-dosing of prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant Factor VIIa could be considered and titrated depending on improvement of bleeding.

However, these agents have not been evaluated in clinical studies.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

There is no clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received APIXABAN-APX. Effects of 4-factor PCCs on the pharmacodynamics of apixaban were studied in healthy subjects. Following administration of apixaban dosed to steady state, endogenous thrombin potential (ETP) returned to pre-apixaban levels approximately 4 hours after the initiation of a 30 minute PCC infusion, compared to 45 hours with placebo. Mean ETP levels continued to increase and exceeded pre-apixaban levels reaching a maximum (34-51% increase over pre-apixaban levels) at 21 hours after initiating PCC and remained elevated (21–27% increase) at the end of the study (69 hours after initiation of PCC). The clinical relevance of this increase in ETP is unknown.

Apixaban also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in the Rotachrom® Heparin chromogenic assay data from clinical studies. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban 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, with anti-FXa activity compared with clotting tests.

Table 6 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 6: Predicted apixaban steady-state exposure (ng/mL) and anti-Xa activity (IU/mL)

	Apix. C_{max} (ng/mL)	**Apix. C_{min} (ng/mL)**	**Apix. Anti-Xa Activity Max (IU/mL)**	**Apix. Anti-Xa Activity Min (IU/mL)**
	Median [5th, 95th Percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg BID	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAF				
2.5 mg BID*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg BID	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of VTE				
2.5 mg BID	67 [30, 153]	32 [11, 90]	1.1 [0.47, 2.4]	0.51 [0.17, 1.4]
5 mg BID	132 [59, 302]	63 [22, 177]	2.1 [0.93, 4.8]	1.0 [0.35, 2.8]
10 mg BID	251 [111, 572]	120 [41, 335]	4.0 [1.8, 9.1]	1.9 [0.65, 5.3]

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

Although treatment with apixaban at the recommended dose does not require routine monitoring of exposure, the use of a calibrated quantitative anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose or emergency surgery.

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

Mechanism of Action

Apixaban is a reversible, direct and highly selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, 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 caused negligible prolongation of prothrombin time and bleeding time in rabbits and dogs, but more than 2-fold increases in prothrombin time and bleeding time in rats.

Clinical Trials

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of venous thromboembolic events (VTE) in a broad range of adult patients undergoing elective hip or knee replacement. A total of 8,464 patients were randomised in two pivotal, double-blind, multi-national studies, comparing apixaban 2.5 mg given orally twice daily (4,236 patients) or enoxaparin 40 mg once daily (4,228 patients). Included in this total were 1,262 patients (618 in the apixaban group) of age 75 or older, 1,004 patients (499 in the apixaban group) with low body weight (≤60 kg), 1,495 patients (743 in the apixaban group) with BMI ≥33 kg/m^2 and 437 patients with severe or moderate renal impairment (217 patients in the apixaban group). The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement (mean age: 61 years; 53% female), and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement (mean age: 66 years; 72% female). Apixaban was not studied in patients undergoing hip fracture surgery.

Adult patients scheduled for hip or knee replacement surgery could be enrolled provided they had no active bleeding or high risk of bleeding, no active hepatobiliary disease, their creatinine clearance was not less than 30 mL/min, their ALT or AST level was not greater than twice the upper limit of normal (ULN) and they were not on treatment with medications affecting coagulation or platelet function unless they could be withdrawn.

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

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

Efficacy analyses of the pivotal studies utilised a pre-specified testing sequence that allowed testing for superiority on the primary endpoint only after non-inferiority (NI) was established. The NI margin used for the primary endpoint was 1.25, i.e. the upper bound of the 95% confidence interval (CI) for the relative risk was not to exceed 1.25. Similarly, testing for superiority on the key secondary endpoint of Major VTE was only conducted after non-inferiority on this endpoint was established.

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 7).

Table 7: Efficacy results from pivotal phase III studies

Study	**ADVANCE-3 (hip)**			**ADVANCE-2 (knee)**		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po bid 35 ± 3 d	Enoxaparin 40 mg sc od 35 ± 3 d	p-value	Apixaban 2.5 mg po bid 12 ± 2 d	Enoxaparin 40 mg sc od 12 ± 2 d	p-value
Total VTE/all-cause death						
Number of events/subjects Event Rate (%)	27/1,949 1.39	74/1,917 3.86	<0.0001	147/976 15.06	243/997 24.37	<0.0001

Study	ADVANCE-3 (hip)			ADVANCE-2 (knee)		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po bid 35 ± 3 d	Enoxaparin 40 mg sc od 35 ± 3 d	p-value	Apixaban 2.5 mg po bid 12 ± 2 d	Enoxaparin 40 mg sc od 12 ± 2 d	p-value
Relative Risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Absolute Risk Difference (%) 95% CI	-2.47 (-3.54,- 1.50)			-9.27 (-12.74, -5.79)		
Components of primary endpoint[a]						
Distal or proximal DVT Event rate (%) 95% CI	1.13 (0.74, 1.72)	3.56 (2.81, 4.50)		14.62 (12.54, 17.00)	24.37 (21.81, 27.14)	
Non-fatal PE Event rate (%) 95% CI	0.07 (0.00, 0.29)	0.19 (0.07, 0.45)		0.20 (0.04, 0.61)	0.00 (0.00, 0.31)	
All-cause death Event rate (%) 95% CI	0.11 (0.02, 0.35)	0.04 (0.00, 0.24)		0.13 (0.01, 0.52)	0.0 (0.00, 0.31)	
Major VTE						
Number of events/subjects Event Rate (%)	10/2,199 0.45	25/2,195 1.14	0.0107	13/1,195 1.09	26/1,199 2.17	0.0373
Relative Risk 95% CI	0.40 (0.15, 0.80)			0.50 (0.26, 0.97)		
Absolute Risk Difference (%) 95% CI	-0.68 (-1.27,- 0.17)			-1.04 (-2.03, -0.05)		
Components of Major VTE endpoint[a]						
Proximal DVT Event rate (%) 95% CI	0.32 (0.14, 0.68)	0.91 (0.59, 1.42)		0.76 (0.38, 1.46)	2.17 (1.47, 3.18)	
Non-fatal PE Event rate (%) 95% CI	0.07 (0.00, 0.29)	0.19 (0.07, 0.45)		0.20 (0.04, 0.61)	0.00 (0.00, 0.31)	
VTE-related death Event rate (%) 95% CI	0.04 (0.00, 0.24)	0.00 (0.00, 0.18)		0.07 (0.00, 0.42)	0.00 (0.00, 0.31)	

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

The safety endpoints of major bleeding, the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 8). Major bleeding was defined as a decrease in haemoglobin of 20 g/L or more over a 24 hour period, transfusion of 2 or more units of packed red cells, bleeding into a critical site (e.g. intracranial haemorrhage) or fatal. CRNM bleeding was defined as significant epistaxis, gastrointestinal bleed, significant haematuria, significant haematoma, bruising or ecchymosis, or haemoptysis. All the bleeding criteria included surgical site bleeding.

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

Table 8 shows the bleeding results from the treatment period and the post-surgery treatment period.

Table 8: Bleeding results from pivotal phase III studies†

	ADVANCE-3		ADVANCE-2	
	Apixaban 2.5 mg po bid 35 ± 3 d	**Enoxaparin 40 mg sc od 35 ± 3 d**	**Apixaban 2.5 mg po bid 12 ± 2 d**	**Enoxaparin 40 mg sc od 12 ± 2 d**
All treated	n = 2673	n = 2659	n = 1501	n = 1508
	n (%)	n (%)	n (%)	n (%)
Treatment Period				
Major	22 (0.8)	18 (0.7)	9 (0.6)	14 (0.9)
Fatal	0	0	0	0
Major + CRNM	129 (4.8)	134 (5.0)	53 (3.5)	72 (4.8)
All	313 (11.7)	334 (12.6)	104 (6.9)	126 (8.4)
Post-surgery treatment period				
Major	9 (0.3)	11 (0.4)	4 (0.3)	9 (0.6)
Fatal	0	0	0	0
Major + CRNM	96 (3.6)	115 (4.3)	41 (2.7)	56 (3.7)
All	261 (9.8)	293 (11.0)	89 (5.9)	103 (6.8)

† all the bleeding criteria included surgical site bleeding

Prevention of Stroke and Systemic Embolism: Non-valvular 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 vitamin K antagonists (VKA) (ARISTOTLE) and in patients unsuitable for VKA (AVERROES). Both studies were active-controlled (vs. warfarin in ARISTOTLE and vs. acetylsalicylic acid (ASA) in AVERROES), randomised, double-blind, parallel-arm, multi-national studies in patients with nonvalvular, persistent, paroxysmal, or permanent atrial fibrillation (AF) or atrial flutter (AFl) and one or more of the following additional risk factors:

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

Adult patients could be enrolled provided they had no AF due to reversible causes, clinically significant (moderate or severe) mitral stenosis, no contraindication to anticoagulation, no serious bleeding in the last 6 months or increased bleeding risk, no persistent, uncontrolled hypertension, no active infective endocarditis, no planned major surgery or planned AF or flutter ablation surgery, no ischaemic stroke within 7 days, could comply with INR monitoring (ARISTOTLE), had no other condition requiring anticoagulation, their creatinine clearance was not less than 25 mL/min, their ALT or AST level was not greater than 2 x ULN nor total bilirubin greater than 1.5 x ULN, their platelet count was not less than 100 x 10^9/L, their

haemoglobin level was not less than 90 g/L, they did not require treatment with aspirin >165 mg/day (ARISTOTLE) and were either not on treatment with a thienopyridine (AVERROES) nor on treatment with both aspirin and a thienopyridine (ARISTOTLE).

Prohibited therapies while taking the study medication in ARISTOTLE were potent inhibitors of CYP3A4, glycoprotein (GP) IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban) or other antithrombotic agents (e.g. unfractionated heparin [UFH], low molecular weight heparin [LMWH], direct thrombin inhibitors, fondaparinux).

Patients with other valvular abnormalities, such as mitral regurgitation or aortic stenosis, were eligible to be enrolled.

Table 9: Patient demographic characteristics in the clinical studies

	ARISTOTLE	AVERROES
Randomised Subjects	18,201	5,598
Mean Age	69.1	69.9
≥ 65 years	69.9%	69.3%
≥ 75 years	31.2%	33.8%
Gender		
Male	64.7%	58.5%
Female	35.3%	41.5%
Race		
White/Caucasian	82.6%	78.6%
Asian	14.5%	19.4%
Black/African American	1.2%	0.6%
Prior stroke or TIA	18.6%	13.6%
Hypertension	87.4%	86.4%
Diabetes	25.0%	19.6%
Heart failure	(or LVEF ≤40%) 35.4%	(or LVEF ≤35%) 33.7%
Mean $CHADS_2$ Score	2.1	2.0
$CHADS_2$ ≤1	34.0%	38.3%
$CHADS_2$ = 2	35.8%	35.2%
$CHADS_2$ ≥3	30.2%	26.5%

ARISTOTLE Study

Patients were randomised to treatment with apixaban (9,120 patients) 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, 4.7%) or warfarin (9,081 patients), dosed to achieve a target international normalised ratio (INR) range 2.0-3.0, and treated for a median of 89.86 weeks for apixaban and 87.79 weeks for warfarin. The apixaban 2.5 mg twice daily dose was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 µmol/L). 43% were VKA naive, defined as not previously received or have received ≤30 consecutive days of treatment with warfarin or another VKA. Coronary artery disease was present in 33.2% of patients.

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

The primary objective of the study was to determine if apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) was non-inferior to warfarin for the prevention of stroke (ischaemic, haemorrhagic, or unspecified) and systemic embolism. Assessments of superiority of apixaban versus warfarin were also prespecified for the primary endpoint, for death due to any cause and ISTH Major bleeding.

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

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, $p=0.0114$).

Statistically significant superiority was also achieved in all-cause death (see Table 10). Numeric reductions were observed for both cardiovascular (CV) and non-CV deaths.

Table 10: Key efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N=9120 n (%/yr)	**Warfarin N=9081 n (%/yr)**	**Hazard Ratio (95% CI)**	**P-Value**
Stroke or systemic embolism*	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114 (<0.0001)‡
Stroke				
Ischaemic or undetermined	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	
Haemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	
All-cause death*†	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465

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

Centres were ranked *post hoc* by the percentage of time that warfarin-treated patients were in therapeutic range (INR 2-3). Findings for stroke/systemic embolism, major bleeds, and all cause mortality are shown for centres above and below the median level of INR control in Table 11. The benefits of apixaban relative to warfarin were consistent in patients enrolled at centres with INR control below or above the median.

Table 11: Centre INR control in the ARISTOTLE study

	Centres with INR control below the median of 66% Hazard Ratio (95% Confidence Interval)	Centres with INR control above the median of 66% Hazard Ratio (95% Confidence Interval)
Stroke/systemic embolism	0.78 (0.62, 0.98)	0.81 (0.61, 1.08)
Major bleed	0.56 (0.45, 0.70)	0.82 (0.68, 1.00)
All cause death	0.86 (0.74, 1.00)	0.93 (0.79, 1.10)

AVERROES Study

Patients were randomised to treatment with apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, 6.4%) or acetylsalicylic acid (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 randomisation.

In the study, VKA therapy had been tried but discontinued in 40% of patients prior to enrollment. Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS2 score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

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

These key study outcomes were prespecified and tested in a sequential, hierarchical manner to conserve overall Type 1 error. Apixaban was tested compared with ASA for: (1) superiority on the composite endpoint of stroke and systemic embolism; (2) superiority on the composite endpoint of stroke of any type, 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 predefined interim analysis revealed clear evidence of apixaban providing a clinically important reduction in stroke and systemic embolism and acceptable safety profile.

In the study, apixaban demonstrated statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 12). A clinically important reduction was observed in the key secondary composite endpoint of stroke, systemic embolism, myocardial infarction, or vascular death (see Table 12).

Table 12: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study

	Apixaban N=2807 n (%/year)	ASA N=2791 n (%/year)	Hazard Ratio (95% CI)	P-Value
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischaemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	
Haemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	
Stroke, systemic embolism, MI, or vascular death*†	132 (4.21)	197 (6.35)	0.66 (0.53, 0.83)	0.003^
Myocardial infarction	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	
Vascular Death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	
All-cause death*†	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068^

Due to early termination, the study was underpowered to evaluate all of the secondary endpoints.
* Assessed by sequential testing strategy designed to control the overall Type I error in the trial
† Secondary endpoint
^ not statistically significant
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints

Bleeding in Patients with Atrial Fibrillation

In the ARISTOTLE and AVERROES studies, the primary safety endpoint was major bleeding, which was defined as acute clinically overt bleeding that was accompanied by one or more of the following: a decrease in haemoglobin of 20 g/L or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; bleeding that is fatal. Intracranial haemorrhage included intracerebral (including haemorrhagic stroke), subarachnoid, and subdural bleeds.

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

ARISTOTLE Study

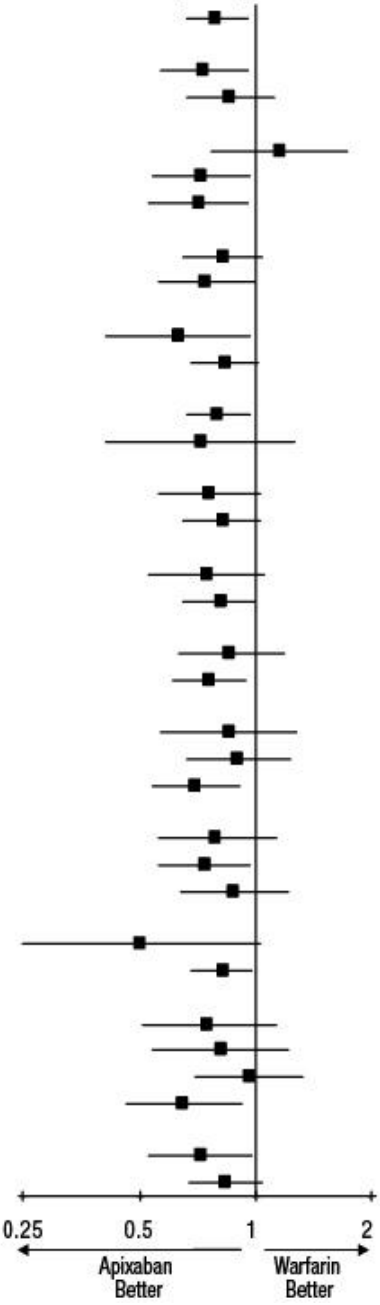
There was a statistically superior reduction in the incidence of ISTH major bleeding in the apixaban treatment group compared to the warfarin treatment group (see section 4.8, Table 2). There was also a significant reduction in the incidence of ISTH major+CRNM and all bleeding.

Subpopulation Analysis

Figure 1: Stroke and systemic embolism (A), and bleeding (B) ratios by baseline characteristics – ARISTOTLE

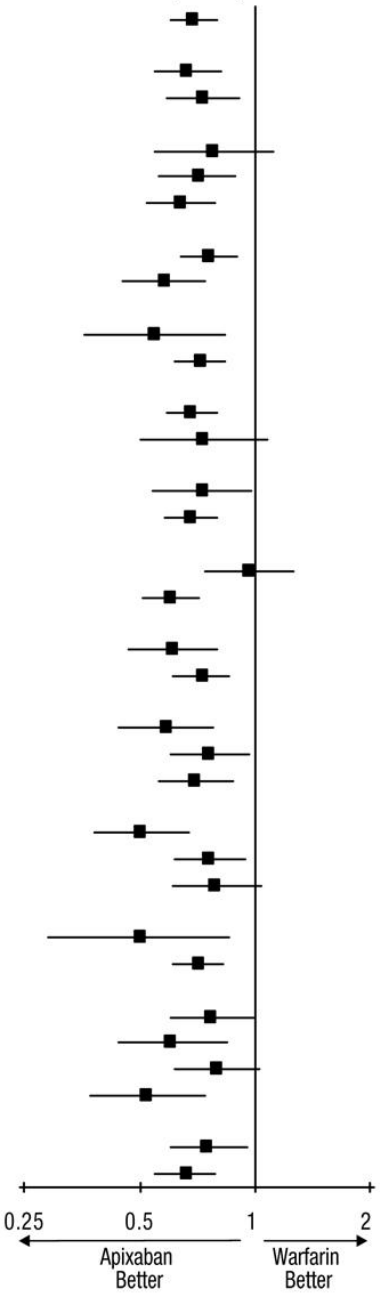
A. Primary Efficacy Outcome: Stroke and Systemic Embolism

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



B. Major Bleeding

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



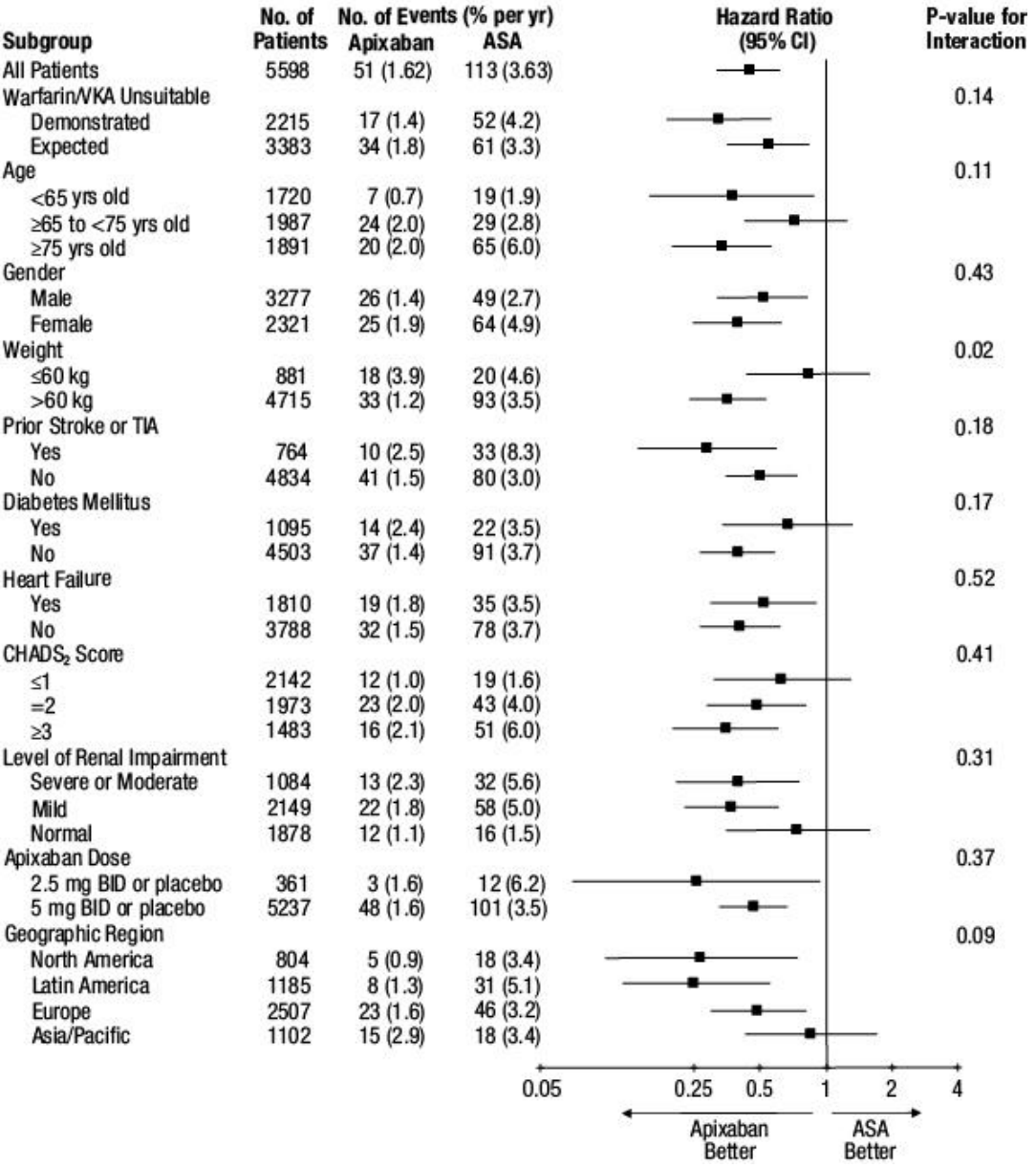
The ARISTOTLE study shows that the risk of stroke, death and major bleeding increases significantly with age. Apixaban compared with warfarin was shown to reduce these outcomes in a consistent manner regardless of age (see section 4.4, Use in the Elderly).

AVERROES Study

There was an increase in the incidence of major bleeding in the apixaban treatment group compared to the ASA treatment group, which was not statistically significant. Furthermore, there was a significant increase in the Major + CRNM and all bleeding events in the subjects treated with apixaban compared with ASA. The frequency of fatal and intracranial bleeding was similar in the two treatment groups (see section 4.8, Table 3).

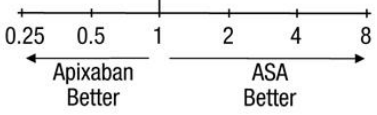
Figure 2: Stroke and systemic embolism (A), and bleeding (B) ratios by baseline characteristics – AVERROES

A. Primary Efficacy Outcome: Stroke and Systemic Embolism



B. Major Bleeding

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



In a clinical study in high risk acute coronary syndrome patients, as characterised by advanced age and multiple cardiac and non-cardiac co-morbidities (e.g. diabetes, heart failure), receiving apixaban 5 mg twice daily versus placebo, a significant increase in bleeding risk, including gastrointestinal and intracranial bleeding, was reported with the triple combination of apixaban, ASA and clopidogrel (see section 4.5, Effect of Other Medicines on apixaban).

NVAF Patients with ACS and/or undergoing PCI

AUGUSTUS, an open-label, randomised, controlled trial, randomised 4,614 patients with NVAF who had ACS and/or underwent PCI. Fifty-six percent underwent PCI and 43% developed ACS at enrollment. All patients received background therapy with a P2Y12 inhibitor prescribed per local standard of care (90.3% of patients received clopidogrel).

Patients were randomised up to 14 days after the ACS and/or PCI to either apixaban 5 mg twice daily (2.5 mg twice daily if two or more of the dose-reduction criteria were met; 4.2% received

lower dose) or VKA (target INR of 2.0 to 3.0) and to either ASA (81 mg once daily) or placebo. The mean age was 69.9 years; 94% of patients randomised had a CHA_2DS_2 VASc score >2 and 47% had a HASBLED score >3.

The primary safety endpoint was ISTH major or CRNM bleeding. The secondary efficacy endpoints were (a) all-cause death or all-cause re-hospitalisation and (b) all-cause death or ischaemic events (stroke, myocardial infarction, stent thrombosis, urgent coronary revascularisation).

For the apixaban versus VKA-comparison, there was a statistically significant reduction in the risk of the primary endpoint of adjudicated ISTH major or CRNM bleeding at month 6 in the apixaban treatment arm (HR=0.69, 95% CI: 0.58, 0.82; 2-sided p<0.0001 for non-inferiority and p<0.0001 for superiority). See Table 13 for results of the primary safety and secondary efficacy outcomes for the apixaban vs. VKA comparison.

Table 13: Results in the AUGUSTUS study - Apixaban vs VKA

	Apixaban	VKA	Hazard Ratio (95% CI)	Two-sided P Value
ISTH major or CRNM bleeding				
N	2290	2259		
No. of patients with event (%)	241 (10.5)	332 (14.7)	0.69 (0.58-0.82)	<0.0001
Event rate per 100 patient-yr	24.7	35.8		
Death or re-hospitalisation				
N	2306	2308		
No. of patients with event (%)	541 (23.5)	632 (27.4)	0.84 (0.75-0.94)	0.003
Event rate per 100 patient-yr	57.2	69.2		

All subjects received a P2Y12 inhibitor with or without ASA.

For the ASA versus placebo comparison, the addition of ASA to anticoagulation (with either apixaban or VKA) on top of P2Y12 inhibitor significantly increased the risk of ISTH major or CRNM bleeding (HR=1.88, 95% CI 1.58, 2.23; two-sided p<0.0001). A subgroup analysis found that concomitant use of ASA resulted in a near doubling of the risk of major or CRNM bleeding in both apixaban-treated and VKA treated subjects. See Table 14 for results of the primary safety outcome.

Table 14: Safety Results in the AUGUSTUS Study - ASA vs. Placebo

ISTH major or CRNM bleeding	ASA N=2277	Placebo N=2277	Hazard Ratio (95% CI)	Two-sided P Value
Apixaban or VKA				
No. of patients with event (%)	367 (16.2)	204 (9.0)	1.88 (1.58-2.23)	<0.0001
Event rate per 100 patient-yr	40.5	21.0		

All subjects received a P2Y12 inhibitor and an anticoagulant (either apixaban or VKA).
Clinical Study Report Table 8.1.1-2 (overall)

Patients Undergoing Cardioversion

EMANATE, an open-label, multi-center, exploratory study, enrolled 1,500 patients who were either oral anticoagulant naïve or pre-treated less than 48 hours, and scheduled for cardioversion for NVAF.

Patients were randomised 1:1 to apixaban or to heparin and/or VKA for the prevention of cardiovascular events. Electrical and/or pharmacologic cardioversion was conducted after at least 5 doses of 5 mg twice daily apixaban [or 2.5 mg twice daily in selected patients (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation) or at least 2 hours after a 10 mg loading dose [or a 5 mg loading dose in selected patients (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation)] if earlier cardioversion was required. In the apixaban group, 342 patients received a loading dose (331 patients received the 10 mg dose and 11 patients received the 5 mg dose).

There were no strokes (0%) in the apixaban group (n=753) and 6 (0.80%) strokes in the heparin and/or VKA group (n=747; RR 0, 95% CI 0.0, 0.64). All-cause death occurred in 2 patients (0.27%) in the apixaban group and 1 patient (0.13%) in the heparin and/or VKA group. No systemic embolism events were reported.

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

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

Treatment of VTE

The clinical program was designed to demonstrate the efficacy and safety of apixaban for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (AMPLIFY study), 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 randomised, 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 15: Patient demographic characteristics in the clinical studies

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

Table 16: Patient risk factors for DVT/PE in the clinical studies

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

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

^ Cases which had no identifiable provoking risk factors

AMPLIFY Study

Patients were randomised to treatment with apixaban 10 mg twice daily orally for 7 days followed by apixaban 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2) and warfarin (target INR range 2.0-3.0) orally for 6 months. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, or active bleeding were excluded from the studies. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

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

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

In the study, apixaban was shown to be noninferior to enoxaparin/warfarin in the combined endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death (see Table 17).

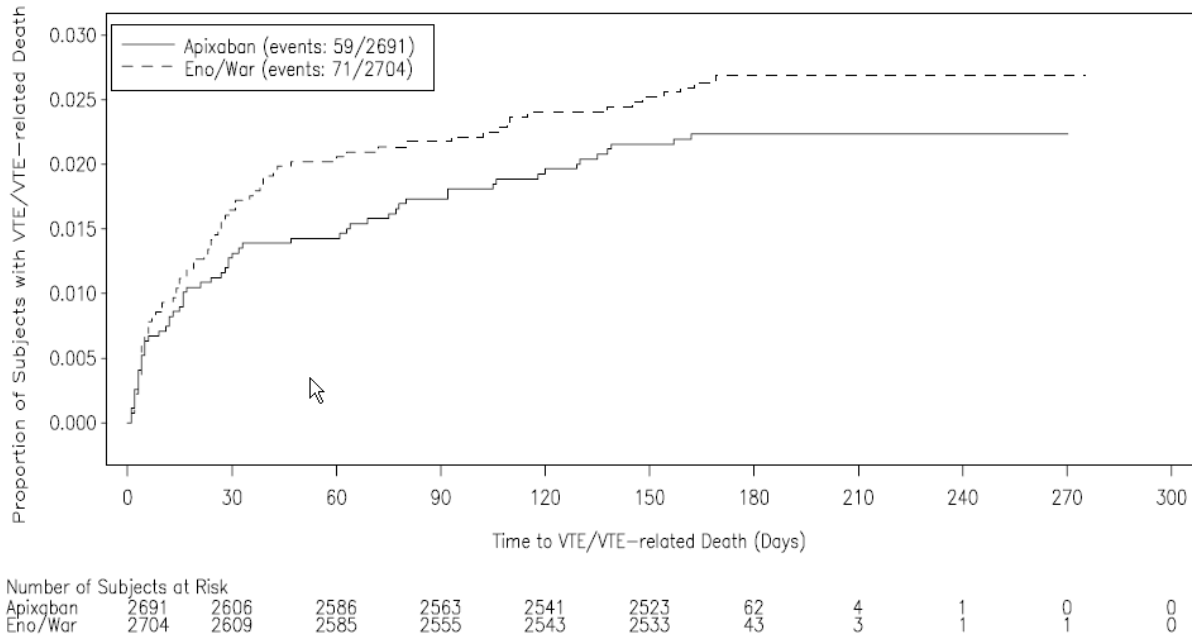
Table 17: Efficacy results in the AMPLIFY study

	Apixaban N=2609 n (%)	Enoxaparin/Warfarin N=2635 n (%)	Relative Risk (95% CI)
VTE or VTE-related death*	59 (2.3)	71 (2.7)	0.84 (0.60, 1.18)
DVT	20 (0.7)	33 (1.2)	
PE	27 (1.0)	23 (0.9)	
VTE-related death	12 (0.4)	15 (0.6)	
VTE or all-cause death	84 (3.2)	104 (4.0)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3)	77 (2.9)	0.80 (0.57, 1.11)
VTE, VTE-related death, or major bleeding	73 (2.8)	118 (4.5)	0.62 (0.47, 0.83)

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

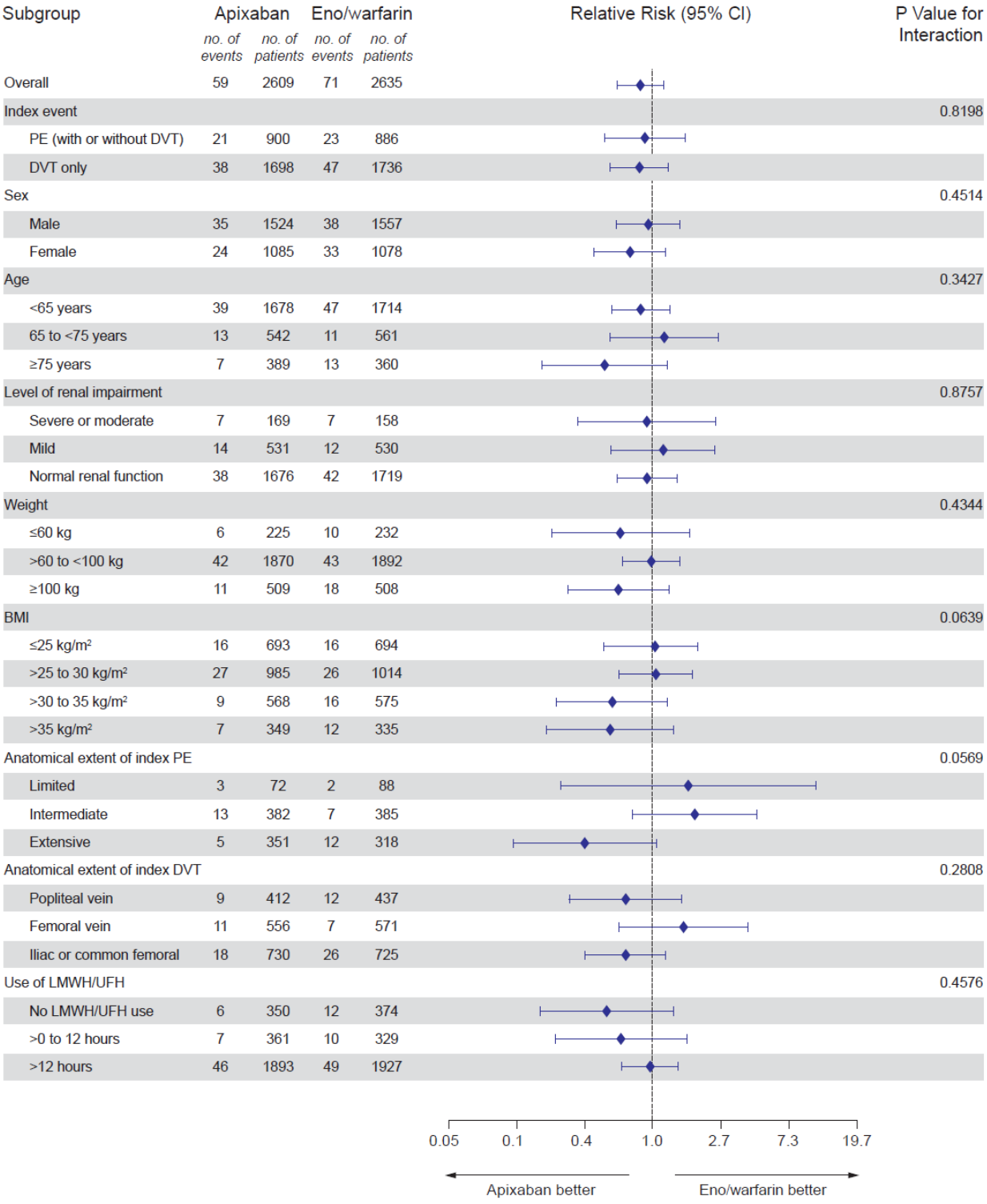
Figure 3 is a plot of the time from randomisation to the occurrence of the first primary efficacy endpoint event in the two treatment groups in the AMPLIFY study.

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

Figure 4: Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death relative risk by baseline characteristics



The primary safety endpoint was major bleeding. In the study, apixaban was statistically superior to enoxaparin/warfarin in the primary safety endpoint [Relative Risk 0.31, 95% confidence interval (0.17, 0.55), P-value <0.0001] (see Table 18).

Table 18: Bleeding results in the AMPLIFY study

	Apixaban N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI*)	P-value
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55)	<0.0001
CRNM†	103 (3.9)	215 (8.0)	0.48 (0.38, 0.60)	
Major + CRNM	115 (4.3)	261 (9.7)	0.44 (0.36, 0.55)	
Minor	313 (11.7)	505 (18.8)	0.62 (0.54, 0.70)	
All	402 (15.0)	676 (25.1)	0.59 (0.53, 0.66)	

* Confidence interval.

† CRNM = clinically relevant nonmajor bleeding.

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

The adjudicated major bleeding and CRNM bleeding at any anatomical site was generally lower in the apixaban group compared to the enoxaparin/warfarin group. Adjudicated ISTH major gastrointestinal bleeding occurred in 6 (0.2%) apixaban-treated patients and 17 (0.6%) enoxaparin/warfarin-treated patients. Adjudicated intracranial bleeding occurred in 3 (0.1%) apixaban-treated patients and 6 (0.2%) enoxaparin/warfarin-treated patients.

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

AMPLIFY-EXT Study

Patients were randomised to treatment with apixaban 2.5 mg twice daily orally, apixaban 5 mg twice daily orally, or placebo for 12 months after completing 6 to 12 months of initial anticoagulant treatment. Approximately one-third of patients participated in the AMPLIFY study prior to enrolment 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 (nonfatal DVT or nonfatal PE) or all-cause death.

In the study, both doses of apixaban were statistically superior to placebo in the primary endpoint of symptomatic, recurrent VTE or all-cause death (see Table 19).

Table 19: Efficacy results in the AMPLIFY-EXT study

	Apixaban 2.5 mg (N=840)	Apixaban 5.0 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI) Apix 2.5 mg vs. Placebo	Relative Risk (95% CI) Apix 5.0 mg vs. Placebo	P-value
		n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15, 0.40)	0.19 (0.11, 0.33)	<0.0001
DVT*	6 (0.7)	7 (0.9)	53 (6.4)			
PE*	7 (0.8)	4 (0.5)	13 (1.6)			

Table 19: Efficacy results in the AMPLIFY-EXT study

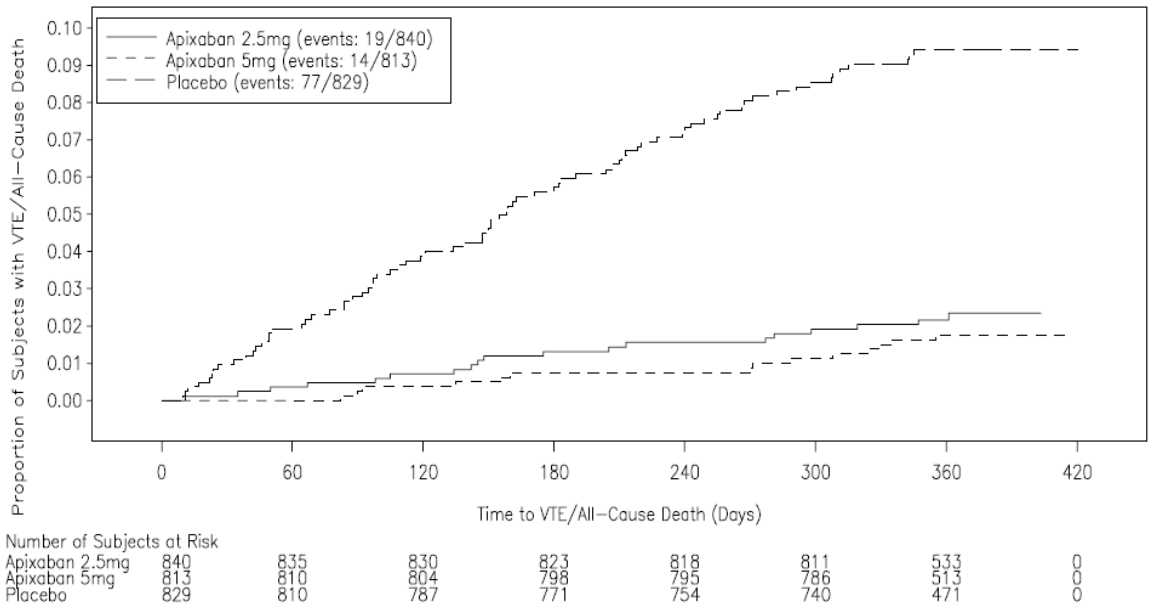
	Apixaban 2.5 mg (N=840)	Apixaban 5.0 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI) Apix 2.5 mg vs. Placebo	Relative Risk (95% CI) Apix 5.0 mg vs. Placebo	P-value
		n (%)				
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)			
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11, 0.33)	0.20 (0.11, 0.34)	
Recurrent VTE or CV-related death	14 (1.7)	14 (1.7)	76 (9.2)	0.18 (0.10, 0.32)	0.19 (0.11, 0.33)	
Nonfatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)	
Nonfatal PE†	8 (1.0)	4 (0.5)	15 (1.8)	0.51 (0.22, 1.21)	0.27 (0.09, 0.80)	
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)	0.28 (0.06, 1.37)	0.45 (0.12, 1.71)	
CV-related death	2 (0.2)	3 (0.4)	10 (1.2)	0.20 (0.04, 0.90)	0.31 (0.09, 1.11)	

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

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

Figure 5 is a plot of the time from randomisation 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 statistically different from the placebo group (see Table 20).

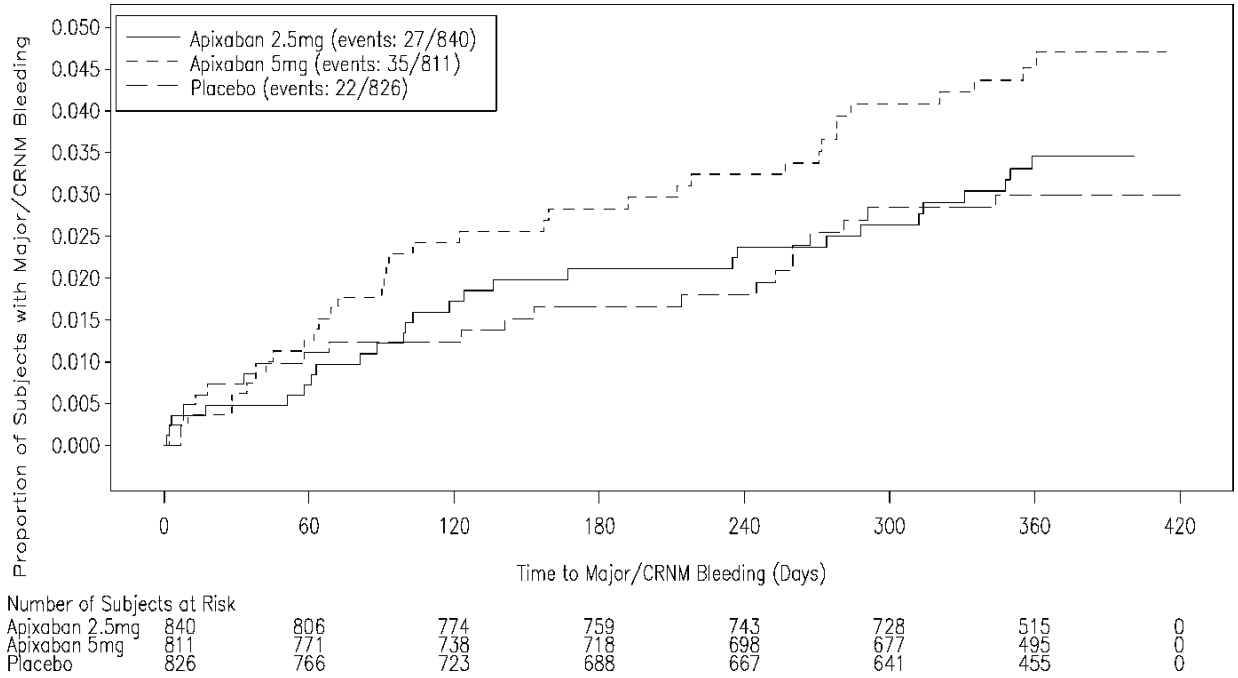
Table 20: Bleeding results in the AMPLIFY-EXT study

	Apixaban	**Apixaban**	**Placebo**	**Relative Risk (95% CI*)**	
	2.5 mg (N=840)	**5.0 mg** (N=811)	(N=826)	**Apix 2.5 mg** vs. Placebo	**Apix 5.0 mg** vs. Placebo
		n (%)			
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)
CRNM†	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72, 2.33)	1.82 (1.05, 3.18)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69, 2.10)	1.62 (0.96, 2.73)
Minor	75 (8.9)	98 (12.1)	58 (7.0)	1.26 (0.91, 1.75)	1.70 (1.25, 2.31)
All	94 (11.2)	121 (14.9)	74 (9.0)	1.24 (0.93, 1.65)	1.65 (1.26, 2.16)

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

Figure 6 is a plot of the time from randomisation 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. Adjudicated intracranial bleeding occurred in none of the apixaban-treated patients and 1 (0.1%) placebo-treated patient.

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was comparable to exposure after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, C_{max} and $AUC_{(inf)}$ and $AUC_{(0\text{-}T)}$ were, respectively, 21.2%, 16.5% and 16.8% lower respectively, when compared to administration of 2 intact 5 mg tablets.

Following administration of a crushed 5 mg apixaban tablet suspended in 60 mL of 5% dextrose in water (D5W) and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical trials involving healthy subjects receiving a single oral 5 mg apixaban tablet dose.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (V_{ss}) is approximately 21 litres.

Metabolism and Elimination

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

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

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

Special Populations

Elderly

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher. No dose adjustment is required, except for atrial fibrillation patients with at least two of the following criteria; age ≥80 years, body weight ≤60 kg, serum creatinine ≥133 µmol/L (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation, Use in the Elderly, Use in Renal Impairment and Body Weight).

Children and Adolescents

The efficacy and safety of APIXABAN-APX in children and adolescents below age 18 have not been established. No data are available.

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

Body Weight

Compared with apixaban exposure in subjects with body weight of 65 to 85 kg, body weight >120 kg was associated with approximately 30% lower exposure and body weight <50 kg was associated with approximately 30% higher exposure. No dose adjustment is required; except for atrial fibrillation patients with at least two of the following criteria; a body weight ≤60 kg and age ≥80 years, serum creatinine ≥133 µmol/L (see section 4.2).

Renal Impairment

If there is a suspicion of renal impairment, the degree of renal impairment must be determined accurately. Caution must be exercised when renal function estimates are based on eGFR.

In clinical trials, renal function was determined using the calculated creatinine clearance, using the Cockcroft-Gault Formula as follows:

For serum creatinine concentration in mg/100 mL:

$$\textit{Creatinine Clearance [mL/min]} = \frac{\textit{(140–age [years]) x weight [kg]}}{\textit{72 x serum creatinine [mg/100 mL]}} \textit{ x (0.85 for women)}$$

For serum creatinine concentration in µmol/L:

$$\textit{Creatinine Clearance [mL/min]} = \frac{\textit{1.23 x (140–age [years]) x weight [kg]}}{\textit{serum creatinine [µmol/L]}} \textit{ x (0.85 for women)}$$

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

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36%, compared to that seen in subjects with normal renal function, when a single dose of apixaban 5 mg was administered immediately after haemodialysis. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14% in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min.

No dose adjustment is necessary in patients with mild or moderate renal impairment.

As there is no clinical experience in patients with renal impairment <15 mL/min or in patients undergoing dialysis APIXABAN-APX is contraindicated in these patients. There is limited experience in patients with renal impairment 15 mL to <25 mL/min with increased apixaban exposure, therefore, APIXABAN-APX is also contraindicated in these patients (see section 4.3).

Dose adjustment is recommended for atrial fibrillation patients with at least two of the following criteria; serum creatinine ≥133 µmol/L, age ≥80 years, body weight ≤60 kg (see section 4.2, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation and section 4.4, Use in Renal Impairment).

Hepatic Impairment

Apixaban has not been studied in patients with severe hepatic impairment or active hepatobiliary disease. Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see section 4.3).

No dose adjustment is required in patients with mild or moderate hepatic impairment; however, given the limited number of subjects studied, caution is advised when using APIXABAN-APX

in this population (see section 4.2, Use in Hepatic Impairment and section 4.4, Use in Hepatic Impairment).

In a study comparing subjects with mild and moderate hepatic impairment (classified as Child-Pugh A and B, respectively) to healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-FXa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Pharmacokinetic/Pharmacodynamic Relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5-50 mg). The relationship between apixaban plasma concentration and anti-FXa activity was best described by a linear model. The PK/PD relationship observed in patients who received apixaban in phase II or phase III clinical studies was consistent with that established in healthy subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Apixaban did not induce gene mutations in bacteria (Salmonella typhimurium) or chromosomal damage in mammalian cells (Chinese hamster ovary cells) *in vitro* and lymphocytes in rats *in vivo*. There was no evidence of genotoxic potential in a micronucleus test in rats. The oral doses in the rat lymphocyte chromosome aberration study at up to 600 mg/kg/day for 30 days resulted in plasma apixaban concentrations 4 times the human exposure at 5 mg twice daily based on free fraction C_{max}.

Carcinogenicity

Long term studies in mice and rats at dietary doses up to 1500 and 600 mg/kg/day, respectively, did not show any evidence of carcinogenic potential. These doses resulted in plasma apixaban concentrations 42 times (mice) and 8 times (rat) human values at 2.5 mg twice daily, or 9 to 21 times (mouse) and 3 times (rat) human values at 5 mg twice daily based on free fraction AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose
Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate
Magnesium stearate.

Film coating contains:
Lactose monohydrate
Hypromellose
Titanium dioxide
Glycerol triacetate
Yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. This medicine does not require any special storage condition.

6.5 NATURE AND CONTENTS OF CONTAINER

APIXABAN-APX containing 2.5 mg apixaban is available in the following pack configurations:

- Cartons containing PVC/PVDC blisters of 20 or 60 film-coated tablets.

APIXABAN-APX containing 5 mg apixaban is available in the following pack configurations:

- Cartons containing PVC/PVDC blisters of 60 film-coated tablets.

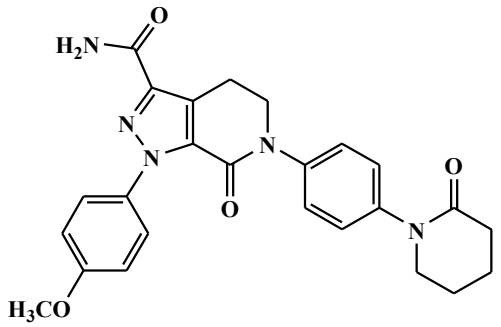
Not all pack sizes and container types may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Apixaban, a selective inhibitor of the coagulation Factor Xa (FXa), is chemically described as 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. Its molecular formula is $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



CAS Number: 503612-47-3

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. The octanol/water partition coefficient is 44.7 at pH 7.4.

7 MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine.

8 SPONSOR

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Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

DISTRIBUTED BY:

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9 DATE OF FIRST APPROVAL

22 January 2026

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information