



## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

APACLOT 5 mg Film Coated Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

**Active substance:**

Apixaban..... 5 mg

**Excipients with known effect:**

Anhydrous lactose (from cow's milk)..... 100.5 mg

Lactose monohydrate (from bovine milk)..... 3.2 mg

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink-colored, oval, biconvex film-coated tablets.

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age  $\geq$  75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class  $\geq$  II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for hemodynamically unstable PE patients).

#### 4.2. Posology and method of administration

##### Posology, frequency and duration of administration

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

The recommended dose of APACLOT is 5 mg taken orally twice daily.

##### Dose reduction

The recommended dose of APACLOT is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age  $\geq$  80 years, body weight  $\leq$  60 kg, or serum creatinine  $\geq$  1.5 mg/dL (133 micromole/L). Therapy should be continued long-term.

##### Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (Treatment of VTE)

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

The recommended dose of APACLOT for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with APACLOT 5 mg twice daily or with another anticoagulant, as indicated in table below (see also section 5.1).



**Table 1: Dose recommendation for treatment of VTE**

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be individualized after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

### Method of administration

For oral use. APACLOT should be swallowed with water, with or without food.

For patients unable to swallow whole tablets, APACLOT tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally (see section 5.2). Alternatively, APACLOT tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube (see section 5.2). Crushed APACLOT tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

### Additional information on special populations

#### Renal impairment

In patients with mild or moderate renal impairment, the following recommendations apply:

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, no dose adjustment is necessary (see section 5.2).
- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf) and serum creatinine  $\geq 1.5$  mg/dL (133 micromole/L) associated with age  $\geq 80$  years or body weight  $\leq 60$  kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2).

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

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, APACLOT is to be used with caution;
- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf), patients should receive the lower dose of APACLOT 2.5 mg twice daily.

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

#### Hepatic impairment

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

APACLOT is not advised in patients with severe hepatic impairment (see sections 4.4. and 5.2).

APACLOT should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST)  $> 2$  x ULN or total bilirubin  $\geq 1.5$  x ULN were excluded in clinical studies. Therefore, apixaban should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating apixaban, liver function testing should be performed.



### **Pediatric population**

The safety and efficacy of apixaban in children and adolescents below age 18 have not been established. Currently available data on thromboembolism prevention are described in section 5.1 but no recommendation on a posology can be made.

### **Geriatric population**

Treatment of VTE: No dose adjustment required (see sections 4.4 and 5.2).

NVAF: No dose change needed, unless criteria for dose reduction are met (see section 4.2 Dose reduction).

### **Patients undergoing catheter ablation**

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

### **Patients undergoing cardioversion**

Apixaban can be initiated or continued in NVAF patients who may require cardioversion.

For patients not previously treated with anticoagulants, exclusion of left atrial thrombus using an image-guided approach (e.g. transesophageal echocardiography (TEE) or computed tomographic scan (CT)) prior to cardioversion should be considered, in accordance with established medical guidelines.

For patients initiating treatment with apixaban, 5 mg should be given twice daily for at least 2.5 days (5 consecutive doses in total) before cardioversion to ensure adequate anticoagulation (see section 5.1). The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 consecutive doses in total), if the patient meets the criteria for dose reduction (see sections OF Dose reduction and Renal impairment).

If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction (see sections of Dose reduction and Renal impairment). The administration of the loading dose should be given at least 2 hours before cardioversion (see section 5.1).

For all patients undergoing cardioversion, confirmation should be sought prior to cardioversion that the patient has taken apixaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

### **Patients with NVAF and acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI)**

There is limited experience of treatment with apixaban at the recommended dose for NVAF patients when used in combination with antiplatelet agents in patients with ACS and/or undergoing PCI after hemostasis is achieved (see sections 4.4, 5.1).

### **Body weight**

Treatment of VTE: No dose adjustment required (see sections 4.4 and 5.2).

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

### **Gender**

No dose adjustment required (see section 5.2).



### Switching from other medicines to APACLOT

Switching treatment from parenteral anticoagulants to APACLOT (and vice versa) can be done at the next scheduled dose (see section 4.5). These medicinal products should not be administered simultaneously.

### Switching from vitamin K antagonist (VKA) therapy to APACLOT

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

### Switching from APACLOT to VKA therapy

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

### Missed dose

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

## 4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active clinically significant bleeding.
- Hepatic disease related to coagulopathy and clinically relevant bleeding risk (see section 5.2).
- Lesion or condition if considered a significant risk factor for 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 hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2), when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter or when unfractionated heparin is given during catheter ablation for atrial fibrillation (see sections 4.4 and 4.5).

## 4.4. Special warnings and precautions for use

### Hemorrhage risk

As with other anticoagulants, patients taking APACLOT are to be carefully observed for signs of bleeding. APACLOT is recommended to be used with caution in conditions with increased risk of hemorrhage. APACLOT administration should be discontinued if severe hemorrhage occurs (see sections 4.8 and 4.9).

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

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



#### Interaction with other medicinal products affecting hemostasis

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

Concomitant APACLOT use with antiplatelet agents increases the risk of bleeding (see section 4.5).

Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with APACLOT (see section 4.5).

In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with apixaban.

In a clinical trial of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.1%) use of concomitant dual antiplatelet therapy (see section 5.1).

A clinical trial enrolled patients with atrial fibrillation with ACS and/or undergoing PCI and a planned treatment period with a P2Y12 inhibitor, with or without ASA, and oral anticoagulant (either apixaban or VKA) for 6 months. Concomitant use of ASA increased the risk of ISTH (International Society on Thrombosis and Hemostasis) major or CRNM (Clinically Relevant Non-Major) bleeding in apixaban treated subjects from 16.4% per year to 33.1% per year (see section 5.1).

In a clinical trial of high-risk post-acute coronary syndrome patients without atrial fibrillation, characterized by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).

#### Use of thrombolytic agents for the treatment of acute ischemic stroke

There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered apixaban (see section 4.5).

#### Patients with prosthetic heart valves

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

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that 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.

#### Surgery and invasive procedures

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



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

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

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

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

#### Temporary discontinuation

Discontinuing anticoagulants, including APACLOT, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with APACLOT must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

#### Hemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

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

#### Patients with active cancer

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

#### Patients with renal impairment

Limited clinical data indicate that apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15-29 mL/min) which may lead to an increased bleeding risk.

For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, APACLOT is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min) (see sections 4.2 and 5.2).

For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine  $\geq 1.5$  mg/dL (133 micromole/L) associated with age  $\geq 80$  years or body weight  $\leq 60$  kg should receive the lower dose of APACLOT 2.5 mg twice daily (see section 4.2).

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

#### Elderly patients

Increasing age may increase hemorrhagic risk (see section 5.2).

In addition, the coadministration of APACLOT with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

#### Body weight

Low body weight ( $< 60$  kg) may increase hemorrhagic risk (see section 5.2).



#### Patients with hepatic impairment

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

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

APACLOT should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2 and 5.2).

Patients with elevated liver enzymes  $ALT/AST > 2 \times ULN$  or total bilirubin  $\geq 1.5 \times ULN$  were excluded in clinical trials. Therefore, apixaban should be used cautiously in this population (see section 5.2). Prior to initiating apixaban, liver function testing should be performed.

#### Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)

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

#### Interaction with inducers of both CYP3A4 and P-gp

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

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the prevention of recurrent DVT and PE, APACLOT should be used with caution;
- For the treatment of DVT and treatment of PE, APACLOT should not be used since efficacy may be compromised

#### Laboratory parameters

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

#### Information about excipients

APACLOT contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### **4.5. Interaction with other medicinal products and other forms of interaction**

#### Inhibitors of CYP3A4 and P-gp

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

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

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg., amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to



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

#### Inducers of CYP3A4 and P-gp

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

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

#### Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated except under specific circumstances of switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (see section 4.3).

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

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

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

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

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are coadministered with apixaban. Apixaban should be used with caution when coadministered with SSRIs/SNRIs or NSAIDs, ASA and/or P2Y<sub>12</sub> inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

There is limited experience of co-administration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfinpyrazone) or thrombolytic agents. As such agents increase the bleeding risk, co-administration of these products with Apixaban is not



recommended (see section 4.4).

#### Other concomitant therapies

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

#### Effect of apixaban on other medicinal products

*In vitro* apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 ( $IC_{50} > 45 \mu M$ ) and weak inhibitory effect on the activity of CYP2C19 ( $IC_{50} > 20 \mu M$ ) 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  $\mu M$ . Therefore, apixaban is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

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

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

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

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

#### Activated charcoal

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

### **Additional information on special populations**

#### Pediatric population

Interaction studies have been conducted in adults only.

### **4.6. Fertility, pregnancy and lactation**

#### **General recommendation**

Pregnancy category “B”.

#### **Women of childbearing potential / Contraception**

Women of childbearing potential are recommended to use an effective method of contraception during treatment with apixaban.

#### **Pregnancy**

As a precaution, it is preferable to avoid the use of APACLOT during pregnancy. There are no data on the use of apixaban during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity



(see section 5.3).

### **Breast-feeding**

It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk (see section 5.3). A risk to newborns and infants cannot be excluded.

A decision must be made either to discontinue breast-feeding or to discontinue/abstain from apixaban therapy. While making this decision, the benefits of breastfeeding for the child and the necessity of treatment for the mother should be considered.

### **Reproductive ability / Fertility**

Studies in animals dosed with apixaban have shown no effect on fertility (see section 5.3).

### **4.7. Effects on ability to drive and use machines**

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

### **4.8. Undesirable effects**

#### Summary of the safety profile

Apixaban safety has been searched in 4 Phase III clinical studies including more than 15,000 patients: more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment studies, for an average total exposure of 1.7 years and 221 days respectively (see section 5.1).

Common adverse reactions were hemorrhage, contusion, epistaxis, and hematoma. Adverse reaction profile is given below based on indication.

In the NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and 9.6% in the apixaban vs acetylsalicylic acid study.

In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

In the VTE treatment studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15.6% in the apixaban vs enoxaparin/warfarin study and 13.3% in the apixaban vs placebo study (see section 5.1).

#### List of adverse reactions

The adverse reactions ranked under headings of system organ class and frequency using the following convention: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data)



**Table 2: Tabulated list of adverse reactions**

System Organ Class	Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors	Treatment of DVT and PE, and prevention of recurrent DVT and PE (Treatment of VTE)
<b>Blood and lymphatic system disorders</b>		
Anemia	Common	Common
Thrombocytopenia	Uncommon	Common
<b>Immune system disorders</b>		
Hypersensitivity, allergic edema and anaphylaxis	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon*
Angioedema	Not known	Not known
<b>Nervous system disorders</b>		
Brain hemorrhage <sup>†</sup>	Uncommon	Rare
<b>Eye disorders</b>		
Eye hemorrhage (including conjunctival hemorrhage)	Common	Uncommon
<b>Vascular disorders</b>		
Hemorrhage, hematoma	Common	Common
Hypotension (including procedural hypotension)	Common	Uncommon
Intra-abdominal hemorrhage	Uncommon	Not known
<b>Respiratory, thoracic and mediastinal disorders</b>		
Epistaxis	Common	Common
Hemoptysis	Uncommon	Uncommon
Respiratory tract hemorrhage	Rare	Rare
<b>Gastrointestinal disorders</b>		
Nausea	Common	Common
Gastrointestinal hemorrhage	Common	Common
Hemorrhoidal hemorrhage	Uncommon	Uncommon
Mouth hemorrhage	Uncommon	Common
Hematochezia	Uncommon	Uncommon
Rectal hemorrhage, gingival bleeding	Common	Common
Retroperitoneal hemorrhage	Rare	Not known
<b>Hepatobiliary disorders</b>		
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon



System Organ Class	Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors	Treatment of DVT and PE, and prevention of recurrent DVT and PE (Treatment of VTE)
Gamma-glutamyltransferase increased	Common	Common
Alanine aminotransferase increased	Uncommon	Common
<b>Skin and subcutaneous tissue disorders</b>		
Skin rash	Uncommon	Common
Alopecia	Uncommon	Uncommon
Erythema multiforme	Very rare	Not known
Cutaneous vasculitis	Not known	Not known
<b>Musculoskeletal and connective tissue disorders</b>		
Muscle hemorrhage	Rare	Uncommon
<b>Renal and urinary disorders</b>		
Hematuria	Common	Common
<b>Reproductive system and breast disorders</b>		
Abnormal vaginal hemorrhage, urogenital hemorrhage	Uncommon	Common
<b>General disorders and administration site conditions</b>		
Application site bleeding	Uncommon	Uncommon
<b>Investigations</b>		
Ocult blood positive	Uncommon	Uncommon
<b>Injury, poisoning and procedural complications</b>		
Contusion	Common	Common
Post procedural hemorrhage (including post procedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage), wound secretion, incision site hemorrhage (including incision site hematoma), operative hemorrhage	Uncommon	Uncommon
Traumatic hemorrhage	Uncommon	Uncommon

\* There were no occurrences of generalized pruritus in CV185057 (long-term prevention of VTE)

† The term "Brain hemorrhage" encompasses all intracranial or intraspinal hemorrhages (i.e., hemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural hemorrhages).

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

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 via the national reporting system.

#### 4.9. Overdose

Overdose of APACLOT may result in a higher risk of bleeding. In the event of hemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical hemostasis, the transfusion of fresh frozen plasma or the administration of a reversal agent for factor Xa inhibitors should be considered.

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

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

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). Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered. Reversal of apixaban pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 4-factor PCC 30 minute infusion in healthy subjects. However, there is no clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received apixaban. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.

Hemodialysis decreased apixaban AUC by 14% in subjects with end-stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, hemodialysis is unlikely to be an effective means of managing apixaban overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Direct factor Xa inhibitors

ATC code: B01AF02

#### Mechanism of action

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

#### Pharmacodynamic effects

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



recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-FXa kits, however results differ across kits. Data from clinical trials are only available for the Rotachrom® Heparin chromogenic assay. 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 approximately linear over a wide dose range of apixaban.

The following table shows the predicted steady state exposure and anti-Factor Xa activity. In NVAF patients taking apixaban for the prevention of stroke and systemic embolism, the results demonstrate a less than 1.7-fold fluctuation in peak-to-trough levels. In patients taking apixaban for the treatment of DVT and PE or prevention of recurrent DVT and PE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

**Table 3. Predicted apixaban steady-state exposure and anti-Factor Xa activity**

	Apixaban C <sub>max</sub> (ng/ml)	Apixaban C <sub>min</sub> (ng/ml)	Apixaban anti-Factor Xa Activity Max (IU/mL)	Apixaban anti-Factor Xa Activity Min (IU/mL)
Median [5th, 95th Percentile]				
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69 - 221]	79 [34 - 162]	1.8 [1 - 3.3]	1.2 [0.51 - 2.4]
5 mg twice daily	171 [91 - 321]	103 [41 - 230]	2.6 [1.4 - 4.8]	1.5 [0.61 - 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (treatment of VTE)				
2.5 mg twice daily	67 [30 - 153]	32 [11 - 90]	1 [0.46 - 2.5]	0.49 [0.17 - 1.4]
5 mg twice daily	132 [59 - 302]	63 [22 - 177]	2.1 [0.91 - 5.2]	1 [0.33 - 2.9]
10 mg twice daily	251 [111 - 572]	120 [41 - 335]	4.2 [1.8 - 10.8]	1.9 [0.64 - 5.8]

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

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

### Clinical efficacy and safety

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

- prior stroke or transient ischemic attack (TIA)
- age  $\geq$ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class  $\geq$  II)

### ARISTOTLE STUDY

In the ARISTOTLE study, a total of 18,201 patients were randomized to double-blind treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [4.7%], see section 4.2) or warfarin (target INR range 2.0-3.0), patients were exposed to study drug for a mean of 20 months. The mean age was 69.1 years, the mean CHADS2 score was 2.1 and 18.9% of patients had prior



stroke or TIA.

In the study, apixaban achieved statistically significant superiority in primary endpoint of prevention of stroke (hemorrhagic or ischemic) and systemic embolism (see table 4) compared with warfarin.

**Table 4: Efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study**

	Apixaban N=9,120 n (%/year)	Warfarin N=9,081 n (%/year)	Hazard ratio (95% CI)	p-value
Stroke or systemic embolism	212 (1.27)	265 (1.6)	0.79 (0.66-0.95)	0.0114
Stroke				
- Ischemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74-1.13)	
- Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35-0.75)	
Systemic embolism	15 (0.09)	17 (0.1)	0.87 (0.44-1.75)	

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

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

Key secondary endpoints of major bleeding and all cause death were tested in a pre-specified hierarchical testing strategy to control the overall type 1 error in the trial. Statistically significant superiority was also achieved in the key secondary endpoints of both major bleeding and all-cause death (see table 5). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

**Table 5: Secondary endpoints in patients with atrial fibrillation in the ARISTOTLE study**

	Apixaban N=9,088 n (%/year)	Warfarin N=9,052 n (%/year)	Hazard Ratio (95% CI)	p-value
<b>Bleeding outcomes</b>				
Major*	327 (2.13)	462 (3.09)	0.69 (0.6- 0.8)	<0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM†	613 (4.07)	877 (6.01)	0.68 (0.61- 0.75)	<0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68- 0.75)	<0.0001
<b>Other endpoints</b>				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80- 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66- 1.17)	

\* Major bleeding defined per ISTH criteria.

† Clinically Relevant Non-Major

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

The efficacy results for prespecified subgroups, including CHADS<sub>2</sub> score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

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



The major bleeding results for prespecified subgroups including CHADS<sub>2</sub> score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the results for the overall population studied in the trial.

**AVERROES study**

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomized to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], see section 4.2) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study drug for a mean of 14 months. The mean age was 69.9 years, the mean CHADS<sub>2</sub> score was 2.0 and 13.6% of patients had prior stroke or TIA.

Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS<sub>2</sub> score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medicinal product instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

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

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

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (hemorrhagic, ischemic or unspecified) or systemic embolism (see table 6) compared to ASA.

**Table 6: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study**

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

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

† Secondary endpoint.

There was no statistically significant difference in the incidence of major bleeding between apixaban (see table 7).

**Table 7: Bleeding events in patients with atrial fibrillation in the AVERROES study**

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

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

† Clinically Relevant Non-Major

NVAF patients with ACS and/or undergoing PCI

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

Patients were randomized up to 14 days after the ACS and/or PCI to either apixaban 5 mg twice daily (2.5 mg twice daily if two or more of the dose-reduction criteria were met; 10% received lower dose) or VKA and to either ASA (81 mg once daily) or placebo. The mean age was 69.9 years, 94% of patients randomized had a CHA2DS2-VASc score > 2, and 47% had a HAS-BLED score > 3. For patients randomized to VKA, the proportion of time in therapeutic range (TTR) (INR 2-3) was 56%, with 32% of time below TTR and 12% above TTR.

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

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

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

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

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

In the ASA versus placebo comparison, the composite endpoint of death or re-hospitalization



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

#### Patients undergoing cardioversion

EMANATE, an open-label, multi-center study, enrolled 1500 patients who were either oral anticoagulant naïve or pre-treated less than 48 hours and scheduled for cardioversion for NVAF. Patients were randomized 1:1 to apixaban or to heparin and/or VKA for the prevention of cardiovascular events. Electrical and/or pharmacologic cardioversion was conducted after at least 5 doses of 5 mg twice daily apixaban (or 2.5 mg twice daily in selected patients (see section 4.2)) or at least 2 hours after a 10 mg loading dose (or a 5 mg loading dose in selected patients (see section 4.2)) if earlier cardioversion was required. In the apixaban group, 342 patients received a loading dose (331 patients received the 10 mg dose and 11 patients received the 5 mg dose).

There were no strokes (0%) in the apixaban group (n=753) and 6 (0.8%) strokes in the heparin and/or VKA group (n=747; RR 0.00, 95% CI 0.00, 0.64). All-cause death occurred in 2 patients (0.27%) in the apixaban group and 1 patient (0.13%) in the heparin and/or VKA group. No systemic embolism events were reported.

Major bleeding and CRNM bleeding events occurred in 3 (0.41%) and 11 (1.5%) patients, respectively, in the apixaban group, compared to 6 (0.83%) and 13 (1.8%) patients in the heparin and/or VKA group.

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

#### Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (Treatment of VTE)

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

#### AMPLIFY study

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

The mean age was 56.9 years and 89.8% of randomized patients had unprovoked VTE events. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9. Apixaban showed a reduction in recurrent symptomatic VTE or VTE-related death across the different levels of center TTR; within the highest quartile of TTR according to center, the relative risk for apixaban vs enoxaparin/warfarin was 0.79 (95% CI, 0.39, 1.61).

In the study, apixaban was shown to be non-inferior to enoxaparin/warfarin in the combined primary endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death (see table 8).



**Table 8: Efficacy results in the AMPLIFY study**

	<b>Apixaban N=2,609 n (%)</b>	<b>Enoxaparin/Warfarin N=2,635 n (%)</b>	<b>Relative Risk (%95 CI)</b>
VTE or VTE-related death	59 (2.3)	71 (2.7)	0.84 (0.6-1.18)*
DVT	20 (0.7)	33 (1.2)	
PE	27 (1)	23 (0.9)	
VTE-related death	12 (0.4)	15 (0.6)	
VTE or all-cause death	84(3.2)	104 (4)	0.82 (0.61-1.08)
VTE or CV-related death	61 (2.3)	77 (2.9)	0.80 (0.57-1.11)
VTE, VTE-related death, or major bleeding	73 (2.8)	118 (4.5)	0.62 (0.47-0.83)

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

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

The primary safety endpoint was major bleeding. In the study, apixaban was statistically superior to enoxaparin/warfarin in the primary safety endpoint [Relative Risk 0.31, 95% confidence interval (0.17, 0.55), P-value <0.0001] (see table 9).

**Table 9: Bleeding results in the AMPLIFY study**

	<b>Apixaban N=2,676 n (%)</b>	<b>Enoxaparin/Warfarin N=2,689 n (%)</b>	<b>Relative Risk (95% CI)</b>
Major	15 (0.6)	49 (1.8)	0.31 (0.17-0.55)
Major + CRNM	115 (4.3)	261 (9.7)	0.44 (0.36-0.55)
Minor	313 (11.7)	505 (18.8)	0.62 (0.54-0.7)
All	402 (15)	676 (25.1)	0.59 (0.53-0.66)

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

#### AMPLIFY-EXT study

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

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



In the study, both doses of apixaban were statistically superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death (see table 10).

**Table 10: Efficacy results in the AMPLIFY-EXT study**

	Apixaban	Apixaban	Placebo (N=829)	Relative Risk (95% CI)	
	2.5 mg (N=840)	5 mg (N=813)		Apixaban 2.5 mg vs. placebo	Apixaban 5 mg vs. placebo
	n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15- 0.4)*	0.19 (0.11- 0.33)*
DVT**	6 (0.7)	7 (0.9)	53 (6.4)		
PE**	7 (0.8)	4 (0.5)	13 (1.6)		
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)		
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11-0.33)	0.20 (0.11-0.34)
Recurrent VTE or CV-related death	14 (1.7)	14 (1.7)	76 (9.2)	0.18 (0.10-0.32)	0.19 (0.11-0.33)
Nonfatal DVT***	6 (0.7)	8 (1)	53 (6.4)	0.11 (0.05-0.26)	0.15 (0.07-0.32)
Nonfatal PE***	8 (1)	4 (0.5)	15 (1.8)	0.51 (0.22-1.21)	0.27 (0.09-0.80)
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)	0.28 (0.06-1.37)	0.45 (0.12-1.71)

\*p-value < 0.0001

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

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

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

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo.

There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see table 11).

**Table 11: Bleeding results in the AMPLIFY-EXT study**

	Apixaban	Apixaban	Placebo (N=826)	Relative Risk (95% CI)	
	2.5 mg (N=840)	5 mg (N=811)		Apixaban 2.5 mg vs. placebo	Apixaban 5 mg vs. placebo
	n (%)				
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09-2.64)	0.25 (0.03-2.24)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)	1.2 (0.69-2.10)	1.62 (0.96-2.73)
Minor	75 (8.9)	98 (12.1)	58 (7)	1.26 (0.91-1.75)	1.7 (1.25-2.31)
All	94 (11.2)	121 (14.9)	74 (9)	1.24 (0.93-1.65)	1.65 (1.26-2.16)



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

### Pediatric population

There is no authorized pediatric indication (see section 4.2).

#### Prevention of VTE in pediatric patients with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL)

In the PREVAPIX-ALL study, a total of 512 patients age  $\geq 1$  to  $< 18$  with newly diagnosed ALL or LL, undergoing induction chemotherapy including asparaginase via an indwelling central venous access device, were randomized 1:1 to open-label thromboprophylaxis with apixaban or standard of care (with no systemic anticoagulation). Apixaban was administered according to a fixed-dose, body weight-tiered regimen designed to produce exposures comparable to those seen in adults who received 2.5 mg twice daily (see Table 12). Apixaban was provided as a 2.5 mg tablet, 0.5 mg tablet, or 0.4 mg/mL oral solution. The median duration of exposure in the apixaban arm was 25 days.

**Table 12: Apixaban Dosing in the PREVAPIX-ALL Study**

Weight Range	Dose Schedule
6 to $< 10.5$ kg	0.5 mg twice daily
10.5 to $< 18$ kg	1 mg twice daily
18 to $< 25$ kg	1.5 mg twice daily
25 to $< 35$ kg	2 mg twice daily
$\geq 35$ kg	2.5 mg twice daily

The primary efficacy endpoint was a composite of adjudicated symptomatic and asymptomatic non-fatal deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, and venous thromboembolism-related death. The incidence of the primary efficacy endpoint was 31 (12.1%) in the apixaban arm versus 45 (17.6%) in the standard of care arm. The relative risk reduction did not achieve significance.

Safety endpoints were adjudicated according to ISTH criteria. The primary safety endpoint, major bleeding, occurred in 0.8% of patients in each treatment arm. CRNM bleeding occurred in 11 patients (4.3%) in the apixaban arm and 3 patients (1.2%) in the standard of care arm. The most common CRNM bleeding event contributing to the treatment difference was mild to moderate intensity epistaxis. Minor bleeding events occurred in 37 patients in the apixaban arm (14.5%) and 20 patients (7.8%) in the standard of care arm.

Prevention of thromboembolism (TE) in pediatric patients with congenital or acquired heart disease  
SAXOPHONE was a randomized 2:1 open-label, multi-center comparative study of patients 28 days to  $< 18$  years of age with congenital or acquired heart disease who require anticoagulation. Patients received either apixaban or standard of care thromboprophylaxis with a vitamin K antagonist or low molecular weight heparin. Apixaban was administered according to a fixed-dose, body weight-tiered regimen designed to produce exposures comparable to those seen in adults who received a dose of 5 mg twice daily (see Table 13). Apixaban was provided as a 5 mg tablet, 0.5 mg tablet, or 0.4 mg/mL oral solution. The mean duration of exposure in the apixaban arm was 331 days.

**Table 13: Apixaban Dosing in the SAXOPHONE Study**

Weight Range	Dose Schedule
6 to $< 9$ kg	1 mg twice daily
9 to $< 12$ kg	1.5 mg twice daily



12 to <18 kg	2 mg twice daily
18 to <25 kg	3 mg twice daily
25 to <35 kg	4 mg twice daily
≥35 kg	5 mg twice daily

The primary safety endpoint, a composite of adjudicated ISTH defined major and CRNM bleeding, occurred in 1 (0.8%) of 126 patients in the apixaban arm and 3 (4.8%) of 62 patients in the standard of care arm. The secondary safety endpoints of adjudicated major, CRNM, and all bleeding events were similar in incidence across the two treatment arms. The secondary safety endpoint of drug discontinuation due to adverse event, intolerability, or bleeding was reported in 7 (5.6%) subjects in the apixaban arm and 1 (1.6%) subject in the standard of care arm. No patients in either treatment arm experienced a thromboembolic event. There were no deaths in either treatment arm.

This study was prospectively designed for descriptive efficacy and safety because of the expected low incidence of TE and bleeding events in this population. Due to the observed low incidence of TE in this study, a definitive risk benefit assessment could not be established.

The European Medicines Agency has deferred the obligation to submit the results of studies for the treatment of venous thromboembolism in one or more subsets of the pediatric population (see section 4.2 for information on pediatric use).

## 5.2. Pharmacokinetic properties

### General particulars

#### 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  $\geq 25$  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  $\sim 20\%$  CV and  $\sim 30\%$  CV, respectively.

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 ml of water, exposure was comparable to exposure after oral administration of 2 whole 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets with 30 g of apple puree, the  $C_{max}$  and AUC were 21% and 16% lower, respectively, when compared to administration of 2 whole 5 mg tablets. The reduction in exposure is not considered clinically relevant.

Following administration of a crushed 5 mg apixaban tablet suspended in 60 ml of 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.

Given the predictable, dose-proportional pharmacokinetic profile of apixaban, the bioavailability results from the conducted studies are applicable to lower apixaban doses.

#### Distribution

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

#### Biotransformation

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of



biotransformation. Apixaban is metabolized mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present.

#### Elimination

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with majority recovered in feces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

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

#### Linearity/Nonlinearity:

Apixaban pharmacokinetics are linear and increase proportionally with exposure at oral doses up to 10 mg. Apixaban shows reduced bioavailability with dissolution-limited absorption at doses  $\geq 25$  mg.

### **Characteristics in patients**

#### Renal impairment

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

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

#### Hepatic impairment

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

#### Geriatric population

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

#### Gender

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



#### Ethnic origin and race

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

#### Body weight

Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30% lower exposure and body weight < 50 kg was associated with approximately 30% higher exposure.

#### **Pharmacokinetic/pharmacodynamic relationship**

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-Factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

#### **5.3. Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-fetal development and juvenile toxicity.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the toxicity studies, little to no increase of bleeding tendency was found. However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

In rat milk, a high milk to maternal plasma ratio ( $C_{max}$  about 8, AUC about 30) was found, possibly due to active transport into the milk.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Microcrystalline cellulose  
Anhydrous lactose (from cow's milk)  
Croscarmellose sodium  
Sodium lauryl sulfate  
Magnesium stearate

#### Film coating:

*Aquarius Prime LS Pink BAT310178 contains these components:*

Hypromellose  
Lactose monohydrate (from bovine milk)  
Titanium dioxide  
Triacetin  
Iron oxide red

### **6.2. Incompatibilities**

Not applicable.



### 6.3. Shelf life

24 months.

### 6.4. Special precautions for storage

Store at room temperature below 30°C.

### 6.5. Nature and contents of container

Transparent PVC/PVdC-Aluminum foil is used as primary packaging material for APACLOT 5 mg Film Coated Tablets. Blisters are packed in cardboard boxes. Each cardboard box contains 56 film-coated tablets and a package leaflet.

### 6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment.

## 7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad. No:1

34303 Küçükçekmece – İSTANBUL / TÜRKİYE

## 8. MARKETING AUTHORIZATION NUMBER

2022/98

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 03.03.2022

Date of last renewal :

## 10. DATE OF REVISION OF THE TEXT

10.09.2024