Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arinaya 1.25 mg/ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of oral suspension contains 1.25 mg apixaban.

Excipients with known effect:
Each 1 ml of oral suspension contains

- 0.65 mg of Sodium benzoate (E211),
- 1.90 mg of Sodium metabisulfite (E223) and
- 1.00 mg of peppermint flavour.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.
White oral suspension with peppermint odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1 Therapeutic indications

Adults

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

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 ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ 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 haemodynamically unstable PE patients).

Paediatric population

Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients weighing ≥ 35 kg (see section 4.2).

4.2 Posology and method of administration

Posology

Prevention of VTE (VTEp): elective hip or knee replacement surgery in adults
The recommended dose of apixaban is 2.5 mg (2 ml of suspension) taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window.

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

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

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF)
The recommended dose of apixaban is 5 mg (4 ml of suspension) taken orally twice daily.

Dose reduction
The recommended dose of apixaban is 2.5 mg (2 ml of suspension) taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long-term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in adults
The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg (8 ml of suspension) taken orally twice daily for the first 7 days followed by 5 mg of apixaban (4 ml of suspension) 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, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg (2 ml of suspension) taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg of apixaban (2 ml of suspension) twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg (4 ml of suspension) twice daily or with another anticoagulant, as indicated in Table 1 below (see also section 5.1).

Table 1: Dose recommendation (VTEt)

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg of apixaban (8 ml of suspension) twice daily for the first 7 days	20 mg of apixaban (16 ml of suspension)
	followed by 5 mg of apixaban (4 ml of suspension) twice daily	10 mg of apixaban (8 ml of suspension)
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg of apixaban (2 ml of suspension) twice daily	5 mg of apixaban (4 ml of suspension)

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

Treatment of VTE and prevention of recurrent VTE in paediatric patients
Apixaban treatment for paediatric patients weighing ≥ 35 kg should be initiated following at least 5 days of initial parenteral anticoagulation therapy (see section 5.1).

Treatment with apixaban in paediatric patients is based on weight-tiered dosing. The recommended dose of apixaban in paediatric patients weighing ≥ 35 kg is shown in Table 2.

Table 2: Dose recommendation for treatment of VTE and prevention of recurrent VTE in paediatric patients weighing ≥ 35 kg (after initial parenteral anticoagulation)

	Days 1-7		Day 8 and beyond	
Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
≥ 35	10 mg (8 ml of suspension) twice daily	20 mg (16 ml of suspension)	5 mg (4 ml of suspension) twice daily	10 mg (8 ml of suspension)

Arinaya cannot be used in paediatric patients weighing < 35 kg since the provided syringe is not suitable for accurate dosing in these patients. For paediatric patients weighing < 35 kg, alternative pharmaceutical forms may be available, such as apixaban granules in capsules or sachets. Healthcare professionals should consult the respective SmPC for these products.

Based on VTE treatment guidelines in the paediatric population, duration of overall therapy should be individualised after careful assessment of the treatment benefit and the risk for bleeding (see section 4.4).

Missed dose in adults and paediatric patients
A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning. The patient should continue with the intake of the regular dose twice daily as recommended on the following day.

Switching
Switching treatment from parenteral anticoagulants to Arinaya (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 Arinaya
When converting patients from vitamin K antagonist (VKA) therapy to Arinaya, warfarin or other VKA therapy should be discontinued and Arinaya started when the international normalised ratio (INR) is < 2.

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

No data are available for paediatric patients.

Elderly
VTEp and VTEt - 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).

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

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary (see section 5.2).
- for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg, a dose reduction is necessary (see above subheading regarding dose reduction). In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2).

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

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) apixaban is to be used with caution;
- for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg of apixaban (2 ml of suspension) 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).

Paediatric population
Based on adult data and limited data in paediatric patients (see section 5.2), no dose adjustment is necessary in paediatric patients with mild to moderate renal impairment. Apixaban is not recommended in paediatric patients with severe renal impairment (see section 4.4).

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

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

It 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 ≥ 1.5 x ULN were excluded in clinical studies. Therefore Arinaya should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating Arinaya, liver function testing should be performed.

Apixaban has not been studied in paediatric patients with hepatic impairment.

Body weight
VTEp and VTEt - 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).

Apixaban paediatric administration is based on a fixed-dose by weight-tier regimen (see section 4.2).

Gender
No dose adjustment required (see section 5.2).

Patients undergoing catheter ablation (NVAF)
Patients can continue apixaban use 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 of apixaban (4 ml of suspension) should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation (see section 5.1). The dosing regimen should be reduced to 2.5 mg apixaban of apixaban (2 ml of suspension) given twice daily for at least 2.5 days (5 single doses) if the patient meets the criteria for dose reduction (see above sections *Dose reduction* and *Renal impairment*).

If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg of apixaban (8 ml of suspension) loading dose should be given, followed by 5 mg of apixaban (4 ml of suspension) twice daily. The dosing regimen should be reduced to a 5 mg of apixaban (4 ml of suspension) loading dose followed by 2.5 mg of apixaban (2 ml of suspension) twice daily if the patient meets the criteria for dose reduction (see above sections *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 haemostasis is achieved (see sections 4.4, 5.1).

Paediatric population
The safety and efficacy of apixaban in paediatric patients aged 28 days to less than 18 years have not been established in indications other than treatment of venous thromboembolism (VTE) and prevention of recurrent VTE. No data are available in neonates and for other indications (see also section 5.1). Therefore, apixaban is not recommended for use in neonates and in paediatric patients aged 28 days to less than 18 years in indications other than treatment of VTE and prevention of recurrent VTE.

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

Method of administration in adults and paediatric patients
Oral use.

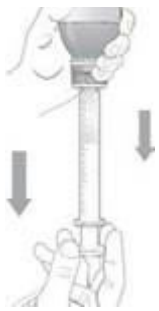
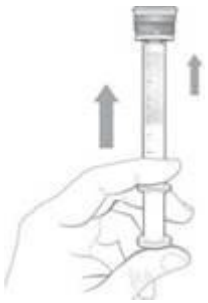
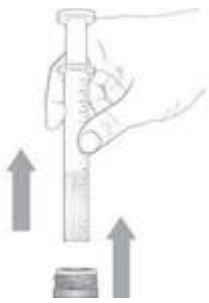
This medicinal product is administered orally as a "ready for-use" oral suspension using an oral syringe. It may be administered directly into the mouth and then swallowed.

Arinaya can be taken with or without food. Arinaya can be taken also with the aid of water, apple juice, tea, cola or coffee. Hold the bottle firmly and vigorously shake at least 10 times before each use to ensure a uniform suspension. It is normal to see small air bubbles.

Incorrect shaking may lead to overdose or underdose of apixaban.

Alternatively, Arinaya may be suspended diluted in 60 mL of water or G5 % dextrose in water (D5W)W and immediately delivered through a nasogastric tube (see section 5.2). Diluted suspension is stable for 48 hours in both room temperature and refrigerator.

How to use the oral syringe:

				
1. Shake the bottle well (at least 10 hands shaking), making sure the bottle is firmly closed.	2. Remove the cap. Note: Keep the cap nearby to close the bottle after each use.	3. Make sure that the plastic adapter is into the neck of the bottle. Note: The adapter must always stay in the bottle.	4. Take the syringe and check the plunger is fully down. 5. Keep the bottle upright and insert the oral syringe firmly into the plastic adapter.	6. Turn the whole bottle with the syringe upside down.
				
7. Slowly pull the plunger down fully so that the syringe fills with medicine. Push the plunger back up completely	8. Check the prescribed dose. Then pull the plunger slowly back to the volume you need for your dose. Check the syringe for any bubbles.	9. Turn the whole bottle with the syringe the right way up and take the syringe out of the bottle.	10. The dose of medicine can now be swallowed directly from the oral syringe. Please ensure that you are sitting upright, and the plunger	11. Replace the child resistant cap after use, leaving the adapter in place. 12. Cleaning: After use,

to expel any large air bubbles that may be trapped inside the oral syringe.	If there are any, empty the syringe back into the bottle and repeat step 8.		must be pushed slowly to allow you to swallow the dose. If your prescribed dose is more than 5 ml, use the syringe more than once (repeat steps 4-10) to draw up and administer the syringe repeatedly until the full prescribed dose has been taken.	dismantle the plunger and rinse both body and plunger with tap water and wipe with a dry, clean tissue or paper.

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 associated with coagulopathy and clinically relevant bleeding risk (see section 5.2)
- Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran etexilate, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2), 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 sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Haemorrhage risk

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

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

A specific reversal agent (andexanet alfa) antagonising the factor Xapharmacodynamic effect of apixaban is available for adults. However, its safety and efficacy have not been established in paediatric patients (refer to the summary of product characteristics of andexanet alfa). Transfusion of fresh frozen plasma, administration of prothrombin complex concentrates (PCCs), or recombinant factor VIIa may be considered. However, there is no clinical experience with the use of 4-factor PCC products to reverse bleeding in paediatric and adult patients who have received apixaban.

Interaction with other medicinal products 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 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 apixaban (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 study of adult 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 study, there was limited (2.1%) use of concomitant dual antiplatelet therapy (see section 5.1).

A clinical study 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 study of high-risk post acute coronary syndrome patients without atrial fibrillation, characterised 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).

In study CV185325, no clinically important bleeding events were reported in the 12 paediatric patients treated with apixaban and ASA ≤ 165 mg daily concomitantly.

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.

Apixaban has not been studied in paediatric patients with prosthetic heart valves; therefore, the use of apixaban is not recommended.

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

Apixaban 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.

Apixaban 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.

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

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

Temporary discontinuation

Discontinuing anticoagulants, including apixaban, 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 apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

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. 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 there is such need and based on the general PK characteristics of apixaban, a time interval of 20-30 hours (i.e., 2 x half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban may be given at least 5 hours after catheter removal. As with all new anticoagulant medicinal products, experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in the presence of neuraxial blockade.

No data are available on the timing of the placement or removal of neuraxial catheter in paediatric patients while on apixaban. In such cases, discontinue apixaban and consider a short acting parenteral anticoagulant.

Haemodynamically 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 haemodynamically 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 venous thromboembolism and bleeding events. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made (see also section 4.3).

Patients with renal impairment

Adult patients
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 prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban 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 NVAF, patients with severe renal impairment (creatinine clearance 15-29 ml/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily (see section 4.2).

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

Paediatric patients
Paediatric patients with severe renal impairment have not been studied and therefore should not receive apixaban (see sections 4.2 and 5.2).

Elderly patients

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

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

Body weight

In adults low body weight (< 60 kg) may increase haemorrhagic risk (see section 5.2).

Patients with hepatic impairment

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

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

It 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 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore apixaban should be used cautiously in this population (see section 5.2). Prior to initiating apixaban, liver function testing should be performed.

Apixaban has not been studied in paediatric patients with hepatic impairment.

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).

No clinical data are available in paediatric patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (see section 4.5).

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 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;
- for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

No clinical data are available in paediatric patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp (see section 4.5).

Hip fracture surgery

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

Laboratory parameters

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

Excipients with known effects

Arinaya contains peppermint flavour
Peppermint flavour can trigger hypersensitivity reactions (including dyspnoea) in sensitized patients.

Arinaya contains sodium benzoate
This medicine contains 0.65 mg Sodium benzoate (E211) in each milliliter. Sodium benzoate (E211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non- conjugated bilirubin deposits in the brain tissue).

Arinaya contains sodium metabisulfite
This medicine contains 1.90 mg Sodium metabisulfite (E223) in each milliliter. Sodium metabisulfite (E223) may rarely cause severe hypersensitivity reactions and bronchospasms.

Arinaya contains sodium
Arinaya contains 1.3 mmol sodium (28.8 mg) per maximum daily dose of 16 ml (20 mg Apixaban). This is equivalent to 1.4% of the recommended maximum daily dietary intake of 2 g sodium for an adult.

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 AUC and a 1.6-fold increase in mean apixaban C_{max}.

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) (see section 4.4).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (e.g., 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, NSAIDs, ASA and/or P2Y12 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 medicinal products with apixaban is not recommended (see section 4.4).

In study CV185325, no clinically important bleeding events were reported in the 12 paediatric patients treated with apixaban and ASA ≤ 165 mg daily concomitantly.

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 (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 coadministered medicinal products 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.

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).

Paediatric population
Interaction studies have not been performed in paediatrics.

The above mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of apixaban during pregnancy.

Breast-feeding

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

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from apixaban therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

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

4.8 Undesirable effects

Summary of the safety profile

In adults the safety of apixaban has been investigated in 7 Phase III clinical studies including more than 21,000 patients: more than 5,000 patients in VTEp studies, more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment (VTEt) studies, for an average total exposure of 20 days, 1.7 years and 221 days respectively (see section 5.1).

Common adverse reactions were haemorrhage, contusion, epistaxis, and haematoma (see Table 2 for adverse reaction profile and frequencies by indication).

In the VTEp studies, in total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with apixaban was 10% in the apixaban vs enoxaparin studies.

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 VTEt 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).

Tabulated list of adverse reactions

Table 3 shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) in adults for VTEp, NVAF and VTEt and in paediatric patients from 28 days to < 18 years of age for VTEt and prevention of recurrent VTE.

The frequencies of adverse reactions reported in Table 3 for paediatric patients are derived from study CV185325, in which they received apixaban for treatment of VTE and prevention of recurrent VTE.

Table 3: Tabulated adverse reactions

System organ class	**Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)**	**Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)**	**Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt) in adult patients**	**Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to lesst than18 yea rs of age**	
Blood and lymphatic system disorders					
Anaemia	Common	Common	Common	Common	
Thrombocytopenia	Uncommon	Uncommon	Common	Common	
Immune system disorders					
Hypersensitivity, allergic oedema and anaphylaxis	Rare	Uncommon	Uncommon	Common‡	
Pruritus	Uncommon	Uncommon	Uncommon*	Common	
Angioedema	Not known	Not known	Not known	Not known	
Nervous system disorders					
Brain haemorrhage†	Not known	Uncommon	Rare	Not known	
Eye disorders					
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon	Not known	
Vascular disorders					
Haemorrhage, haematoma	Common	Common	Common	Common	
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon	Common	
Intra-abdominal haemorrhage	Not known	Uncommon	Not known	Not known	
Respiratory,thoracic and mediastinal disorders					
Epistaxis	Uncommon	Common	Common	Very common	
Haemoptysis	Rare	Uncommon	Uncommon	Not known	
Respiratory tract haemorrhage	Not known	Rare	Rare	Not known	
Gastrointestinal disorders					
Nausea	Common	Common	Common	Common	
Gastrointestinal haemorrhage	Uncommon	Common	Common	Not known	
Haemorrhoidal haemorrhage	Not known	Uncommon	Uncommon	Not known	
Mouth haemorrhage	Not known	Uncommon	Common	Not known	
Haematochezia	Uncommon	Uncommon	Uncommon	Common	
Rectal haemorrhage, gingival bleeding	Rare	Common	Common	Common	
Retroperitoneal haemorrhage	Not known	Rare	Not known	Not known	
Hepatobiliary disorders					
Liver function test abnormal, aspartate aminotransferase	Uncommon	Uncommon	Uncommon	Common	

increased, blood alkaline phosphatase increased, blood bilirubin increased					
Gamma-glutamyltransferase increased	Uncommon	Common	Common	Not known	
Alanine aminotransferase increased	Uncommon	Uncommon	Common	Common	
Skin and subcutaneous tissue disorders					
Skin rash	Not known	Uncommon	Common	Common	
Alopecia	Rare	Uncommon	Uncommon	Common	
Erythema multiforme	Not known	Very rare	Not known	Not known	
Cutaneous vasculitis	Not known	Not known	Not known	Not known	
Musculoskeletal and connective tissue disorders					
Muscle haemorrhage	Rare	Rare	Uncommon	Not known	
Renal and urinary disorders					
Haematuria	Uncommon	Common	Common	Common	
Anticoagulant-related nephropathy	Not known	Not known	Not known	Not known	
Reproductive system and breast disorders					
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common	Very common§	
General disorders and administration site conditions					
Application site bleeding	Not known	Uncommon	Uncommon	Not known	
Investigations					
Occult blood positive	Not known	Uncommon	Uncommon	Not known	
Injury, poisoning and procedural complications					
Contusion	Common	Common	Common	Common	
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	Uncommon	Uncommon	Uncommon	Common	
Traumatic haemorrhage	Not known	Uncommon	Uncommon	Not known	

* There were no occurrences of generalised pruritus in CV185057 (long term prevention of VTE).
† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (i.e., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).
‡ Includes anaphylactic reaction, drug hypersensitivity, and hypersensitivity.
§ Includes heavy menstrual bleeding, intermenstrual bleeding, and vaginal haemorrhage.

The use of apixaban 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 sections 4.4 and 5.1).

Paediatric population

The safety of apixaban has been investigated in 1 Phase I and 3 Phase II/III clinical studies including 970 patients. Of these patients, 568 patients received one or more doses of apixaban for average total exposure of 1, 24, 331 and 80 days, respectively (see section 5.1). The patients received weight adjusted doses of an age-appropriate formulation of apixaban.

Overall, the safety profile of apixaban in paediatric patients 28 days to < 18 years of age was similar to that in adults and was generally consistent across different paediatric age groups.

The most commonly reported adverse reactions in paediatric patients were epistaxis, and abnormal vaginal haemorrhage (see Table 3 for adverse reaction profile and frequencies by indication).

In paediatric patients, epistaxis (very common), abnormal vaginal haemorrhage (very common), hypersensitivity and anaphylaxis (common), pruritus (common), hypotension (common), haematochezia (common), aspartate aminotransferase increased (common), alopecia (common), and post procedural haemorrhage (common) were reported more frequently as compared to adults treated with apixaban, but in the same frequency category as the paediatric patients in the standard of care (SOC) arm; the only exception was abnormal vaginal haemorrhage, which was reported as common in the SOC arm. In all

but one case, hepatic transaminase elevations were reported in paediatric patients receiving concomitant chemotherapy for an underlying malignancy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis, the transfusion of fresh frozen plasma or the administration of a reversal agent for factor Xa inhibitors should be considered (see section 4.4).

In controlled clinical studies, orally-administered apixaban in healthy adult 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 reactions.

In healthy adult 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.

Haemodialysis 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, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

For situations in which reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors (andexanet alfa) is available for adults (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 30 minute 4-factor PCC 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.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of apixaban is not established in the paediatric population (refer to the summary of product characteristics of andexanet alfa). Transfusion of fresh frozen plasma, or administration of PCCs, or recombinant factor VIIa may also be considered.

Depending on local availability, coagulation expert consultation should be considered in case of major bleeding.

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 haemostasis.

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). In adults, 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-Factor Xa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-Factor Xa kits, however results differ across kits. Data from adult clinical studies are only available for the Rotachrom® Heparin chromogenic assay. Anti-Factor Xa 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-Factor Xa activity is approximately linear over a wide dose range of apixaban. Results from apixaban paediatric studies indicate that the linear relationship between apixaban concentration and AXA is consistent with the previously documented relationship in adults. This lends support to the documented mechanism of action of apixaban as a selective inhibitor of FXa.

Table 4 below shows the predicted steady state exposure and anti-Factor Xa activity for each adult indication. In patients taking apixaban for the prevention of VTE following hip or knee replacement surgery, the results demonstrate a less than 1.6-fold fluctuation in peak-to-trough levels. In non-valvular atrial fibrillation patients taking apixaban for the prevention of stroke 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 4: Predicted apixaban steady-state exposure and anti-Factor Xa activity

	Apix. Cmax(ng/mL)	**Apix. Cmin(ng/mL)**	**Apix. anti-Factor Xa activity max (IU/mL)**	**Apix. anti-Factor Xa activity min (IU/mL)**
	Median [5th, 95th percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg twice daily	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 twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 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 (VTEt)				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [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 [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.

Paediatric population

Apixaban paediatric studies used the STA® Liquid Anti-Xa apixaban assay. Results from these studies indicate that the linear relationship between apixaban concentration and anti-Factor Xa activity (AXA) is consistent with the previously documented relationship in adults. This lends support to the documented mechanism of action of apixaban as a selective inhibitor of FXa.

Across weight tiers 9 to ≥ 35 kg in Study CV185155, the geometric mean (%CV) AXA min and AXA max ranged between 27.1 (22.2) ng/mL and 71.9 (17.3) ng/mL, corresponding to geometric mean (%CV) C_{minss} and C_{maxss} of 30.3 (22) ng/mL and 80.8 (16.8) ng/mL. The exposures achieved at these AXA ranges using the paediatric dosing regimen were comparable to those seen in adults who received an apixaban dose of 2.5 mg twice daily.

Across weight tiers 6 to ≥ 35 kg in Study CV185362, the geometric mean (%CV) AXA min and AXA max ranged between 67.1 (30.2) ng/mL and 213 (41.7) ng/mL, corresponding to geometric mean (%CV) C_{minss} and C_{maxss} of 71.3 (61.3) ng/mL and 230

(39.5) ng/mL. The exposures achieved at these AXA ranges using the paediatric dosing regimen were comparable to those seen in adults who received an apixaban dose of 5 mg twice daily.

Across weight tiers 6 to ≥ 35 kg in Study CV185325, the geometric mean (%CV) AXA min and AXA max ranged between 47.1 (57.2) ng/mL and 146 (40.2) ng/mL, corresponding to geometric mean (%CV) C_{minss} and C_{maxss} of 50 (54.5) ng/mL and 144 (36.9) ng/mL. The exposures achieved at these AXA ranges using the paediatric dosing regimen were comparable to those seen in adults who received an apixaban dose of 5 mg twice daily.

The predicted steady state exposure and anti-Factor Xa activity for the paediatric studies suggests that the steady state peak-to-trough fluctuation in apixaban concentrations and AXA levels were approximately 3-fold (min, max: 2.65-3.22) in the overall population.

Clinical efficacy and safety

Prevention of VTE (VTEp): elective hip or knee replacement surgery
The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of VTE in a broad range of adult patients undergoing elective hip or knee replacement. A total of 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 415 patients (203 in the apixaban group) with moderate renal impairment.

The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement, and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement. Subjects received either apixaban 2.5 mg given orally twice daily (po bid) or enoxaparin 40 mg administered subcutaneously once daily (sc od). The first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Both apixaban and enoxaparin were given for 32-38 days in the ADVANCE-3 study and for 10-14 days in the ADVANCE-2 study.

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.

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal DVT, non-fatal PE, and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 5).

Table 5: Efficacy results from pivotal phase III studies

Study	**ADVANCE-3(hip)**			**ADVANCE-2(knee)**		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po twice daily 35 ± 3 d	Enoxaparin 40 mg sc once daily 35 ± 3 d	p-value	Apixaban 2.5 mg po twice daily 12 ± 2 d	Enoxaparin 40 mg sc once daily 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
Relative risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Major VTE						
Number of events/subjects Event rate	10/2,199 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)		

The safety endpoints of major bleeding, the composite of major and CRNM bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 6). All the bleeding criteria included surgical site bleeding.

Table 6: Bleeding results from pivotal phase III studies*

	ADVANCE-3		ADVANCE-2	
	Apixaban 2.5 mg po twice daily 35 ± 3 d	Enoxaparin 40 mg sc once daily 35 ± 3 d	Apixaban 2.5 mg po twice daily 12 ± 2 d	Enoxaparin 40 mg sc once daily 12 ± 2 d
All treated	n = 2,673	n = 2,659	n = 1,501	n = 1,508
Treatment period[1]				
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[2]				
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
[1] Includes events occurring after first dose of enoxaparin (pre-surgery)
[2] Includes events occurring after first dose of apixaban (post-surgery)

The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g., ALT levels) were numerically lower in patients on apixaban compared to enoxaparin in the phase II and phase III studies in elective hip and knee replacement surgery.

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 number of PE.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
A total of 23,799 adult patients were randomised in the clinical program (ARISTOTLE: apixaban versus warfarin, AVERROES: apixaban versus ASA) including 11,927 randomised 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 ischaemic attack (TIA)
- age ≥ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥ II)

ARISTOTLE study
In the ARISTOTLE study a total of 18,201 adult patients were randomised 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 active substance 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 the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 7) compared with warfarin.

Table 7: Efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N=9,120 n(%/yr)	**Warfarin N=9,081 n(%/yr)**	**Hazardratio (95% CI)**	**p-value**
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
Stroke				
Ischaemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	

Haemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

For patients randomised 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 8). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

Table 8: Secondary endpoints in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N=9,088 n(%/year)	**Warfarin N= 9,052 n(%/year)**	**Hazardratio (95% CI)**	**p-value**
Bleeding outcomes				
Major*	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	< 0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM†	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	< 0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	< 0.0001
Other endpoints				
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 International Society on Thrombosis and Haemostasis (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 $CHADS_2$ 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 $CHADS_2$ 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 adult patients considered to be unsuitable for VKA by the investigators were randomised 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 active substance for a mean of 14 months. The mean age was 69.9 years, the mean CHADS2 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%), $CHADS_2$ 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 (haemorrhagic, ischaemic or unspecified) or systemic embolism (see Table 9) compared to ASA.

Table 9: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study

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

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

† Secondary endpoint.

There was no statistically significant difference in the incidence of major bleeding between apixaban and ASA (see Table 10).

Table 10: Bleeding events in patients with atrial fibrillation in the AVERROES study

	Apixaban N=2,798 n(%/year)	ASA N=2,780 n(%/year)	Hazardratio (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 Haemostasis (ISTH) criteria.

† Clinically relevant non-major

NVAF patients with ACS and/or undergoing PCI

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

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 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 HAS-BLED score > 3. For patients randomised 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 a secondary objective of the study, with composite endpoints.

In the apixaban versus VKA comparison, the composite endpoint of death or re-hospitalisation 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 revascularisation) 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-hospitalisation 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 revascularisation) 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 adult 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)) or at least 2 hours after a 10 mg loading dose (or a 5 mg loading dose in selected patients (see section 4.2)) if earlier cardioversion was required. In the apixaban group, 342 patients received a loading dose (331 patients received the 10 mg dose and 11 patients received the 5 mg dose).

There were no strokes (0%) in the apixaban group (n= 753) and 6 (0.80%) strokes in the heparin and/or VKA group (n = 747; RR 0.00, 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 (1.50%) patients, respectively, in the apixaban group, compared to 6 (0.83%) and 13 (1.80%) patients in the heparin and/or VKA group.

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

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)
The adult 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 randomised, 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 adult 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.

The mean age was 56.9 years and 89.8% of randomised patients had unprovoked VTE events.

For patients randomised 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 11).

Table 11: Efficacy results in the AMPLIFY study

	Apixaban N=2,609 n(%)	**Enoxaparin/Warfarin N=2,635 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)

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 12).

Table 12: Bleeding results in the AMPLIFY study

	Apixaban N=2,676 n(%)	**Enoxaparin/ Warfarin N=2,689 n(%)**	**Relative risk (95%CI)**
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, 0.70)
All	402 (15.0)	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 adult 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. 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 randomised 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 13).

Table 13: Efficacy results in the AMPLIFY-EXT study

	Apixaban	**Apixaban**	**Placebo**	**Relative risk(95%CI)**	
	2.5 mg (N=840)	**5.0 mg (N=813)**	**(N=829)**	**Apix2.5 mg vs.placebo**	**Apix5.0 mg vs.placebo**
	n (%)				
Recurrent	19 (2.3)	14 (1.7)	77 (9.3)	0.24	0.19
VTE or all- cause death				(0.15, 0.40)[¥]	(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	14 (1.7)	14 (1.7)	73 (8.8)	0.19	0.20
VTE or VTE-related death				(0.11, 0.33)	(0.11, 0.34)
Recurrent	14 (1.7)	14 (1.7)	76 (9.2)	0.18	0.19
VTE or CV-related death				(0.10, 0.32)	(0.11, 0.33)
Nonfatal	6 (0.7)	8 (1.0)	53 (6.4)	0.11	0.15
DVT[†]				(0.05, 0.26)	(0.07, 0.32)
Nonfatal PE[†]	8 (1.0)	4 (0.5)	15 (1.8)	0.51	0.27
				(0.22, 1.21)	(0.09, 0.80)
VTE-related	2 (0.2)	3 (0.4)	7 (0.8)	0.28	0.45
death				(0.06, 1.37)	(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 (eg, if a subject experienced both a DVT and then a PE, only the DVT was reported)
† Individual subjects could experience more than one event and be represented in both classifications

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 14).

Table 14: 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)	**Apix2.5 mg** vs. placebo	**Apix5.0 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)
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)

Adjudicated 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.

Paediatric population

Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to < 18 years of age
Study CV185325 was a randomised, active controlled, open label, multi-center study of apixaban for the treatment of VTE in paediatric patients. This descriptive efficacy and safety study included 217 paediatric patients; requiring anticoagulation treatment for VTE and prevention of recurrent VTE; 137 patients in age group 1 (12 to < 18 years), 44 patients in age group 2 (2 to < 12 years), 32 patients in age group 3 (28 days to < 2 years) and 4 patients in age group 4 (birth to < 28 days). The index VTE was confirmed by imaging and was independently adjudicated. Prior to randomization, patients were treated with SOC anticoagulation for up to 14 days (mean (SD) duration of treatment with SOC anticoagulation prior to start of study medication was 4.8 (2.5) days, and 92.3% of patients was started ≤ 7 days). Patients were randomised according to a 2:1 ratio to an age-appropriate formulation of apixaban (doses adjusted for weight equivalent to a loading dose of 10 mg twice daily for 7 days followed by 5 mg twice daily in adults) or SOC. For patients 2 to < 18 years, SOC was comprised of low molecular weight heparins (LMWH), unfractionated heparins (UFH) or vitamin K antagonists (VKA). For patients 28 days to < 2 years of age, SOC will be limited to heparins (UFH or LMWH). The main treatment phase lasted 42 to 84 days for patients aged < 2 years, and 84 days in patients aged > 2 years. Patients aged 28 days to < 18 years who were randomized to receive apixaban had the option to continue apixaban treatment for 6 to 12 additional weeks in the extension phase.

The primary efficacy endpoint was the composite of all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE and VTE-related death. No patient in either treatment group had a VTE-related death. A total of 4 (2.8%) patients in the apixaban group and 2 (2.8%) patients in the SOC group had at least 1 adjudicated symptomatic or asymptomatic recurrent VTE event.

The median extent of exposure in 143 treated patients in the apixaban arm was 84.0 days. Exposure exceeded 84 days in 67 (46.9%) patients. The primary safety endpoint of composite of major and CRNM bleeding was seen in 2 (1.4%) patients on apixaban vs 1 (1.4%) patient on SOC, with a RR of 0.99 (95% CI 0.1;10.8). In all cases, this concerned a CRNM bleeding. Minor bleeding was reported in 51 (35.7%) patients in the apixaban group and 21 (29.6%) patients in the SOC group, with a RR of 1.19 (95% CI 0.8; 1.8).

Major bleeding was defined as bleeding that satisfies one or more of the following criteria: a (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/dL) in a 24-hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and (iv) bleeding that requires surgical intervention in an operating suite (including interventional radiology).

CRNM bleeding was defined as bleeding that satisfies one or both of the following: (i) overt bleeding for which a blood product is administered, and which is not directly attributable to the subject's underlying medical condition and (ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.

Minor bleeding was defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding. Menstrual bleeding was classified as a minor bleeding event rather than clinically relevant non-major.

In 53 patients who entered the extension phase and were treated with apixaban, no event of symptomatic and asymptomatic recurrent VTE or VTE related mortality was reported. No patients in the extension phase experienced an adjudicated major or a CRNM bleeding event. Eight (8/53; 15.1%) patients in the extension phase experienced minor bleeding events.

There were 3 deaths in the apixaban group and 1 death in the SOC group, all of which were assessed as not treatment-related by the investigator. None of these deaths were due to a VTE or bleeding event per the adjudication performed by the independent event adjudication committee.

The safety database for apixaban in paediatric patients is based on Study CV185325 for treatment of VTE and prevention of recurrent VTE, supplemented with the PREVAPIX-ALL study and the SAXOPHONE study in VTE primary prophylaxis, and single-dose study CV185118. It includes 970 paediatric patients, 568 of whom received apixaban.

There is no authorised paediatric indication for the primary prophylaxis of VTE.

Prevention of VTE in paediatric patients with acute lymphoblastic leukaemia or lymphoblastic lymphoma (ALL, LL)
In the PREVAPIX-ALL study, a total of 512 patients age ≥ 1 to < 18 with newly diagnosed ALL or LL, undergoing induction chemotherapy including asparaginase via an indwelling central venous access device, were randomised 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 15). 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 15: 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
≥ 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 paediatric patients with congenital or acquired heart disease
SAXOPHONE was a randomised 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 16). 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 16: 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 with apixaban in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

In adults, 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 oral suspension 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 (8 ml of suspension) suspended in 30 ml of water, exposure was comparable to exposure after oral administration of 8 ml suspension.
Following oral administration of 10 mg of apixaban (8 ml of suspension) with 30 g of apple puree, the C_{max} and AUC were 21% and 16% lower, respectively, when compared to administration of 8 ml suspension. The reduction in exposure is not considered clinically relevant.

Following administration of 5 mg apixaban (4 ml of suspension) suspended in 60 ml of G5W and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical studies involving healthy subjects receiving a single oral 5 mg apixaban (4 ml of suspension) dose.

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

Paediatric population

Apixaban is rapidly absorbed, reaching maximum concentration (C_{max}) approximately 2 hours after single-dose administration.

Distribution

In adults, plasma protein binding is approximately 87%. The volume of distribution (Vss) is approximately 21 liters.

No data on apixaban plasma protein binding specific to paediatric population is available.

Biotransformation and elimination

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

In adults, apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours.

In paediatrics, apixaban has a total apparent clearance of about 3.0 L/h.

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 active substance-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

Elderly

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}.

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-Factor Xa 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 haemodialysis, compared to that seen in subjects with normal renal function. 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. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

In paediatric patients ≥ 2 years of age, severe renal impairment is defined as an estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2 body surface area (BSA). In Study CV185325, in patients less than 2 years of age, the thresholds defining severe renal impairment by sex and post-natal age are summarized in Table 17 below; each corresponds to an eGFR < 30 ml/min/1.73 m^2 BSA for patients ≥ 2 years of age.

Table 17: eGFR eligibility thresholds for study CV185325

Postnatal age (gender)	**GFR reference range(mL/min/1.73 m^2)**	**Eligibility threshold for eGFR***
1 week (males and females)	41 ± 15	≥ 8
2–8 weeks (males and females)	66 ± 25	≥ 12
> 8 weeks to < 2 years (males and females)	96 ± 22	≥ 22
2–12 years (males and females)	133 ± 27	≥ 30
13–17 years (males)	140 ± 30	≥ 30
13–17 years (females)	126 ± 22	≥ 30

*Eligibility threshold for CV185325 study participation, where estimated glomerular filtration rate (eGFR) was calculated per the updated bedside Schwartz equation (Schwartz, GJ et al., CJASN 2009). This per protocol threshold corresponded to the eGFR below which a prospective patient was considered to have "inadequate renal function" that precluded participation in Study CV185325. Each threshold was defined as an eGFR < 30% of 1 standard deviation (SD) below the GFR reference range for age and gender. Threshold values for patients < 2 years of age correspond to an eGFR < 30 ml/min/1.73 m^2, the conventional definition of severe renal failure in patients > 2 years of age.

Paediatric patients with glomerular filtration rates ≤ 55 ml/min/1.73 m^2 did not participate in Study CV185325, although those with mild to moderate levels of renal impairment (eGFR ≥ 30 to < 60 ml/min/1.73 m^2 BSA) were eligible. Based on adult data and limited data in all apixaban-treated paediatric patients, no dose adjustment is necessary in paediatric patients with mild to moderate renal impairment. Apixaban is not recommended in paediatric patients with severe renal impairment (see sections 4.2 and 4.4).

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.

Apixaban has not been studied in paediatric patients with hepatic impairment.

Gender

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

Gender differences in pharmacokinetic properties were not studied in paediatric patients.

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.

Differences in pharmacokinetic properties relating to ethnic origin and race were not studied in paediatric patients.

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.

Administration of apixaban to paediatric patients is based on a fixed-dose by weight-tier regimen.

Pharmacokinetic/pharmacodynamic relationship

In adults, the pharmacokinetic /pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-Factor Xa activity, [AXA], 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.

Similarly, results from apixaban paediatric PK/PD assessment indicate a linear relationship between apixaban concentration and AXA. This is consistent with the previously documented relationship in adults.

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-foetal 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

Sucralose (E955)
Peppermint flavour[1)]
Sodium benzoate (E211)
Sodium metabisulfite (E223)
Disodium edetate (E385)
Saccharin sodium (E954)
Xanthan gum (E415)
Citric acid (E330)
Sodium citrate (E331)
Purified water

[1)] The Peppermint flavour contains maize maltodextrin and modified maize starch.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

21 months

After first opening of the bottle, do not store above 25°C. The suspension can be stored for 40 days.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after opening the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass bottle (type III) with a child-proof and tamper evident plastic cap in a colorful, carton box. A 5 ml oral syringe with 0.1 ml graduation, an adapter (which fits on the bottle as well as allow the oral syringe to fit) and a Patient Alert Card are also provided.

Pack size: 75 ml, 100 ml, 150 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Str. 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 6th July 2026

10 DATE OF REVISION OF THE TEXT