ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg apixaban.

Excipient(s) with known effect

Each 2.5 mg film-coated tablet contains 51 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Yellow, round tablets (diameter of 6 mm) debossed with 893 on one side and 2½ on the other side.

4. CLINICAL PARTICULARS

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 from 28 days to less than 18 years of age.

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 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 taken orally twice daily.

Dose reduction
The recommended dose of apixaban is 2.5 mg 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 taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg 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 twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be 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 from 28 days to less than 18 years of age 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 twice daily	20 mg	5 mg twice daily	10 mg

For paediatric patients weighing < 35 kg, refer to the summary of product characteristics for Eliquis granules in capsules for opening and Eliquis coated granules in sachets.

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

Switching from Eliquis to VKA therapy
When converting patients from Eliquis to VKA therapy, administration of Eliquis should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Eliquis with VKA therapy, an INR should be obtained prior to the next scheduled dose of Eliquis. Coadministration of Eliquis 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 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
Eliquis 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 Eliquis should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating Eliquis, 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 in adults (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 adult patients who may require cardioversion.

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

For patients initiating treatment with apixaban, 5 mg should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation (see section 5.1). The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 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 loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction (see

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 and 5.1).

Paediatric population
The safety and efficacy of Eliquis 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, Eliquis 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 Eliquis 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
Eliquis should be swallowed with water, with or without food.

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

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 pharmacodynamic 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 ischaemic stroke

There is very limited experience with the use of thrombolytic agents for the treatment of acute ischaemic 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 CYP 3A4 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 CYP 3A4 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).

Information about excipients

Eliquis contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

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

Eliquis 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 3 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 less than 18 years 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

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 less than 18 years of age
Hepatobiliary disorders				
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon	Common
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

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 less than 18 years of age
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 the national reporting system listed in Appendix V.

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 (AXA) 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. C_{max} (ng/mL)	**Apix. C_{min} (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]

	Apix. C_{max} (ng/mL)	Apix. C_{min} (ng/mL)	Apix. anti-Factor Xa activity max (IU/mL)	Apix. anti-Factor Xa activity min (IU/mL)
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 hyperlipidaemia, 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%)

	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
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 $CHADS_2$ 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)	Hazard ratio (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)	Hazard ratio (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 $CHADS_2$ 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%), CHADS2 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)**	**Hazard ratio (95% CI)**	**p-value**
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
Ischaemic or 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)	Hazard ratio (95% CI)	p-value
Major*	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal, n	5 (0.16)	5 (0.16)		
Intracranial, n	11 (0.34)	11 (0.35)		
Major + CRNM†	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

*Major bleeding defined per International Society on Thrombosis and 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 ischaemic 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 ischaemic 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)**	**Apix 2.5 mg vs. placebo**	**Apix 5.0 mg vs. placebo**
	n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15, 0.40)[¥]	0.19 (0.11, 0.33)[¥]
DVT*	6 (0.7)	7 (0.9)	53 (6.4)		
PE*	7 (0.8)	4 (0.5)	13 (1.6)		
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)		
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11, 0.33)	0.20 (0.11, 0.34)
Recurrent VTE or CV-related death	14 (1.7)	14 (1.7)	76 (9.2)	0.18 (0.10, 0.32)	0.19 (0.11, 0.33)
Nonfatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)
Nonfatal PE†	8 (1.0)	4 (0.5)	15 (1.8)	0.51 (0.22, 1.21)	0.27 (0.09, 0.80)
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)	0.28 (0.06, 1.37)	0.45 (0.12, 1.71)

[¥] p-value < 0.0001
* For patients with more than one event contributing to the composite endpoint, only the first event was reported (e.g., if a subject experienced both a DVT and then a PE, only the DVT was reported)
† Individual subjects could experience more than one event and be represented in both classifications

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

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see Table 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)	**Apix 2.5 mg** vs. placebo	**Apix 5.0 mg** vs. placebo
		n (%)			
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)
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-centre 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 randomised 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 Eliquis 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 tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

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

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

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

Tablet core

Lactose
Microcrystalline cellulose (E460)
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate (E470b)

Film coat

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-PVC/PVdC blisters. Cartons of 10, 20, 60, 168 and 200 film-coated tablets.
Alu PVC/PVdC perforated unit dose blisters of 60x1 and 100x1 film-coated tablets.

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

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/001
EU/1/11/691/002
EU/1/11/691/003
EU/1/11/691/004
EU/1/11/691/005
EU/1/11/691/013
EU/1/11/691/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 May 2011
Date of latest renewal: 11 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg apixaban.

Excipients with known effect

Each 5 mg film-coated tablet contains 103 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Pink, oval tablets (10 mm x 5mm) debossed with 894 on one side and 5 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

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 from 28 days to less than 18 years of age.

4.2 Posology and method of administration

Posology

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

Dose reduction
The recommended dose of apixaban is 2.5 mg 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 taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg 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 twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be 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 from 28 days to less than 18 years of age 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 twice daily	20 mg	5 mg twice daily	10 mg

For paediatric patients weighing < 35 kg, refer to the summary of product characteristics for Eliquis granules in capsules for opening and Eliquis coated granules in sachets.

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

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

No data are available for paediatric patients.

Elderly
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 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 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 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 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
Eliquis 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 Eliquis should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating Eliquis, liver function testing should be performed.

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

Body weight
VTEt - No dose adjustment required in adults (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 adult patients who may require cardioversion.

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

For patients initiating treatment with apixaban, 5 mg should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation (see section 5.1). The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 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 loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction (see 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 and 5.1).

Paediatric population
The safety and efficacy of Eliquis in paediatric patients aged 28 days to less than 18 years have not been established in indications other than treatment of VTE and prevention of recurrent VTE. No data

are available in neonates and for other indications (see also section 5.1). Therefore, Eliquis 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 Eliquis 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
Eliquis should be swallowed with water, with or without food.

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

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 pharmacodynamic 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 Eliquis.

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 ischaemic stroke

There is very limited experience with the use of thrombolytic agents for the treatment of acute ischaemic 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 postoperative 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 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 co-administration 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 CYP 3A4 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 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 CYP 3A4 and P-gp (see section 4.5).

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).

Information about excipients

Eliquis contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

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 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

Eliquis 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, and 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 3 for adverse reaction profile and frequencies by indication).

In the NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and 9.6% in the apixaban vs acetylsalicylic acid study. In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

In the 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 NVAF and VTEp or 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 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 less than 18 years of age.**
Blood and lymphatic system disorders			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Common	Common
Immune system disorders			
Hypersensitivity, allergic oedema and Anaphylaxis	Uncommon	Uncommon	Common‡
Pruritus	Uncommon	Uncommon*	Common
Angioedema	Not known	Not known	Not known
Nervous system disorders			
Brain haemorrhage†	Uncommon	Rare	Not known
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Common	Uncommon	Not known
Vascular disorders			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Common	Uncommon	Common
Intra-abdominal haemorrhage	Uncommon	Not known	Not known

System organ class	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 less than 18 years of age.
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Common	Common	Very common
Haemoptysis	Uncommon	Uncommon	Not known
Respiratory tract haemorrhage	Rare	Rare	Not known
Gastrointestinal disorders			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Common	Common	Not known
Haemorrhoidal haemorrhage	Uncommon	Uncommon	Not known
Mouth haemorrhage	Uncommon	Common	Not known
Haematochezia	Uncommon	Uncommon	Common
Rectal haemorrhage, gingival bleeding	Common	Common	Common
Retroperitoneal haemorrhage	Rare	Not known	Not known
Hepatobiliary disorders			
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Common
Gamma-glutamyltransferase increased	Common	Common	Not known
Alanine aminotransferase increased	Uncommon	Common	Common
Skin and subcutaneous tissue disorders			
Skin rash	Uncommon	Common	Common
Alopecia	Uncommon	Uncommon	Common
Erythema multiforme	Very rare	Not known	Not known
Cutaneous vasculitis	Not known	Not known	Not known
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	Uncommon	Not known
Renal and urinary disorders			
Haematuria	Common	Common	Common
Anticoagulant-related nephropathy	Not known	Not known	Not known

System organ class	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 less than 18 years of age.
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Common	Very common[§]
General disorders and administration site conditions			
Application site bleeding	Uncommon	Uncommon	Not known
Investigations			
Occult blood positive	Uncommon	Uncommon	Not known
Injury, poisoning and procedural complications			
Contusion	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	Common
Traumatic haemorrhage	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. 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 the national reporting system listed in Appendix V.

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 prothrombin complex concentrates (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 (AXA) 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 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. C_{max} (ng/mL)	**Apix. C_{min} (ng/mL)**	**Apix. anti-Factor Xa activity max (IU/mL)**	**Apix. anti-Factor Xa activity min (IU/mL)**
	Median [5th, 95th percentile]			
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 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]

	Apix. C_{max} (ng/mL)	Apix. C_{min} (ng/mL)	Apix. anti-Factor Xa activity max (IU/mL)	Apix. anti-Factor Xa activity min (IU/mL)
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 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 $CHADS_2$ score was 2.1, 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 5) compared with warfarin.

Table 5: Efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N = 9,120 n (%/yr)	**Warfarin N = 9,081 n (%/yr)**	**Hazard ratio (95% CI)**	**p-value**
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
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 6). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

Table 6: Secondary endpoints in patients with atrial fibrillation in the ARISTOTLE study

	Apixaban N = 9,088 n (%/year)	**Warfarin N = 9,052 n (%/year)**	**Hazard ratio (95% CI)**	**p-value**
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 $CHADS_2$ 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%), CHADS2 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 7) compared to ASA.

Table 7: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study

	Apixaban N = 2,807 n (%/year)	**ASA N = 2,791 n (%/year)**	**Hazard ratio (95% CI)**	**p-value**
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
Ischaemic or 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 8).

Table 8: Bleeding events in patients with atrial fibrillation in the AVERROES study

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

*Major bleeding defined per International Society on Thrombosis ad 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 ischaemic 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 ischaemic 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 9).

Table 9: 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 10).

Table 10: 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 11).

Table 11: 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)**	**Apix 2.5 mg vs. placebo**	**Apix 5.0 mg vs. placebo**
	n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15, 0.40)[¥]	0.19 (0.11, 0.33)[¥]
DVT*	6 (0.7)	7 (0.9)	53 (6.4)		
PE*	7 (0.8)	4 (0.5)	13 (1.6)		
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)		
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11, 0.33)	0.20 (0.11, 0.34)
Recurrent VTE or CV-related death	14 (1.7)	14 (1.7)	76 (9.2)	0.18 (0.10, 0.32)	0.19 (0.11, 0.33)
Nonfatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)
Nonfatal PE†	8 (1.0)	4 (0.5)	15 (1.8)	0.51 (0.22, 1.21)	0.27 (0.09, 0.80)
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)	0.28 (0.06, 1.37)	0.45 (0.12, 1.71)

[¥] p-value < 0.0001
* For patients with more than one event contributing to the composite endpoint, only the first event was reported (e.g., if a subject experienced both a DVT and then a PE, only the DVT was reported)
† Individual subjects could experience more than one event and be represented in both classifications

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

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see Table 12).

Table 12: Bleeding results in the AMPLIFY-EXT study

	Apixaban	Apixaban	Placebo	Relative risk (95% CI)	
	2.5 mg (N = 840)	**5.0 mg** (N = 811)	(N = 826)	**Apix 2.5 mg** vs. placebo	**Apix 5.0 mg** vs. placebo
		n (%)			
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)
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 less than 18 years of age

Study CV185325 was a randomised, active controlled, open label, multi-centre 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 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 BID for 7 days followed by 5 mg BID 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 subjects aged > 2 years. Subjects aged 28 days to < 18 years who were randomised 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%) of 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%) patients 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 13). 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 13: 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 14). 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 14: 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 Eliquis 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 tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

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

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

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 15 below; each corresponds to an eGFR < 30 mL/min/1.73 m^2 BSA for patients ≥ 2 years of age.

Table 15: 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

Tablet core

Lactose
Microcrystalline cellulose (E460)
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate (E470b)

Film coat

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-PVC/PVdC blisters. Cartons of 14, 20, 28, 56, 60, 168 and 200 film-coated tablets.
Alu-PVC/PVdC perforated unit dose blisters of 100x1 film coated tablets.

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

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/006
EU/1/11/691/007
EU/1/11/691/008
EU/1/11/691/009
EU/1/11/691/010
EU/1/11/691/011
EU/1/11/691/012
EU/1/11/691/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 May 2011
Date of latest renewal: 11 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 0.15 mg granules in capsules for opening

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.15 mg apixaban

Excipient(s) with known effect

Each capsule of 0.15 mg contains up to 124 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules in capsules for opening.
The granules are white to off white in colour. They are provided in a hard capsule with a clear body and yellow opaque cap, which must be opened prior to administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

4.2 Posology and method of administration

Posology

Treatment of VTE and prevention of recurrent VTE in paediatric patients weighing 4 kg < 5 kg
Apixaban treatment for paediatric patients from 28 days to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation therapy (see section 5.1).

The recommended dose of apixaban is based on the patient's weight as shown in Table 1. The dose should be adjusted according to weight-tier as treatment progresses. For patients weighing ≥ 35 kg, Eliquis 2.5 mg and 5 mg film coated tablets can be administered twice daily, not to exceed the maximum daily dose. Refer to the Eliquis 2.5 mg and 5 mg film coated tablets Summary of Product Characteristics for dosing instructions.

For weight not listed in the dosing table, no dosing recommendation can be provided.

Table 1: Dose recommendations for treatment of VTE and prevention of recurrent VTE in paediatric patients, by weight in kg (after initial parenteral anticoagulation)

		Days 1-7		Day 8 and beyond	
Pharmaceutical forms	Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
Granules in capsules for opening 0.15 mg	4 to < 5	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
Coated granules in sachet 0.5 mg, 1.5 mg, 2.0 mg	5 to < 6	1 mg twice daily	2 mg	0.5 mg twice daily	1 mg
	6 to < 9	2 mg twice daily	4 mg	1 mg twice daily	2 mg
	9 to < 12	3 mg twice daily	6 mg	1.5 mg twice daily	3 mg
	12 to < 18	4 mg twice daily	8 mg	2 mg twice daily	4 mg
	18 to < 25	6 mg twice daily	12 mg	3 mg twice daily	6 mg
	25 to < 35	8 mg twice daily	16 mg	4 mg twice daily	8 mg
Film-coated tablets 2.5 mg and 5.0 mg	≥ 35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

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

Switching from Eliquis to VKA therapy
No data are available for paediatric patients.
When converting patients from Eliquis to VKA therapy, administration of Eliquis should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Eliquis with VKA therapy, an INR should be obtained prior to the next scheduled dose of Eliquis. Coadministration of Eliquis and VKA therapy should be continued until the INR is ≥ 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 (for details, refer to the Summary of Product Characteristics for Eliquis 2.5 mg film-coated tablets). 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 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
Apixaban has not been studied in paediatric patients with hepatic impairment.

Eliquis 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 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 from clinical studies. Therefore Eliquis should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating Eliquis, liver function testing should be performed.

Body weight
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).

Paediatric population
The safety and efficacy of Eliquis 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, Eliquis 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 Eliquis 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

Oral use
Each capsule for opening is for single use only.

The capsule for opening should NOT be swallowed. The capsule must be opened and the entire contents should be sprinkled in liquid and administered. Eliquis granules should be mixed with either water or baby formula as described in the instructions for use (IFU). The liquid mixture should be administered within 2 hours of preparation. Alternatively, for patients who have difficulty swallowing, the liquid mixture can be delivered through a gastrostomy tube and nasogastric tube.

Detailed instructions for the use of this medicinal product are provided in the instructions for use.

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 pharmacodynamic 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 also be considered. However, there is no clinical experience with the use of 4factor 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 study CV185325, no clinically important bleeding events were reported in the 12 paediatric patients treated with apixaban and ASA ≤ 165 mg daily concomitantly.

Patients with prosthetic heart valve

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

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.

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.

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

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).

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).

Body weight

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

Patients with hepatic impairment

Apixaban has not been studied in paediatric 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.

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

No clinical data are available in paediatrics patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp (see section 4.5).

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

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure.

In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (see section 4.5):

- for the treatment of VTE 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 CYP 3A4 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).

Information about excipients

Eliquis contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have not been performed in paediatrics. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

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 Pgp. For example, diltiazem (360 mg once a day), considered a moderate CYP3A4 and a weak Pgp 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 Pgp 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 co-administered 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

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

4.8 Undesirable effects

Summary of the safety profile

Adult population
Apixaban has been investigated in over 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 2 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 2 for paediatric patients are derived from study CV185325, in which they received apixaban for treatment of VTE and prevention of recurrent VTE.

Table 2: 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 less than 18 years 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

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 less than 18 years of age
Hepatobiliary disorders				
Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon	Common
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

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 less than 18 years of age
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).
‡ This 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 568 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 2 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 arm (SOC); 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 the national reporting system listed in Appendix V.

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 adult 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 prothrombin complex concentrates (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 (AXA) as evident by reduction in Factor Xa enzyme activity in multiple commercial AXA kits, however results differ across kits. 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. The AXA results presented below was obtained using the STA® Liquid Anti-Xa Apixaban assay.

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.

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

Clinical efficacy and safety

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-centre 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 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 BID for 7 days followed by 5 mg BID 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 randomised 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%) of 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 3). 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 3: 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 4). 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 4: 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 Eliquis in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

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 tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

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

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

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

Distribution

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

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).

Renal impairment

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 5 below; each corresponds to an eGFR < 30 mL/min/1.73 m^2 BSA for patients ≥ 2 years of age.

Table 5: 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).

In adults, 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 adult 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.

Hepatic impairment

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

In an adult 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.

Gender

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

In adults, exposure to apixaban was approximately 18% higher in females than in males.

Ethnic origin and race

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

Body weight

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

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

Pharmacokinetic/pharmacodynamic relationship

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). 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

Granules content

Hypromellose (E464)
Sugar spheres (composed of sugar syrup, maize starch (E1450), and sucrose)

Capsule shell

Gelatin (E441)
Titanium dioxide (E171)
Iron oxide yellow (E172)

Black printing ink

Shellac (E904)
Propylene glycol (E1520)
Iron oxide black

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years
Once mixed with water or baby formula, the liquid mixture must be used within 2 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a foil induction seal and a child-resistant polypropylene cap packed into a carton.
Each bottle contains 28 capsules for opening.

6.6 Special precautions for disposal

Detailed instructions for the preparation and administration of the dose are provided in instructions for use.

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 May 2011
Date of latest renewal: 11 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 0.5 mg coated granule in sachet
Eliquis 1.5 mg coated granules in sachet
Eliquis 2 mg coated granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eliquis 0.5 mg coated granule in sachet
Each sachet contains one 0.5 mg apixaban coated granule.

Excipient with known effect
Each sachet contains 10 mg lactose (see section 4.4).

Eliquis 1.5 mg coated granules in sachet
Each sachet contains three 0.5 mg (1.5 mg) apixaban coated granules.

Excipient with known effect
Each sachet contains 30 mg lactose (see section 4.4).

Eliquis 2.0 mg coated granules in sachet
Each sachet contains four 0.5 mg (2 mg) apixaban coated granules.

Excipient with known effect
Each sachet contains 40 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

0.5 mg coated granules packaged in 0.5, 1.5, and 2 mg sachets.
Pink colour and round shape (diameter 3 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

4.2 Posology and method of administration

Posology

Treatment of VTE and prevention of recurrent VTE in paediatric patients weighing 5 kg < 35 kg
Apixaban treatment for paediatric patients from 28 days to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation therapy (see section 5.1).

The recommended dose of apixaban is based on the patient's weight as shown in Table 1. The dose should be adjusted according to weight tier as treatment progresses. For patients weighing ≥ 35 kg, Eliquis 2.5 mg and 5 mg film coated tablets can be administered twice daily, not to exceed the maximum daily dose. Refer to the Eliquis 2.5 mg and 5 mg film coated tablets summary of product characteristics for dosing instructions.

For weight not listed in the dosing table, no dosing recommendation can be provided.

Table 1: Dose recommendations for treatment of VTE and prevention of recurrent VTE in paediatric patients, by weight in kg (after initial parenteral anticoagulation)

		Days 1-7		Day 8 and beyond	
Pharmaceutical forms	Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
Granules in capsules for opening 0.15 mg	4 to < 5	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
Coated granules in sachet 0.5 mg, 1.5 mg, 2.0 mg	5 to < 6	1 mg twice daily	2 mg	0.5 mg twice daily	1 mg
	6 to < 9	2 mg twice daily	4 mg	1 mg twice daily	2 mg
	9 to < 12	3 mg twice daily	6 mg	1.5 mg twice daily	3 mg
	12 to < 18	4 mg twice daily	8 mg	2 mg twice daily	4 mg
	18 to < 25	6 mg twice daily	12 mg	3 mg twice daily	6 mg
	25 to < 35	8 mg twice daily	16 mg	4 mg twice daily	8 mg
Film-coated tablets 2.5 mg and 5.0 mg	≥ 35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

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

Switching from Eliquis to VKA therapy
No data are available for paediatric patients.
When converting patients from Eliquis to VKA therapy, administration of Eliquis should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Eliquis with VKA therapy, an INR should be obtained prior to the next scheduled dose of Eliquis. Coadministration of Eliquis and VKA therapy should be continued until the INR is ≥ 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 (for details, refer to the Summary of Product Characteristics for Eliquis 2.5 mg film-coated tablets). 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 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
Apixaban has not been studied in paediatric patients with hepatic impairment.

Eliquis 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 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 from clinical studies. Therefore Eliquis should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating Eliquis, liver function testing should be performed.

Body weight
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).

Paediatric population
The safety and efficacy of Eliquis 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, Eliquis 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 Eliquis 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

Oral use

Each sachet is for single use only. Eliquis coated granules should be mixed with water, baby formula, apple juice, or apple puree as described in the instructions for use (IFU). The liquid mixture should be administered within 2 hours. The mixture in apple puree should be administered immediately. Alternatively, for patients who have difficulty swallowing, the liquid mixture can be delivered through a gastrostomy tube and nasogastric tube.

Detailed instructions for the use of this medicinal product are provided in the instructions for use.

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 pharmacodynamic 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 also be considered. However, there is no clinical experience with the use of 4factor 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 study CV185325, no clinically important bleeding events were reported in the 12 paediatric patients treated with apixaban and ASA ≤ 165 mg daily concomitantly.

Patients with prosthetic heart valve

Apixaban has not been studied in paediatric patients with a prosthetic heart valve. 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

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.

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.

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

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).

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).

Body weight

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

Patients with hepatic impairment

Apixaban has not been studied in paediatric 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.

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

No clinical data are available in paediatrics patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp (see section 4.5).

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

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure.

In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (see section 4.5):

- for the treatment of VTE 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 CYP 3A4 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).

Information about excipients

Eliquis contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per coated granule, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have not been performed in paediatric patients.

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

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

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

4.8 Undesirable effects

Summary of the safety profile

Adult population
Apixaban has been investigated in over 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 2 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 2 for paediatric patients are derived from study CV185325, in which they received apixaban for treatment of VTE and prevention of recurrent VTE:

Table 2: 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 less than 18 years 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

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 less than 18 years of age
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, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon	Common
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

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 less than 18 years of age
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).
‡ This 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 568 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 2 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 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 the national reporting system listed in Appendix V

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 adult 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 prothrombin complex concentrates (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 (AXA) as evident by reduction in Factor Xa enzyme activity in multiple commercial AXA kits, however results differ across kits. 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. The AXA results presented below were obtained using the STA® Liquid Anti-Xa Apixaban assay.

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.

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

Clinical efficacy and safety

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-centre 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 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 BID for 7 days followed by 5 mg BID 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 randomised 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%) of 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 venous thromboembolism (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 3). 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 3: 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 4). 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 4: 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 Eliquis in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

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 tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

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

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

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

Distribution

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

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).

Renal impairment

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 5 below; each corresponds to an eGFR < 30 mL/min/1.73 m^2 BSA for patients ≥ 2 years of age.

Table 5: 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

insufficiency. Apixaban is not recommended in paediatric patients with severe renal impairment (see sections 4.2 and 4.4).

In adults, 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 adult 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.

Hepatic impairment

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

In an adult 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.

Gender

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

In adults, exposure to apixaban was approximately 18% higher in females than in males.

Ethnic origin and race

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

Body weight

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

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

Pharmacokinetic/pharmacodynamic relationship

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). 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

Granule core

Lactose
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Magnesium stearate (E470b)

Film coat

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Once mixed with water, baby formula or apple juice, the liquid mixture must be used within 2 hours.

The mixture with apple puree must be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Child-resistant aluminium foil sachet with the 1 x 0.5 mg coated granule.
Child-resistant aluminium foil sachet with the 3 x 0.5 mg coated granules.
Child-resistant aluminium foil sachet with the 4 x 0.5 mg coated granules.

Each carton contains 28 sachets.

6.6 Special precautions for disposal

Detailed instructions for the preparation and administration of the dose are provided in the instructions for use.

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/017
EU/1/11/691/018
EU/1/11/691/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 May 2011
Date of latest renewal: 11 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale Casilina, 41
03012 Anagni (FR)
Italy

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell Newbridge
Co. Kildare
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Eliquis is marketed, all healthcare professionals who are expected to prescribe Eliquis have access to/are provided with the following educational materials:

- Summary of Product Characteristics
- Patient Cards

All patients and/or caregivers of paediatric patients who receive Eliquis shall be provided with a Patient Card (provided within each medicine pack).

Key Elements of the Patient Card:

- Signs or symptoms of bleeding and when to seek attention from a health care provider
- Importance of treatment compliance
- Necessity to carry the Patient card with them at all times
- The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 2.5 mg

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg film-coated tablets
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg apixaban.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

10 film-coated tablets
20 film-coated tablets
60 film-coated tablets
60 x 1 film-coated tablets
100 x 1 film-coated tablets
168 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/001
EU/1/11/691/002
EU/1/11/691/003
EU/1/11/691/004
EU/1/11/691/005
EU/1/11/691/013
EU/1/11/691/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 2.5 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 2.5 mg

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 2.5 mg (Symbol)

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

sun as symbol
moon as symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg film-coated tablets
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg apixaban.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
100x 1 film-coated tablets
168 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/006
EU/1/11/691/007
EU/1/11/691/008
EU/1/11/691/009
EU/1/11/691/010
EU/1/11/691/011
EU/1/11/691/012
EU/1/11/691/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 5 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON & BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 0.15 mg granules in capsules for opening
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule for opening contains 0.15 mg apixaban.

3. LIST OF EXCIPIENTS

Contains sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in capsules for opening
28 capsules for opening

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and the Instructions for Use before use.
Do not swallow the capsule for opening. Open and mix the contents with liquid.
For oral use after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/016 (28 capsules for opening containing granules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton : Eliquis 0.15 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 0.5 mg coated granule in sachet
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 mg sachet contains 1 x 0.5 mg apixaban coated granule.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Coated granules in sachet
28 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and the Instructions for Use before use.
For oral use after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/017 (28 sachets, each sachet containing 1 coated granule)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 0.5 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Eliquis 0.5 mg coated granule
apixaban
oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. NAME OF THE MARKETING AUTHORISATION HOLDER

BMS/Pfizer EEIG

4. EXPIRY DATE

EXP

5. BATCH NUMBER

Lot

6. OTHER

1 granule (0.5 mg)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 1.5 mg coated granules in sachet
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1.5 mg sachet contains 3 x 0.5 mg apixaban coated granules.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Coated granules in sachet
28 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and the Instructions for Use before use.
For oral use after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/018 (28 sachets, each sachet containing 3 coated granules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 1.5 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Eliquis 1.5 mg coated granules
apixaban
oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. NAME OF THE MARKETING AUTHORISATION HOLDER

BMS/Pfizer EEIG

4. EXPIRY DATE

EXP

5. BATCH NUMBER

Lot

6. OTHER

3 granules (1.5 mg)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2 mg coated granules in sachet
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2.0 mg sachet contains 4 x 0.5 mg apixaban coated granules.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Coated granules in sachet
28 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and the Instructions for Use before use.
For oral use after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/019 (28 sachets, each sachet containing 4 coated granules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 2 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Eliquis 2 mg coated granules
apixaban
oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. NAME OF THE MARKETING AUTHORISATION HOLDER

BMS/Pfizer EEIG

4. EXPIRY DATE

EXP

5. BATCH NUMBER

Lot

6. OTHER

4 granules (2 mg)

PATIENT CARD

Eliquis (apixaban)

Patient Card

This card should be with you / the child / the caregiver at all times

Show this card to the pharmacist, dentist and any other healthcare professionals before treatment.

I am under anticoagulation treatment with Eliquis (apixaban) to prevent blood clots

Please complete this section or ask the doctor to do it
Name:
Birth Date:
Indication:
Weight:
Dose: mg twice daily
Doctor's Name:
Doctor's telephone:

Information for patients / caregivers
- Take / give Eliquis regularly as instructed. If you miss a morning dose, take / give it as soon as you remember and it may be taken / given together with the evening dose. A missed evening dose can only be taken / given during the same evening. Do not take / give two doses the next morning, instead continue to follow the dosing schedule twice daily as recommended on the next day.
- Do not stop taking / giving Eliquis without talking to the doctor, as you are / the patient is at risk of suffering a stroke / blood clot or other complications.
- Eliquis helps to thin the blood. However, this may increase the risk of bleeding.
- Signs and symptoms of bleeding include bruising or bleeding under the skin, tar-coloured stools, blood in urine, nose-bleed, dizziness, tiredness, paleness or weakness, sudden severe headache, coughing up blood or vomiting blood.
- If the bleeding does not stop on its own, **seek medical attention immediately**.
- If you / the patient need(s) surgery or any invasive procedure, inform the doctor that you are / the patient is taking Eliquis.

{MMM YYYY}

Information for healthcare professionals
- Eliquis (apixaban) is an oral anticoagulant acting by direct selective inhibition of factor Xa.
- Eliquis may increase the risk of bleeding. In case of major bleeding events, it should be stopped immediately.
- Treatment with Eliquis does not require routine monitoring of exposure. A calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations, e.g., overdose and emergency surgery (prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin time (aPTT) clotting tests are not recommended) – see SmPC.
  An agent to reverse the anti-factor Xa activity 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).

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Eliquis 2.5 mg film-coated tablets
apixaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eliquis is and what it is used for

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in adults:
- to prevent blood clots (deep vein thrombosis [DVT]) from forming after hip or knee replacement operations. After an operation to the hip or knee you may be at a higher risk of developing blood clots in your leg veins. This can cause the legs to swell, with or without pain. If a blood clot travels from your leg to your lungs, it can block blood flow causing breathlessness, with or without chest pain. This condition (pulmonary embolism) can be life-threatening and requires immediate medical attention.

- to prevent a blood clot from forming in the heart in patients with an irregular heart beat (atrial fibrillation) and at least one additional risk factor. Blood clots may break off and travel to the brain and lead to a stroke or to other organs and prevent normal blood flow to that organ (also known as a systemic embolism). A stroke can be life-threatening and requires immediate medical attention.

- to treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

Eliquis is used in children aged 28 days to less than 18 years to treat blood clots and to prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs.

For body weight appropriate recommended dose, see section 3.

2. What you need to know before you take Eliquis

Do not take Eliquis if
- **you are allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6);
- you are **bleeding excessively**;
- you have a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of your stomach or bowel, **recent bleeding in your brain**);
- you have a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy);
- you are **taking medicines to prevent blood clotting** (e.g., warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment, while having a venous or arterial line and you get heparin through this line to keep it open, or if a tube is inserted into your blood vessel (catheter ablation) to treat an irregular heartbeat (arrhythmia).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you take this medicine if you have any of the following:
- an **increased risk of bleeding**, such as:
  - **bleeding disorders**, including conditions resulting in reduced platelet activity;
  - **very high blood pressure**, not controlled by medical treatment;
  - you are older than 75 years;
  - you weigh 60 kg or less;
- a **severe kidney disease or if you are on dialysis**;
- a **liver problem or a history of liver problems**;
  - This medicine will be used with caution in patients with signs of altered liver function.
- **had a tube (catheter) or an injection into your spinal column** (for anaesthesia or pain reduction), your doctor will tell you to take this medicine 5 hours or more after catheter removal;
- if you have a **prosthetic heart valve**;
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.

Take special care with Eliquis
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask your doctor.

Children and adolescents
This medicine is not recommended in children and adolescents with a body weight of less than 35 kg.

Other medicines and Eliquis
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

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

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:
- some **medicines for fungal infections** (e.g., ketoconazole, etc.);
- some **antiviral medicines for HIV/AIDS** (e.g., ritonavir);
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.);

- **anti-inflammatory** or **pain medicines** (e.g., acetylsalicylic acid or naproxen). Especially, if you are older than 75 years and are taking acetylsalicylic acid, you may have an increased chance of bleeding;
- **medicines for high blood pressure or heart problems** (e.g., diltiazem);
- **antidepressant medicines** called **selective serotonin re-uptake inhibitors** or **serotonin norepinephrine re-uptake inhibitors**.

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:
- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.);
- **St John's Wort** (a herbal supplement used for depression);
- **medicines to treat tuberculosis** or **other infections** (e.g., rifampicin).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

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

It is not known if Eliquis passes into human breast milk. Ask your doctor, pharmacist or nurse for advice before taking this medicine while breast-feeding. They will advise you whether to stop breast-feeding or to stop/not start taking this medicine.

Driving and using machines
Eliquis has not been shown to impair your ability to drive or use machines.

Eliquis contains lactose (a type of sugar) and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Eliquis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Dose
Swallow the tablet with a drink of water. Eliquis can be taken with or without food.
Try to take the tablets at the same times every day to have the best treatment effect.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Eliquis. The tablet may be crushed and mixed with water, or 5% glucose in water, or apple juice or apple puree, immediately before you take it.

Instructions for crushing:
- Crush the tablets with a pestle and mortar.
- Transfer all the powder carefully into a suitable container then mix the powder with a little e.g., 30 mL (2 tablespoons), water or one of the other liquids mentioned above to make a mixture.
- Swallow the mixture.
- Rinse the pestle and mortar you used for crushing the tablet and the container, with a little water or one of the other liquids (e.g., 30 mL), and swallow the rinse.

If necessary, your doctor may also give you the crushed Eliquis tablet mixed in 60 mL of water or 5% glucose in water, through a nasogastric tube.

Take Eliquis as recommended for the following:

To prevent blood clots from forming after hip or knee replacement operations.
The recommended dose is one tablet of Eliquis 2.5 mg twice a day. For example, one in the morning and one in the evening.
You should take the first tablet 12 to 24 hours after your operation.

If you have had a major **hip** operation you will usually take the tablets for 32 to 38 days.
If you have had a major **knee** operation you will usually take the tablets for 10 to 14 days.

To prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.
The recommended dose is one tablet of Eliquis **5 mg** twice a day.

The recommended dose is one tablet of Eliquis **2.5 mg** twice a day if:
- you have **severely reduced kidney function**;
- **two or more of the following apply to you:**
  - your blood test results suggest poor kidney function (value of serum creatinine is 1.5 mg/dL (133 micromole/L) or greater);
  - you are 80 years old or older;
  - your weight is 60 kg or lower.

The recommended dose is one tablet twice a day, for example, one in the morning and one in the evening. Your doctor will decide how long you must continue treatment for.

To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs
The recommended dose is **two tablets** of Eliquis **5 mg** twice a day for the first 7 days, for example, two in the morning and two in the evening.
After 7 days the recommended dose is **one tablet** of Eliquis **5 mg** twice a day, for example, one in the morning and one in the evening.

For preventing blood clots from re-occurring following completion of 6 months of treatment
The recommended dose is one tablet of Eliquis **2.5 mg** twice a day for example, one in the morning and one in the evening.
Your doctor will decide how long you must continue treatment for.

Use in children and adolescents

For treating blood clots and to prevent re-occurrence of blood clots in the veins or in the blood vessels of your lungs.

Always take or give this medicine exactly as your or the child's doctor or pharmacist has told you. Check with your or the child's doctor, pharmacist or nurse if you are not sure.

Try to take or give the dose at the same times every day to have the best treatment effect.

The dose of Eliquis depends on the body weight, and will be calculated by the doctor.
The recommended dose for children and adolescents weighing at least 35 kg is **four tablets** of Eliquis **2.5 mg** twice a day for the first 7 days, for example, four in the morning and four in the evening.
After 7 days the recommended dose is **two tablets** of Eliquis **2.5 mg** twice a day, for example, two in the morning and two in the evening.

For parents or caregivers: please observe the child to ensure that the full dose is taken.

It is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes.

Your doctor might change your anticoagulant treatment as follows:

- *Changing from Eliquis to anticoagulant medicines*

Stop taking Eliquis. Start treatment with the anticoagulant medicines (for example heparin) at the time you would have taken the next tablet.

- *Changing from anticoagulant medicines to Eliquis*

Stop taking the anticoagulant medicines. Start treatment with Eliquis at the time you would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing vitamin K antagonist (e.g., warfarin) to Eliquis*

Stop taking the medicine containing a vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to start taking Eliquis.

- *Changing from Eliquis to anticoagulant treatment containing vitamin K antagonist (e.g., warfarin).*

If your doctor tells you that you have to start taking the medicine containing a vitamin K antagonist, continue to take Eliquis for at least 2 days after your first dose of the medicine containing a vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to stop taking Eliquis.

Patients undergoing cardioversion
If your abnormal heartbeat needs to be restored to normal by a procedure called cardioversion, take this medicine at the times your doctor tells you, to prevent blood clots in blood vessels in your brain and other blood vessels in your body.

If you take more Eliquis than you should
Tell your doctor immediately if you have taken more than the prescribed dose of this medicine. Take the medicine pack with you, even if there are no tablets left.

If you take more Eliquis than recommended, you may have an increased risk of bleeding. If bleeding occurs, surgery, blood transfusions, or other treatments that may reverse anti-factor Xa activity may be required.

If you forget to take Eliquis
- If you miss a morning dose, take it as soon as you remember and it may be taken together with the evening dose.
- A missed evening dose can only be taken during the same evening. Do not take two doses the next morning, instead continue to follow the dosing schedule twice daily as recommended on the next day.

If you are not sure what to do or have missed more than one dose, ask your doctor, pharmacist or nurse.

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

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Eliquis can be given for three different medical conditions. The known side effects and how frequently they occur for each of these medical conditions may differ and are listed separately below. For these conditions,

the most common general side effect of this medicine is bleeding which may be potentially life threatening and require immediate medical attention.

The following side effects are known if you take Eliquis to prevent blood clots from forming after hip or knee replacement operations.

Common side effects (may affect up to 1 in 10 people)
- Anaemia which may cause tiredness or paleness;
- Bleeding including:
  - bruising and swelling;
- Nausea (feeling sick).

Uncommon side effects (may affect up to 1 in 100 people)
- Reduced number of platelets in your blood (which can affect clotting);
- Bleeding:
  - occurring after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
  - in your stomach, bowel or bright/red blood in the stools;
  - blood in the urine;
  - from your nose;
  - from the vagina;
- Low blood pressure which may make you feel faint or have a quickened heartbeat;
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes;
- Itching.

Rare side effects (may affect up to 1 in 1,000 people)
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.
- Bleeding:
  - into a muscle;
  - in your eyes;
  - from your gums and blood in your spit when coughing;
  - from your rectum;
- Hair loss.

Not known (frequency cannot be estimated from the available data)
- Bleeding:
  - in your brain or in your spinal column;
  - in your lungs or your throat;
  - in your mouth;
  - into your abdomen or space behind your abdominal cavity;
  - from a haemorrhoid;
  - tests showing blood in the stools or in the urine;
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme);
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.

- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

The following side effects are known if you take Eliquis to prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
  - in your eyes;
  - in your stomach or bowel;
  - from your rectum;
  - blood in the urine;
  - from your nose;
  - from your gums;
  - bruising and swelling;
- Anaemia which may cause tiredness or paleness;
- Low blood pressure which may make you feel faint or have a quickened heartbeat;
- Nausea (feeling sick);
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT).

Uncommon side effects (may affect up to 1 in 100 people)
- Bleeding:
  - in your brain or in your spinal column;
  - in your mouth or blood in your spit when coughing;
  - into your abdomen, or from the vagina;
  - bright/red blood in the stools;
  - bleeding occurring after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
  - from a haemorrhoid;
  - tests showing blood in the stools or in the urine;
- Reduced number of platelets in your blood (which can affect clotting);
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes;
- Skin rash;
- Itching;
- Hair loss;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.

Rare side effects (may affect up to 1 in 1,000 people)
- Bleeding:
  - in your lungs or your throat;
  - into the space behind your abdominal cavity;
  - into a muscle.

Very rare side effects (may affect up to 1 in 10,000 people)
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme).

Not known (frequency cannot be estimated from the available data)
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.

- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

The following side effects are known if you take Eliquis to treat or prevent re-occurrence of blood clots in the veins of your legs and blood clots in the blood vessels of your lungs.

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
  - from your nose;
  - from your gums;
  - blood in the urine;
  - bruising and swelling;
  - in your stomach, your bowel, from your rectum;
  - in your mouth;
  - from the vagina;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in your blood (which can affect clotting);
- Nausea (feeling sick);
- Skin rash;
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT) or alanine aminotransferase (ALT).

Uncommon side effects (may affect up to 1 in 100 people)
- Low blood pressure which may make you feel faint or have a quickened heartbeat
- Bleeding:
  - in your eyes;
  - in your mouth or blood in your spit when coughing;
  - bright/red blood in the stools;
  - tests showing blood in the stools or in the urine;
  - bleeding occurring after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
  - from a haemorrhoid;
  - into a muscle;
- Itching;
- Hair loss;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.

Rare side effects (may affect up to 1 in 1,000 people)
- Bleeding:
  - in your brain or in your spinal column;
  - in your lungs.

Not known (frequency cannot be estimated from the available data)
- Bleeding:
  - into your abdomen or the space behind your abdominal cavity.
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme);*
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.

- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

Additional side effects in children and adolescents

Tell the child's doctor immediately if you observe any of these symptoms;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. The frequency of these side effects is common (may affect up to 1 in 10 people).

In general, the side effects observed in children and adolescents treated with Eliquis were similar in type to those observed in adults and were primarily mild to moderate in severity. Side effects that were observed more often in children and adolescents were nose bleed and abnormal vaginal bleeding.

Very Common side effects (may affect more than 1 in 10 people)
- Bleeding including:
  - from the vagina;
  - from the nose.

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
  - from the gums;
  - blood in the urine;
  - bruising and swelling;
  - from the bowel or rectum;
  - bright/red blood in the stools;
  - bleeding after an operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
- Hair loss;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in the child's blood (which can affect clotting);
- Nausea (feeling sick);
- Skin rash;
- Itching;
- Low blood pressure which may make the child feel faint or have a quickened heartbeat;
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in alanine aminotransferase (ALT).

Not known (frequency cannot be estimated from the available data)
- Bleeding:
  - into the abdomen or the space behind the abdominal cavity;
  - in the stomach;
  - in the eyes;
  - in the mouth;
  - from a haemorrhoid;
  - in the mouth or blood in the spit when coughing;
  - in the brain or in the spinal column;
  - in the lungs;
  - into a muscle;
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme);*

- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising;
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT);
  - tests showing blood in the stools or in the urine.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eliquis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eliquis contains
- The active substance is apixaban. Each tablet contains 2.5 mg of apixaban.
- The other ingredients are:
  - Tablet core: **lactose** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), microcrystalline cellulose, croscarmellose sodium (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), sodium laurilsulfate, magnesium stearate (E470b);
  - Film coat: **lactose monohydrate** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), hypromellose (E464), titanium dioxide (E171), triacetin, yellow iron oxide (E172).

What Eliquis looks like and contents of the pack
The film-coated tablets are yellow, round (diameter of 6 mm) and marked with “893” on one side and “2½” on the other side.

- They come in blisters in cartons of 10, 20, 60, 168 and 200 film-coated tablets.
- Unit dose blisters in cartons of 60x1 and 100x1 film-coated tablets for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Patient Card: handling information
Inside the Eliquis pack together with the package leaflet you will find a Patient Card or your doctor might give you a similar card.
This Patient Card includes information that will be helpful to you and alert other doctors that you are taking Eliquis. **You should keep this card with you at all times.**

1. Take the card.
2. Separate your language as needed (this is facilitated by the perforated edges).
3. Complete the following sections or ask your doctor to do it:
   - Name:
   - Birth Date:
   - Indication:
   - Dose: .....mg twice daily
   - Doctor's Name:
   - Doctor's telephone:
4. Fold the card and keep it with you at all times

Marketing Authorisation Holder
Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale Casilina, 41
03012 Anagni (FR)
Italy

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell Newbridge
Co. Kildare
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +370 5 251 4000

Luxembourg/Luxemburg
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

Česká republika
Pfizer, spol. s r.o.
Tel.: +420 283 004 111
Medical.information@pfizer.com

Danmark
Bristol-Myers Squibb Denmark
Tlf: + 45 45 93 05 06
medinfo.denmark@bms.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: 0800 0752002 (+ 49 89 121 42 350)
medwiss.info@bms.com

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Bristol-Myers Squibb, S.A.
Tel: + 34 91 456 53 00
informacion.medica@bms.com

France
Bristol-Myers Squibb SAS
Tél: + 33 (0)1 58 83 84 96
infomed@bms.com

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Bristol-Myers Squibb Pharmaceuticals uc
Tel: 1 800 749 749 (+ 353 (0)1 483 3625)
medical.information@bms.com

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Bristol-Myers Squibb S.r.l.
Tel: + 39 06 50 39 61
medicalinformation.italia@bms.com

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Nederland
Bristol-Myers Squibb B.V.
Tel: + 31 (0)30 300 2222
medischeafdeling@bms.com

Norge
Bristol-Myers Squibb Norway AS
Tlf: + 47 67 55 53 50
medinfo.norway@bms.com

Österreich
Bristol-Myers Squibb GesmbH
Tel: + 43 1 60 14 30
medinfo.austria@bms.com

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Bristol-Myers Squibb Farmacêutica Portuguesa, S.A.
Tel: + 351 21 440 70 00
portugal.medinfo@bms.com

România
Pfizer Romania S.R.L
Tel: +40 (0)21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: + 386 (0) 1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: **+421-2-3355 5500**

Suomi/Finland
Oy Bristol-Myers Squibb (Finland) Ab
Puh/Tel: + 358 9 251 21 230
medinfo.finland@bms.com

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel.: +371 670 35 775

Sverige
Bristol-Myers Squibb Aktiebolag
Tel: + 46 8 704 71 00
medinfo.sweden@bms.com

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

Package leaflet: Information for the user

Eliquis 5 mg film-coated tablets
apixaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eliquis is and what it is used for

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in adults:
- to prevent a blood clot from forming in the heart in patients with an irregular heart beat (atrial fibrillation) and at least one additional risk factor. Blood clots may break off and travel to the brain and lead to a stroke or to other organs and prevent normal blood flow to that organ (also known as a systemic embolism). A stroke can be life-threatening and requires immediate medical attention.
- to treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

Eliquis is used in children aged 28 days to less than18 years to treat blood clots and to prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs.

For body weight appropriate recommended dose, see section 3.

2. What you need to know before you take Eliquis

Do not take Eliquis if
- **you are allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6);
- you are **bleeding excessively**;
- you have a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of your stomach or bowel, **recent bleeding in your brain**);
- you have a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy);
- you are **taking medicines to prevent blood clotting** (e.g., warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment, while having a venous or arterial line

and you get heparin through this line to keep it open, or if a tube is inserted into your blood vessel (catheter ablation) to treat an irregular heartbeat (arrhythmia).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you take this medicine if you have any of the following:
- an **increased risk of bleeding**, such as:
  - **bleeding disorders**, including conditions resulting in reduced platelet activity;
  - **very high blood pressure**, not controlled by medical treatment;
  - you are older than 75 years;
  - you weigh 60 kg or less;
- a **severe kidney disease or if you are on dialysis**;
- a **liver problem or a history of liver problems**;
  - This medicine will be used with caution in patients with signs of altered liver function.
- **had a tube (catheter) or an injection into your spinal column** (for anaesthesia or pain reduction), your doctor will tell you to take this medicine 5 hours or more after catheter removal;
- if you have a **prosthetic heart valve**;
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.

Take special care with Eliquis
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask your doctor.

Children and adolescents
This medicine is not recommended in children and adolescents with a body weight of less than 35 kg.

Other medicines and Eliquis
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

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

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:
- some **medicines for fungal infections** (e.g., ketoconazole, etc.);
- some **antiviral medicines for HIV/AIDS** (e.g., ritonavir);
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.);
- **anti-inflammatory** or **pain medicines** (e.g., acetylsalicylic acid or naproxen). Especially, if you are older than 75 years and are taking acetylsalicylic acid, you may have an increased chance of bleeding;
- **medicines for high blood pressure or heart problems** (e.g., diltiazem);
- **antidepressant medicines** called **selective serotonin re-uptake inhibitors** or **serotonin norepinephrine re-uptake inhibitors**.

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:
- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.);
- **St John's Wort** (a herbal supplement used for depression);
- **medicines to treat tuberculosis** or **other infections** (e.g., rifampicin).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

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

It is not known if Eliquis passes into human breast milk. Ask your doctor, pharmacist or nurse for advice before taking this medicine while breast-feeding. They will advise you whether to stop breast-feeding or to stop/not start taking this medicine.

Driving and using machines
Eliquis has not been shown to impair your ability to drive or use machines.

Eliquis contains lactose (a type of sugar) and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Eliquis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Dose
Swallow the tablet with a drink of water. Eliquis can be taken with or without food.
Try to take the tablets at the same times every day to have the best treatment effect.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Eliquis. The tablet may be crushed and mixed with water, or 5% glucose in water, or apple juice or apple puree, immediately before you take it.

Instructions for crushing:
- Crush the tablets with a pestle and mortar.
- Transfer all the powder carefully into a suitable container then mix the powder with a little e.g., 30 mL (2 tablespoons), water or one of the other liquids mentioned above to make a mixture.
- Swallow the mixture.
- Rinse the pestle and mortar you used for crushing the tablet and the container, with a little water or one of the other liquids (e.g., 30 mL), and swallow the rinse.

If necessary, your doctor may also give you the crushed Eliquis tablet mixed in 60 mL of water or 5% glucose in water, through a nasogastric tube.

Take Eliquis as recommended for the following:

<u>To prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.</u>
The recommended dose is one tablet of Eliquis **5 mg** twice a day.

The recommended dose is one tablet of Eliquis **2.5 mg** twice a day if:
- you have **severely reduced kidney function**;

- **two or more of the following apply to you:**
  - your blood test results suggest poor kidney function (value of serum creatinine is 1.5 mg/dL (133 micromole/L) or greater);
  - you are 80 years old or older;
  - your weight is 60 kg or lower.

The recommended dose is one tablet twice a day, for example, one in the morning and one in the evening.
Your doctor will decide how long you must continue treatment for.

To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs
The recommended dose is **two tablets** of Eliquis **5 mg** twice a day for the first 7 days, for example, two in the morning and two in the evening.
After 7 days the recommended dose is **one tablet** of Eliquis **5 mg** twice a day, for example, one in the morning and one in the evening.

For preventing blood clots from re-occurring following completion of 6 months of treatment
The recommended dose is one tablet of Eliquis **2.5 mg** twice a day for example, one in the morning and one in the evening.
Your doctor will decide how long you must continue treatment for.

Use in children and adolescents

For treating blood clots and to prevent re-occurrence of blood clots in the veins or in the blood vessels of your lungs.

Always take or give this medicine exactly as your or the child's doctor or pharmacist has told you. Check with your or the child's doctor, pharmacist or nurse if you are not sure.

Try to take or give the dose at the same time every day to have the best treatment effect.

The dose of Eliquis depends on the body weight, and will be calculated by the doctor.
The recommended dose for children and adolescents weighing at least 35 kg is **two tablets** of Eliquis **5 mg** twice a day for the first 7 days, for example, two in the morning and two in the evening.
After 7 days the recommended dose is **one tablet** of Eliquis **5 mg** twice a day, for example, one in the morning and one in the evening.

For parents or caregivers: please observe the child to ensure that the full dose is taken.

It is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes.

Your doctor might change your anticoagulant treatment as follows:

- *Changing from Eliquis to anticoagulant medicines*

Stop taking Eliquis. Start treatment with the anticoagulant medicines (for example heparin) at the time you would have taken the next tablet.

- *Changing from anticoagulant medicines to Eliquis*

Stop taking the anticoagulant medicines. Start treatment with Eliquis at the time you would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing vitamin K antagonist (e.g., warfarin) to Eliquis*

Stop taking the medicine containing a vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to start taking Eliquis.

- *Changing from Eliquis to anticoagulant treatment containing vitamin K antagonist (e.g., warfarin).*

If your doctor tells you that you have to start taking the medicine containing a vitamin K antagonist, continue to take Eliquis for at least 2 days after your first dose of the medicine containing a vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to stop taking Eliquis.

Patients undergoing cardioversion
If your abnormal heartbeat needs to be restored to normal by a procedure called cardioversion, take this medicine at the times your doctor tells you, to prevent blood clots in blood vessels in your brain and other blood vessels in your body.

If you take more Eliquis than you should
Tell your doctor immediately if you have taken more than the prescribed dose of Eliquis. Take the medicine pack with you, even if there are no tablets left.

If you take more Eliquis than recommended, you may have an increased risk of bleeding. If bleeding occurs, surgery, blood transfusions, or other treatments that may reverse anti-factor Xa activity may be required.

If you forget to take Eliquis
- If you miss a morning dose, take it as soon as you remember and it may be taken together with the evening dose.
- A missed evening dose can only be taken during the same evening. Do not take two doses the next morning, instead continue to follow the dosing schedule twice daily as recommended on the next day.

If you are not sure what to do or have missed more than one dose, ask your doctor, pharmacist or nurse.

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

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common general side effect of this medicine is bleeding which may be potentially life threatening and require immediate medical attention.

<u>The following side effects are known if you take Eliquis to prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.</u>

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
  - in your eyes;
  - in your stomach or bowel;
  - from your rectum;
  - blood in the urine;
  - from your nose;
  - from your gums;
  - bruising and swelling;
- Anaemia which may cause tiredness or paleness;
- Low blood pressure which may make you feel faint or have a quickened heartbeat;

- Nausea (feeling sick);
- Blood tests may show:
    - an increase in gamma-glutamyltransferase (GGT).

Uncommon side effects (may affect up to 1 in 100 people)
- Bleeding:
    - in your brain or in your spinal column;
    - in your mouth or blood in your spit when coughing;
    - into your abdomen, or from the vagina;
    - bright/red blood in the stools;
    - bleeding occurring after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
    - from a haemorrhoid;
    - tests showing blood in the stools or in the urine;
- Reduced number of platelets in your blood (which can affect clotting);
- Blood tests may show:
    - abnormal liver function;
    - an increase in some liver enzymes;
    - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.
- Skin rash;
- Itching;
- Hair loss;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.

Rare side effects (may affect up to 1 in 1,000 people)
- Bleeding:
    - in your lungs or your throat;
    - into the space behind your abdominal cavity;
    - into a muscle.

Very rare side effects (may affect up to 1 in 10,000 people)
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme).

Not known (frequency cannot be estimated from the available data)
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

<u>The following side effects are known if you take Eliquis to treat or prevent re-occurrence of blood clots in the veins of your legs and blood clots in the blood vessels of your lungs.</u>

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
    - from your nose;
    - from your gums;
    - blood in the urine;
    - bruising and swelling;
    - in your stomach, your bowel, from your rectum;
    - in your mouth;
    - from the vagina;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in your blood (which can affect clotting);

- Nausea (feeling sick);
- Skin rash;
    - Blood tests may show:
        - an increase in gamma-glutamyltransferase (GGT) or alanine aminotransferase (ALT).

Uncommon side effects (may affect up to 1 in 100 people)
- Low blood pressure which may make you feel faint or have a quickened heartbeat;
- Bleeding:
    - in your eyes;
    - in your mouth or blood in your spit when coughing;
    - bright/red blood in the stools;
    - tests showing blood in the stools or in the urine;
    - bleeding occurring after any operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
    - from a haemorrhoid;
    - into a muscle;
- Itching;
- Hair loss;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms;
    - Blood tests may show:
        - abnormal liver function;
        - an increase in some liver enzymes;
        - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.

Rare side effects (may affect up to 1 in 1,000 people)
- Bleeding:
    - in your brain or in your spinal column;
    - in your lungs.

Not known (frequency cannot be estimated from the available data)
- Bleeding:
    - into your abdomen or the space behind your abdominal cavity.
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme);*
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

<u>Additional side effects in children and adolescents</u>

Tell the child's doctor immediately if you observe any of these symptoms;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. The frequency of these side effects is common (may affect up to 1 in 10 people).

In general, the side effects observed in children and adolescents treated with Eliquis were similar in type to those observed in adults were primarily mild to moderate in severity. Side effects that were observed more often in children and adolescents were nose bleed and abnormal vaginal bleeding.

Very Common side effects (may affect more than 1 in 10 people)

- Bleeding including:
  - from the vagina;
  - from the nose.

Common side effects (may affect up to 1 in 10 people)

- Bleeding including:
  - from the gums;
  - blood in the urine;
  - bruising and swelling;
  - from the bowel or rectum;
  - bright/red blood in the stools;
  - bleeding after an operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
- Hair loss;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in the child's blood (which can affect clotting);
- Nausea (feeling sick);
- Skin rash;
- Itching;
- Low blood pressure which may make the child feel faint or have a quickened heartbeat
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in alanine aminotransferase (ALT).

Not known (frequency cannot be estimated from the available data)

- Bleeding:
  - into the abdomen or the space behind the abdominal cavity;
  - in the stomach;
  - in the eyes;
  - in the mouth;
  - from a haemorrhoid;
  - in the mouth or blood in the spit when coughing;
  - in the brain or in the spinal column;
  - in the lungs;
  - into a muscle;
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme);*
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising;
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT);
  - tests showing blood in the stools or in the urine.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eliquis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eliquis contains
- The active substance is apixaban. Each tablet contains 5 mg of apixaban.
- The other ingredients are:
  - Tablet core: **lactose** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), microcrystalline cellulose, croscarmellose sodium (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), sodium laurilsulfate, magnesium stearate (E470b);
  - Film coat: **lactose monohydrate** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), hypromellose (E464), titanium dioxide (E171), triacetin, red iron oxide (E172).

What Eliquis looks like and contents of the pack
The film coated tablets are pink, oval 10 mm x 5 mm) and marked with “894” on one side and “5” on the other side.

- They come in blisters in cartons of 14, 20, 28, 56, 60, 168 and 200 film-coated tablets.
- Unit dose blisters in cartons of 100x1 film-coated tablets for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Patient Card: handling information
Inside the Eliquis pack together with the package leaflet you will find a Patient Card or your doctor might give you a similar card.
This Patient Card includes information that will be helpful to you and alert other doctors that you are taking Eliquis. **You should keep this card with you at all times.**

1. Take the card.
2. Separate your language as needed (this is facilitated by the perforated edges).
3. Complete the following sections or ask your doctor to do it:
   - Name:
   - Birth Date:
   - Indication:
   - Dose: .....mg twice daily
   - Doctor’s Name:
   - Doctor’s telephone:
4. Fold the card and keep it with you at all times.

Marketing Authorisation Holder
Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale Casilina, 41
03012 Anagni (FR)
Italy

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell Newbridge
Co. Kildare
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer, spol. s r.o.
Tel.: +420 283 004 111
Medical.information@pfizer.com

Danmark
Bristol-Myers Squibb Denmark
Tlf: + 45 45 93 05 06
medinfo.denmark@bms.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: 0800 0752002 (+ 49 89 121 42 350)

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +370 5 251 4000

Luxembourg/Luxemburg
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Nederland
Bristol-Myers Squibb B.V.
Tel: + 31 (0)30 300 2222

medwiss.info@bms.com

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Bristol-Myers Squibb, S.A.
Tel: + 34 91 456 53 00
informacion.medica@bms.com

France
Bristol-Myers Squibb SAS
Tél: + 33 (0)1 58 83 84 96
infomed@bms.com

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Bristol-Myers Squibb Pharmaceuticals uc
Tel: 1 800 749 749 (+ 353 (0)1 483 3625)
medical.information@bms.com

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Bristol-Myers Squibb S.r.l.
Tel: + 39 06 50 39 61
medicalinformation.italia@bms.com

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel.: +371 670 35 775

medischeafdeling@bms.com

Norge
Bristol-Myers Squibb Norway AS
Tlf: + 47 67 55 53 50
medinfo.norway@bms.com

Österreich
Bristol-Myers Squibb GesmbH
Tel: + 43 1 60 14 30
medinfo.austria@bms.com

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Bristol-Myers Squibb Farmacêutica Portuguesa, S.A.
Tel: + 351 21 440 70 00
portugal.medinfo@bms.com

România
Pfizer Romania S.R.L
Tel: +40 (0)21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: + 386 (0) 1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: **+421-2-3355 5500**

Suomi/Finland
Oy Bristol-Myers Squibb (Finland) Ab
Puh/Tel: + 358 9 251 21 230
medinfo.finland@bms.com

Sverige
Bristol-Myers Squibb Aktiebolag
Tel: + 46 8 704 71 00
medinfo.sweden@bms.com

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

Package leaflet: Information for the user

Eliquis 0.15 mg granules in capsules for opening
apixaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. This leaflet has been written for the patients ("you") and the parent or caregiver who will give this medicines to the child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eliquis is and what it is used for

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in children aged 28 days to less than 18 years to treat blood clots and prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs.

For body weight appropriate recommended dose, see section 3.

2. What you need to know before you give Eliquis

Do not give Eliquis if
- **the child is allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6);
- **the child is bleeding excessively**;
- the child has a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of stomach or bowel, **recent bleeding in brain**);
- the child has a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy);
- **the child is taking medicines to prevent blood clotting** (e.g., warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment, while having a venous or arterial line and the child gets heparin through this line to keep it open, or if a tube is inserted into blood vessel (catheter ablation) to treat an irregular heartbeat (arrhythmia).

Warnings and precautions
Talk to the child's doctor, pharmacist or nurse before you give this medicine if the child has any of the following:
- an **increased risk of bleeding**, such as:
  - **bleeding disorders**, including conditions resulting in reduced platelet activity;
  - **very high blood pressure**, not controlled by medical treatment;

- a **severe kidney disease or if the child is on dialysis**;
- a **liver problem or a history of liver problems**;
  - This medicine will be used with caution in patients with signs of altered liver function.
- **had a tube (catheter) or an injection into spinal column** (for anaesthesia or pain reduction), the child's doctor will tell you to give this medicine 5 hours or more after catheter removal;
- if the child has an artificial **heart valve**;
- if the child's doctor determines that the child's blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from the child's lungs is planned.

Take special care with Eliquis
- if you know that the child has a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell the child's doctor who will decide if the treatment may need to be changed.

If the child needs to have surgery or a procedure which may cause bleeding, the child's doctor might ask you to temporarily stop giving this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask the child's doctor.

Children and adolescents
Eliquis granules in a capsule for opening is to be used for children weighing from 4 kg to 5 kg to treat blood clots and prevent re-occurrence of blood clots in the veins. There is not enough information on its use in children and adolescents in other indications.

Other medicines and Eliquis
Tell the child's doctor, pharmacist or nurse if the child is taking, has recently taken or might take any other medicines.

Some medicines may increase the effects of Eliquis and some may decrease its effects. The child's doctor will decide, if the child should be treated with Eliquis when taking these medicines and how closely the child should be monitored.

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:
- some **medicines for fungal infections** (e.g., ketoconazole, etc.);
- some **antiviral medicines for HIV / AIDS** (e.g., ritonavir);
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.);
- **anti-inflammatory** or **pain medicines** (e.g., acetylsalicylic acid or naproxen);
- **medicines for high blood pressure or heart problems** (e.g., diltiazem);
- **antidepressant medicines** called **selective serotonin re-uptake inhibitors** or **serotonin norepinephrine re-uptake inhibitors**.

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:
- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.);
- **St John's Wort** (a herbal supplement used for depression);
- **medicines to treat tuberculosis** or **other infections** (e.g., rifampicin).

Pregnancy and breast-feeding
If the adolescent is pregnant or breast-feeding, think the adolescent may be pregnant or is planning to have a baby, ask the adolescent's doctor, pharmacist or nurse for advice before taking this medicine.

The effects of Eliquis on pregnancy and the unborn child are not known. You should not give this medicine if the adolescent is pregnant. **Contact the adolescent's doctor immediately** if the adolescent becomes pregnant while taking this medicine.

Adolescents who have periods, may experience heavier menstrual bleeding with Eliquis. Please contact the child's doctor for any questions.

It is not known if Eliquis passes into human breast milk. Ask the adolescent's doctor, pharmacist or nurse for advice before giving this medicine to the adolescent if they are breast-feeding. They will advise you whether the adolescent should stop breast-feeding while receiving Eliquis or, instead, should stop taking this medicine.

Driving and using machines
Eliquis has not been shown to impair ability to drive or use machines.

Eliquis contains sucrose
If you have been told by the child's doctor that the child has an intolerance to some sugars, contact the child's doctor before giving this medicine.

3. How to give Eliquis

Always give the child this medicine exactly as the child's doctor has told you. Check with the child's doctor, pharmacist or nurse if you are not sure.

Dose

Try to give the dose at the same time every day to have the best treatment effect.

If the child has difficulty swallowing you may be able to give the liquid mixture through a gastrostomy tube or nasogastric tube. Talk to your doctor about other ways to give Eliquis.

As the Eliquis dose is based on body weight it is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes. This ensures that the child receives the correct dose of Eliquis. Your doctor may adjust the child's dose when needed. Below is the table that your doctor will use. Do not adjust the dose yourself.

Table 1: Recommended dose for Eliquis in children

	Days 1-7		Day 8 and beyond	
Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
4 to < 5	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
5 to < 6	1 mg twice daily	2 mg	0.5 mg twice daily	1 mg
6 to < 9	2 mg twice daily	4 mg	1 mg twice daily	2 mg
9 to < 12	3 mg twice daily	6 mg	1.5 mg twice daily	3 mg
12 to < 18	4 mg twice daily	8 mg	2 mg twice daily	4 mg
18 to < 25	6 mg twice daily	12 mg	3 mg twice daily	6 mg
25 to < 35	8 mg twice daily	16 mg	4 mg twice daily	8 mg
≥ 35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

Please observe the child to ensure the full dose is taken. Your doctor will decide how long you must continue treatment for.

<u>If the child spits up the dose or vomits:</u>
- within 30 minutes after taking the dose, repeat the dose
- more than 30 minutes after taking the dose do not repeat the dose. Continue to give the next Eliquis dose at the next scheduled time. Contact the doctor if the child repeatedly spits up the dose or vomits after taking Eliquis.

The child's doctor might change anticoagulant treatment as follows:

- *Changing from anticoagulant medicines to Eliquis*

Stop giving the anticoagulant medicines. Start treatment with Eliquis at the time the child would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing vitamin K antagonist (e.g., warfarin) to Eliquis*

Stop giving the medicine containing a vitamin K antagonist. The child's doctor needs to do blood-measurements and instruct you when to start giving the child Eliquis.

If you give the child more Eliquis than you should

Tell the child's doctor immediately if you have given the child more than the prescribed dose of this medicine. Take the medicine pack with you, even if there are no medicine left.

If you give the child more Eliquis than recommended, the child may have an increased risk of bleeding. If bleeding occurs, surgery, blood transfusions, or other treatments that may reverse anti-factor Xa activity may be required.

If you forget to give the child Eliquis

- If the child has missed a morning dose, give it as soon as you remember and it may be given together with the evening dose.
- A missed evening dose can only be given during the same evening. Do not give two doses the next morning, instead continue to follow the dosing schedule twice daily as recommended on the next day.

If the child has missed more than one dose of Eliquis, ask the child's doctor, pharmacist or nurse what to do.

If the child stops taking Eliquis:

Do not stop giving this medicine to the child without talking to the child's doctor first, because the risk of developing a blood clot could be higher if the child stops treatment too early.

If you have any further questions on the use of this medicine, ask the child's doctor, pharmacist or nurse.

4. Possible side effects

- **Tell the child's doctor immediately** if you observe any of these symptoms;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. The frequency of these side effects is common (may affect up to 1 in 10 people).

Like all medicines, this medicine can cause side effects, although not everybody gets them. The known side effects for apixaban to treat blood clots and to prevent re-occurrence of blood clots in the veins or in the blood are listed below. In general, the side effects observed in children and adolescents treated with Eliquis were similar in type to those observed in adults were primarily mild to moderate in severity. Side effects that were observed more often in children and adolescents were nose bleed and abnormal vaginal bleeding.

Very Common side effects (may affect more than 1 in 10 people)

- Bleeding including:
  - from the vagina;
  - from the nose.

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
  - from the gums;
  - blood in the urine;
  - bruising and swelling;
  - from the bowel or rectum;
  - bright/red blood in the stools;
  - bleeding after an operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
- Hair loss;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in the child's blood (which can affect clotting);
- Nausea (feeling sick);
- Skin rash;
- Itching;
- Low blood pressure which may make the child feel faint or have a quickened heartbeat;
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in alanine aminotransferase (ALT).

Not known (frequency cannot be estimated from the available data)
- Bleeding:
  - into the abdomen or the space behind the abdominal cavity;
  - in the stomach;
  - in the eyes;
  - in the mouth;
  - from a haemorrhoid;
  - in the mouth or blood in the spit when coughing;
  - in the brain or in the spinal column;
  - in the lungs;
  - into a muscle;
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme);*
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising;
- Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT);
  - tests showing blood in the stools or in the urine.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

Reporting of side effects
If the child gets any side effects, talk to the child's doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eliquis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eliquis contains
- The active substance is apixaban. Each capsule for opening contains 0.15 mg apixaban.
- The other ingredients are:
  - Granules: hypromellose (E464), sugar spheres (composed of sugar syrup, corn starch (E1450), and sucrose). See section 2 “Eliquis contains sucrose”.
    - Capsule shell: gelatin (E441), titanium dioxide (E171), iron oxide yellow (E172)
    - Black printing ink: shellac (E904), propylene glycol (E1520), iron oxide black

What Eliquis looks like and contents of the pack
Granules are white to off-white in appearance and are presented in containers to be opened (the capsule should not be swallowed whole).

The capsule have a clear body and a yellow opaque top.

Eliquis is available in bottles, inside a carton. Each bottle contains 28 capsules for opening.

Patient Card: handling information
Inside the Eliquis pack together with the package leaflet you will find a Patient Card or the child’s doctor might give you a similar card.

This Patient Card includes information that will be helpful to the child and alert other doctors that the child is taking Eliquis. **This card should be with the child or the caregiver at all times.**

1. Take the card.
2. Separate your language as needed (this is facilitated by the perforated edges).
3. Complete the following sections or ask your doctor to do it:
   - Name:
   - Birth Date:
   - Indication:
   - Weight:
   - Dose: .....mg twice daily:
   - Doctor’s Name:
   - Doctor’s telephone:
4. Fold the card and keep it with the child at all times

Marketing Authorisation Holder
Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer, spol. s r.o.
Tel.: +420 283 004 111
Medical.information@pfizer.com

Danmark
Bristol-Myers Squibb Denmark
Tlf: + 45 45 93 05 06
medinfo.denmark@bms.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: 0800 0752002 (+ 49 89 121 42 350)
medwiss.info@bms.com

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Bristol-Myers Squibb, S.A.
Tel: + 34 91 456 53 00
informacion.medica@bms.com

France
Bristol-Myers Squibb SAS
Tél: + 33 (0)1 58 83 84 96
infomed@bms.com

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Bristol-Myers Squibb Pharmaceuticals uc
Tel: 1 800 749 749 (+ 353 (0)1 483 3625)
medical.information@bms.com

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +370 5 251 4000

Luxembourg/Luxemburg
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Nederland
Bristol-Myers Squibb B.V.
Tel: + 31 (0)30 300 2222
medischeafdeling@bms.com

Norge
Bristol-Myers Squibb Norway AS
Tlf: + 47 67 55 53 50
medinfo.norway@bms.com

Österreich
Bristol-Myers Squibb GesmbH
Tel: + 43 1 60 14 30
medinfo.austria@bms.com

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Bristol-Myers Squibb Farmacêutica Portuguesa, S.A.
Tel: + 351 21 440 70 00
portugal.medinfo@bms.com

România
Pfizer Romania S.R.L
Tel: +40 (0)21 207 28 00

Slovenija

Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: + 386 (0) 1 52 11 400

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Bristol-Myers Squibb S.r.l.
Tel: + 39 06 50 39 61
medicalinformation.italia@bms.com

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel.: +371 670 35 775

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: **+421-2-3355 5500**

Suomi/Finland
Oy Bristol-Myers Squibb (Finland) Ab
Puh/Tel: + 358 9 251 21 230
medinfo.finland@bms.com

Sverige
Bristol-Myers Squibb Aktiebolag
Tel: + 46 8 704 71 00
medinfo.sweden@bms.com

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

INSTRUCTIONS FOR USE ELIQUIS 0.15 MG GRANULES IN CAPSULES FOR OPENING

Important information:

- **For more information about Eliquis, refer to the Package Leaflet or talk with your doctor.**
- **For patients with fluid restrictions, volume of formula or water may be reduced to no less than 2.5 mL.**

Preparing the dose using granules in capsules for opening

READ THE FOLLOWING INSTRUCTIONS BEFORE PREPARING AND GIVING A DOSE.

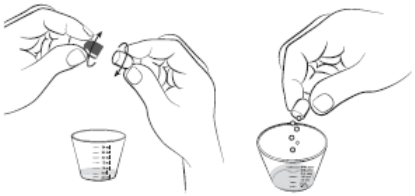
You will need a medicine cup, oral dosing syringe and a small spoon (for mixing) to administer this medicine. You can get these supplies at a pharmacy, if needed.

LIQUID mixing method for granules in capsules for opening

❑ **STEP 1: Prepare supplies** • **Wash and dry** your hands. • **Clean and prepare flat work surface.** • **Gather** your supplies: o Capsule for opening (check the prescription for the number of capsule for opening to use per dose). o Oral syringe (to give medicine to your infant) o Medicine cup (to mix medicine) o Small spoon o **Mixing liquid** (use **baby formula or water).**	Capsule for opening Mixing liquid: use baby formula or Water Small spoon   Medicine cup   Oral syringe
❑ **STEP 2: Add liquid to medicine cup** • **Add approximately 5 mL (a teaspoon)** of liquid to medicine cup. ***Warning: in order to ensure complete dose, DO NOT put the medicine in a baby bottle***	
❑ **STEP 3: Tap capsule for opening** • **Hold** the capsule for opening with the coloured end up. • **Tap** the clear end to get medicine in clear end.	

❑ **STEP 4: Open capsule for opening - Sprinkle medicine into cup**

- **Hold** the capsule for opening over the medicine cup.
- **Twist** both ends of the capsule for opening and slowly pull it apart.
- **Sprinkle** the content of the capsule for opening in the liquid.
- **Check** the capsule for opening shells to make sure they are empty.



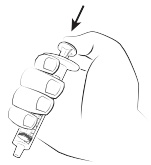
❑ **STEP 5: Mixing**

- **Hold** the medicine cup with one hand.
- **Stir** the medicine in the liquid using a small spoon.
- **Continue to stir** until medicine is dissolved. The medicine should dissolve quickly and will be cloudy.

❑ **STEP 6: Give medicine**

This is a <u>2-part process</u> to ensure ALL the medicine is given.
<u>Follow both Part 1 and Part 2.</u>

<u>Part 1:</u> <u>Pull up ALL liquid mixture with the oral syringe and give all medicine in syringe.</u>

PUSH plunger	**Pull up ALL the liquid mixture so no medicine is left in the dosing cup**	**Administer SLOWLY and give all medicine in syringe**
		

<u>Part 2:</u> <u>Repeat to ensure any remaining medicine is given as follows:</u>

Add approximately 5 mL (a teaspoon) MORE liquid to medicine cup	**GENTLY stir liquid with small spoon**	**PUSH plunger**	**Pull up ALL the liquid mixture so no medicine is left in the dosing cup**	**Administer SLOWLY and give all medicine in syringe**
				

❑ **STEP 7: Wash**

- **Throw** away the empty capsule for opening
- Wash the outside and the inside of the syringe with water.
- Wash the medicine cup and small spoon.

Be sure to give the medicine immediately or at the latest within 2 hours of preparation.

Package leaflet: Information for the user

Eliquis 0.5 mg coated granule in sachet
Eliquis 1.5 mg coated granules in sachet
Eliquis 2 mg coated granules in sachet

apixaban

Read all of this leaflet carefully before you start giving this medicine because it contains important information for you. This leaflet has been written for the patients ("you") and the parent or caregiver who will give this medicines to the child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eliquis is and what it is used for

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in children aged 28 days to less than 18 years to treat blood clots and prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs.

For body weight appropriate recommended dose, see section 3.

2. What you need to know before you give Eliquis

Do not give Eliquis if
- **the child is allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6);
- **the child is bleeding excessively**;
- the child has a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of stomach or bowel, **recent bleeding in brain**);
- the child has a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy);
- **the child is taking medicines to prevent blood clotting** (e.g., warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment, while having a venous or arterial line and the child gets heparin through this line to keep it open, or if a tube is inserted into blood vessel (catheter ablation) to treat an irregular heartbeat (arrhythmia).

Warnings and precautions
Talk to the child's doctor, pharmacist or nurse before you give this medicine if the child has any of the following:
- an **increased risk of bleeding**, such as:
  - **bleeding disorders**, including conditions resulting in reduced platelet activity;
  - **very high blood pressure**, not controlled by medical treatment;
- **severe kidney disease or if the child is on dialysis;**
- a **liver problem or a history of liver problems**;
  - This medicine will be used with caution in patients with signs of altered liver function.
- **had a tube (catheter) or an injection into spinal column** (for anaesthesia or pain reduction), the child's doctor will tell you to give this medicine 5 hours or more after catheter removal;
- if the child has an artificial **heart valve**;
- if the child's doctor determines that the child's blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from the child's lungs is planned.

Take special care with Eliquis
- if you know that the child has a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell the child's doctor who will decide if the treatment may need to be changed.

If the child needs to have surgery or a procedure which may cause bleeding, the child's doctor might ask you to temporarily stop giving this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask the child's doctor.

Children and adolescents
Eliquis coated granules in sachets are to be used for children weighing from 5 kg to less than 35 kg to treat blood clots and prevent re-occurrence of blood clots in the veins. There is not enough information on its use in children and adolescents in other indications.

Other medicines and Eliquis
Tell the child's doctor, pharmacist or nurse if the child is taking, has recently taken, or might take any other medicines.

Some medicines may increase the effects of Eliquis and some may decrease its effects. The child's doctor will decide, if the child should be treated with Eliquis when taking these medicines and how closely the child should be monitored.

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:
- some **medicines for fungal infections** (e.g., ketoconazole, etc.);
- some **antiviral medicines for HIV / AIDS** (e.g., ritonavir);
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.);
- **anti-inflammatory** or **pain medicines** (e.g., acetylsalicylic acid or naproxen);
- **medicines for high blood pressure or heart problems** (e.g., diltiazem);
- **antidepressant medicines** called **selective serotonin re-uptake inhibitors** or **serotonin norepinephrine re-uptake inhibitors**.

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:
- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.);
- **St John's Wort** (a herbal supplement used for depression);
- **medicines to treat tuberculosis** or **other infections** (e.g., rifampicin).

Pregnancy and breast-feeding
If the adolescent is pregnant or breast-feeding, think the adolescent may be pregnant or is planning to have a baby, ask the adolescent's doctor, pharmacist or nurse for advice before taking this medicine.

The effects of Eliquis on pregnancy and the unborn child are not known. You should not give this medicine if the adolescent is pregnant. **Contact the adolescent's doctor immediately** if the adolescent becomes pregnant while taking this medicine.

Adolescents who have periods, may experience heavier menstrual bleeding with Eliquis. Please contact the child's doctor for any questions.

It is not known if Eliquis passes into human breast milk. Ask the adolescent's doctor, pharmacist or nurse for advice before giving this medicine to the adolescent if they are breast-feeding. They will advise you whether the adolescent should stop breast-feeding while receiving Eliquis or, instead, should stop taking this medicine.

Driving and using machines
Eliquis has not been shown to impair ability to drive or use machines.

Eliquis contains lactose (a type of sugar) and sodium
If you have been told by the child's doctor that the child has an intolerance to some sugars, contact the child's doctor before giving this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per coated granule, that is to say essentially "sodium-free".

3. How to give Eliquis

Always give the child this medicine exactly as the child's doctor has told you. Check with the child's doctor, pharmacist or nurse if you are not sure.

Dose

Try to give the dose at the same time every day to have the best treatment effect.

If the child has difficulty swallowing you may be able to give the liquid mixture through a gastrostomy tube or nasogastric tube. Talk to your doctor about other ways to give Eliquis.

As the Eliquis dose is based on body weight it is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes. This ensures that the child receives the correct dose of Eliquis. Your doctor may adjust the child's dose when needed. Below is the table that your doctor will use. Do not adjust the dose yourself.

Table 1: Recommended dose for Eliquis in children

	Days 1-7		Day 8 and beyond	
Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
4 to < 5	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
5 to < 6	1 mg twice daily	2 mg	0.5 mg twice daily	1 mg
6 to < 9	2 mg twice daily	4 mg	1 mg twice daily	2 mg
9 to < 12	3 mg twice daily	6 mg	1.5 mg twice daily	3 mg
12 to < 18	4 mg twice daily	8 mg	2 mg twice daily	4 mg
18 to < 25	6 mg twice daily	12 mg	3 mg twice daily	6 mg
25 to < 35	8 mg twice daily	16 mg	4 mg twice daily	8 mg
≥ 35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

Please observe the child to ensure the full dose is taken. Your doctor will decide how long you must continue treatment for.

If the child spits up the dose or vomits:

- within 30 minutes after taking the dose, repeat the dose.
- more than 30 minutes after taking the dose do not repeat the dose.

Continue to give the next Eliquis dose at the next scheduled time. Contact the doctor if the child repeatedly spits up the dose or vomits after taking Eliquis.

The child's doctor might change anticoagulant treatment as follows:

- *Changing from anticoagulant medicines to Eliquis*

Stop giving the anticoagulant medicines. Start treatment with Eliquis at the time the child would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing vitamin K antagonist (e.g., warfarin) to Eliquis*

Stop giving the medicine containing a vitamin K antagonist. The child's doctor needs to do blood-measurements and instruct you when to start giving the child Eliquis.

If you give the child more Eliquis than you should

Tell the child's doctor immediately if you have given the child more than the prescribed dose of this medicine. Take the medicine pack with you, even if there are no medicine left.

If you give the child more Eliquis than recommended, the child may have an increased risk of bleeding. If bleeding occurs, surgery, blood transfusions, or other treatments that may reverse anti-factor Xa activity may be required.

If you forget to give the child Eliquis

- If the child has missed a morning dose, give it as soon as you remember and it may be given together with the evening dose.
- A missed evening dose can only be given during the same evening. Do not give two doses the next morning, instead continue to follow the dosing schedule twice daily as recommended on the next day.

If the child has missed more than one dose of Eliquis, ask the child's doctor, pharmacist or nurse what to do.

If the child stops taking Eliquis

Do not stop giving this medicine to the child without talking to the child's doctor first, because the risk of developing a blood clot could be higher if the child stops treatment too early.

If you have any further questions on the use of this medicine, ask the child's doctor, pharmacist or nurse.

4. Possible side effects

- **Tell the child's doctor immediately** if you observe any of these symptoms;
- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. The frequency of these side effects is common (may affect up to 1 in 10 people).

Like all medicines, this medicine can cause side effects, although not everybody gets them. The known side effects for apixaban to treat blood clots and to prevent re-occurrence of blood clots in the veins or in the blood are listed below. In general, the side effects observed in children and adolescents treated with Eliquis were similar in type to those observed in adults were primarily mild to moderate in severity. Side effects that were observed more often in children and adolescents were nose bleed and abnormal vaginal bleeding.

Very Common side effects (may affect more than 1 in 10 people)
- Bleeding including:
  - from the vagina;
  - from the nose.

Common side effects (may affect up to 1 in 10 people)
- Bleeding including:
  - from the gums;
  - blood in the urine;
  - bruising and swelling;
  - from the bowel or rectum;
  - bright/red blood in the stools;
  - bleeding after an operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site;
- Hair loss;
- Anaemia which may cause tiredness or paleness;
- Reduced number of platelets in the child's blood (which can affect clotting);
- Nausea (feeling sick);
- Skin rash;
- Itching;
- Low blood pressure which may make the child feel faint or have a quickened heartbeat;
- Blood tests may show:
  - abnormal liver function;
  - an increase in some liver enzymes;
  - an increase in alanine aminotransferase (ALT).

Not known (frequency cannot be estimated from the available data)
- Bleeding:
  - into the abdomen or the space behind the abdominal cavity;
  - in the stomach;
  - in the eyes;
  - in the mouth;
  - from a haemorrhoid;
  - in the mouth or blood in the spit when coughing;
  - in the brain or in the spinal column;
  - in the lungs;
  - into a muscle;
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme);*
- Blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising. Blood tests may show:
  - an increase in gamma-glutamyltransferase (GGT);
  - tests showing blood in the stools or in the urine.
- Bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

Reporting of side effects
If the child gets any side effects, talk to the child's doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eliquis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the sachet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eliquis contains

- The active substance is apixaban. Each sachet contains 0.5 mg, 1.5 mg or 2 mg apixaban.
- The other ingredients are:
  - Granule core: **lactose** (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), microcrystalline cellulose, croscarmellose sodium (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), sodium laurilsulfate, magnesium stearate (E470b);
  - Film coat: lactose monohydrate (see section 2 “Eliquis contains lactose (a type of sugar) and sodium”), hypromellose (E464), titanium dioxide (E171), triacetin, iron oxide red (E172).

What Eliquis looks like and contents of the pack
0.5 mg pink round coated granules in 0.5 mg, 1.5 mg, and 2 mg sachets

- Aluminium foil sachet containing one 0.5 mg coated granule
- Aluminium foil sachet containing three 0.5 mg coated granules
- Aluminium foil sachet containing four 0.5 mg coated granules

Each carton contains 28 sachets.

Patient Card: handling information
Inside the Eliquis pack together with the package leaflet you will find a Patient Card or the child’s doctor might give you a similar card.

This Patient Card includes information that will be helpful to the child and alert other doctors that the child is taking Eliquis. **This card should be with the child or the caregiver at all times.**

1. Take the card.
2. Separate your language as needed (this is facilitated by the perforated edges).
3. Complete the following sections or ask the child’s doctor to do it:
   - Name:
   - Birth Date:
   - Indication:
   - Weight:
   - Dose:.....mg twice daily
   - Doctor's Name:
   - Doctor's telephone:
4. Fold the card and keep it with the child at all times

Marketing Authorisation Holder
Bristol-Myers Squibb/Pfizer EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer, spol. s r.o.
Tel.: +420 283 004 111
Medical.information@pfizer.com

Danmark
Bristol-Myers Squibb Denmark
Tlf: + 45 45 93 05 06
medinfo.denmark@bms.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: 0800 0752002 (+ 49 89 121 42 350)
medwiss.info@bms.com

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Bristol-Myers Squibb, S.A.
Tel: + 34 91 456 53 00
informacion.medica@bms.com

France
Bristol-Myers Squibb SAS
Tél: + 33 (0)1 58 83 84 96
infomed@bms.com

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +370 5 251 4000

Luxembourg/Luxemburg
N.V. Bristol-Myers Squibb Belgium S.A.
Tél/Tel: + 32 2 352 76 11
medicalinfo.belgium@bms.com

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Nederland
Bristol-Myers Squibb B.V.
Tel: + 31 (0)30 300 2222
medischeafdeling@bms.com

Norge
Bristol-Myers Squibb Norway AS
Tlf: + 47 67 55 53 50
medinfo.norway@bms.com

Österreich
Bristol-Myers Squibb GesmbH
Tel: + 43 1 60 14 30
medinfo.austria@bms.com

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Bristol-Myers Squibb Farmacêutica Portuguesa, S.A.
Tel: + 351 21 440 70 00
portugal.medinfo@bms.com

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Bristol-Myers Squibb Pharmaceuticals uc
Tel: 1 800 749 749 (+ 353 (0)1 483 3625)
medical.information@bms.com

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Bristol-Myers Squibb S.r.l.
Tel: + 39 06 50 39 61
medicalinformation.italia@bms.com

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel.: +371 670 35 775

România
Pfizer Romania S.R.L
Tel: +40 (0)21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: + 386 (0) 1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: **+421-2-3355 5500**

Suomi/Finland
Oy Bristol-Myers Squibb (Finland) Ab
Puh/Tel: + 358 9 251 21 230
medinfo.finland@bms.com

Sverige
Bristol-Myers Squibb Aktiebolag
Tel: + 46 8 704 71 00
medinfo.sweden@bms.com

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

INSTRUCTIONS FOR USE ELIQUIS COATED GRANULES IN SACHET

Important information:

- **For more information about Eliquis, refer to the Package Leaflet or talk with your doctor.**
- **For patients with fluid restrictions, volume of formula or water may be reduced to no less than 2.5 mL**

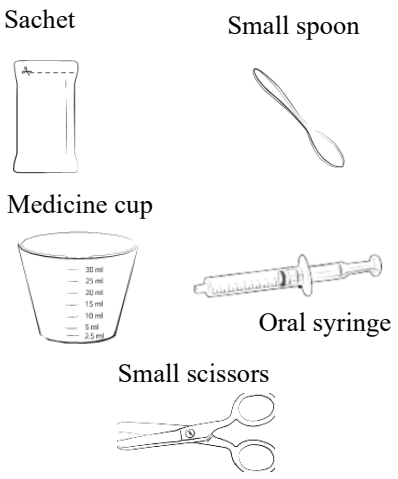
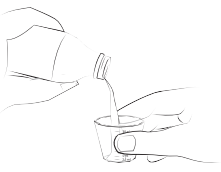
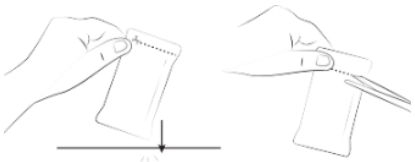
Preparing the dose using sachets

READ THE FOLLOWING INSTRUCTIONS BEFORE PREPARING AND GIVING A DOSE.

There are 2 ways you can mix and give this medicine:
- **LIQUID** method using an oral syringe, **or**
- **FOOD** method using a small bowl and spoon.

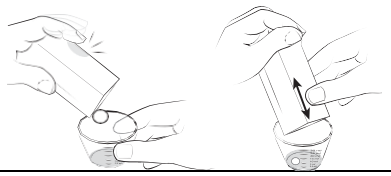
You will need a medicine cup and oral dosing syringe (LIQUID mixing) **or** a cup and small spoon (FOOD mixing) to administer this medicine. You can get these supplies at a pharmacy, if needed.

LIQUID mixing method for sachets

❑ **STEP 1: Prepare supplies** • **Wash and dry** your hands. • **Clean and prepare flat work surface.** • **Gather** your supplies: o **Sachets** (check label on your prescription for the number of sachets your doctor has prescribed to use per dose). o Oral syringe (to give medicine) o Medicine cup (to mix medicine) o Small spoon (to mix medicine) o Small scissors (to open sachet) o **Mixing liquid** (use **baby formula, water or apple juice**).	
❑ **STEP 2: Add liquid to medicine cup** • **Add approximately 10 mL (2 teaspoons)** of liquid to medicine cup. ***Warning: in order to ensure complete dose, DO NOT put the medicine in a baby bottle***	
❑ **STEP 3: Tap and open sachet** • **Tap** sachet to move the coated granule(s) inside to the bottom. • **Cut** the dotted line on the sachet to open it.	

❑ **STEP 4: Empty the sachet**

- **Empty** the coated granule(s) inside the sachet into the medicine cup.
- **Run** your finger over the sachet to remove all coated granules.

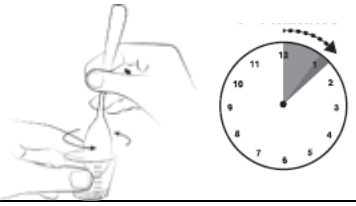


❑ **STEP 5: Mixing**

- **Hold** the medicine cup with one hand and use a small spoon to stir and crush the medicine.
- **Stir until <u>completely</u> dissolved**. This should take 5-7 minutes.

  Dissolving is important for correct dose.

5-7 minutes



❑ **STEP 6: Give medicine**

This is a <u>2-part process</u> to ensure ALL the medicine is given.
<u>Follow both Part 1 and Part 2.</u>

<u>Part 1:</u> Pull up ALL liquid mixture with the oral syringe and give all medicine in syringe.

PUSH plunger

Pull up ALL the liquid mixture so no medicine is left in the dosing cup

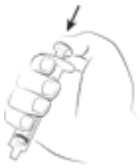
Administer SLOWLY and give all medicine in syringe

<u>Part 2:</u> Repeat to ensure any remaining medicine is given as follows:

Add approximately 5 mL (a teaspoon) MORE liquid to medicine cup

GENTLY stir liquid with small spoon

PUSH plunger



Pull up ALL the liquid mixture so no medicine is left in the dosing cup

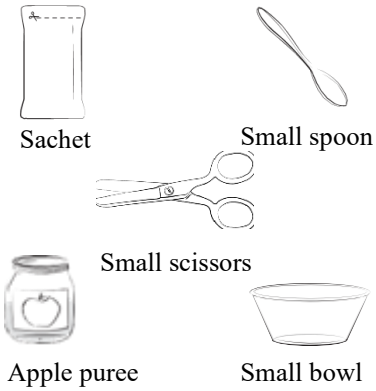
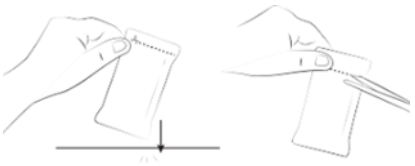
Administer SLOWLY and give all medicine in syringe

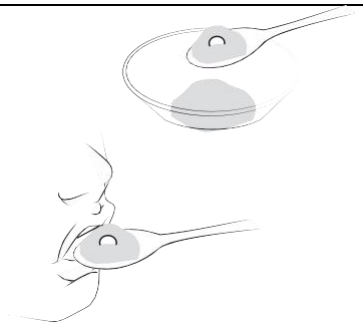
❑ **STEP 7: Wash**

- **Throw** away the empty sachet
- Wash the outside and the inside of the syringe with water.
- Wash the medicine cup and small spoon.

Be sure to give the medicine immediately or at the latest within 2 hours of preparation.

FOOD mixing method for sachet

❑ **STEP 1: Prepare supplies** • **Wash and dry** your hands. • **Clean and prepare flat work surface.** • **Gather** your supplies: o **Sachets** (check the prescription for the number of sachets your doctor has prescribed to use per dose). o Small bowl (to mix medicine) o Small spoon (to mix medicine) o Small scissors (to open sachet) o Apple puree	
❑ **STEP 2: Prepare for mixing** • **Add approximately (15 mL) 1 tablespoon** of food to bowl.	
❑ **STEP 3: Tap and open sachet** • **Tap** sachet to move the coated granules inside to the bottom. • **Cut** the dotted line on the sachet to open it.	
❑ **STEP 4: Empty the sachet** • **Empty** the coated granule(s) inside the sachet into the bowl. • **Run** your finger over the sachet to remove all coated granules.	
❑ **STEP 5: Mixing** • **Hold** the small bowl with one hand and use a small spoon to stir the coated granule(s) into the apple puree. The coated granules do not need to dissolve in the food.	

❑ **STEP 6: Give medicine** • **Give** food and medicine mixture by small spoon. • **Ensure ALL** medicine and food have been given so no medicine is left in the bowl.	
❑ **STEP 7: Wash** • **Throw** away the empty sachet. • Wash cup, small bowl and small spoon.	
Be sure to give the medicine immediately.	