

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Apixaban Accord 2.5 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg apixaban.

### Excipients with known effect

Each 2.5 mg film-coated tablet contains 51.97 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 shaped, approximate 6.00 mm in diameter, biconvex, film-coated tablet debossed with "IU1" on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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  $\geq 75$  years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class  $\geq$  II).

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

### 4.2 Posology and method of administration

#### Posology

#### Prevention of VTE (VTEp): elective hip or knee replacement surgery

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 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  $\geq$  80 years, body weight  $\leq$  60 kg, or serum creatinine  $\geq$  1.5 mg/dL (133 micromole/L).

Therapy should be continued long-term.

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

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).

### *Missed dose*

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

### *Switching*

Switching treatment from parenteral anticoagulants to Apixaban Accord (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 Apixaban Accord*

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

### *Switching from Apixaban Accord to VKA therapy*

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

### 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

In 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  $\geq 1.5$  mg/dL (133 micromole/L) associated with age  $\geq 80$  years or body weight  $\leq 60$  kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2).

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

- for the 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).

### Hepatic impairment

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

### Body weight

VTEp and VTEt - No dose adjustment required (see sections 4.4 and 5.2).

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

### Gender

No dose adjustment required (see section 5.2).

### Patients undergoing catheter ablation (NVAF)

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

### Patients undergoing cardioversion

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

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

For patients initiating treatment with apixaban, 5 mg 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, 5.1).

### Paediatric population

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

### Method of administration

#### Oral use

Apixaban Accord should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Apixaban Accord 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, Apixaban Accord 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 Apixaban Accord 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, 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).

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

##### 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 medicinal products (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 patients with atrial fibrillation, concomitant use of acetylsalicylic acid (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 (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).

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

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

#### Patients with prosthetic heart valves

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

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Surgery and invasive procedures

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.

#### 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

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  $\geq$  1.5 mg/dL (133 micromole/L) associated with age  $\geq$  80 years or body weight  $\leq$  60 kg should receive the lower dose of 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).

#### 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

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  $\geq$  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)

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

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

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

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

- for the prevention of 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.

#### 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

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

#### Inducers of CYP3A4 and P-gp

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

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

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

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

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

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

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

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

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

There is limited experience of co-administration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfinpyrazone) or thrombolytic agents. As

such agents increase the bleeding risk, co-administration of these medicinal products with apixaban is not recommended (see section 4.4).

#### Other concomitant therapies

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

#### Effect of apixaban on other medicinal products

*In vitro* apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 ( $IC_{50} > 45 \mu M$ ) and weak inhibitory effect on the activity of CYP2C19 ( $IC_{50} > 20 \mu M$ ) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to  $20 \mu M$ . Therefore, apixaban is not expected to alter the metabolic clearance of coadministered medicinal products that are 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).

## **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

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

#### 4.8 Undesirable effects

##### Summary of the safety profile

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

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

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

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

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

##### Tabulated list of adverse reactions

Table 2 shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively.

**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)
<i>Blood and lymphatic system disorders</i>			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
<i>Immune system disorders</i>			
Hypersensitivity, allergic oedema and anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon*
Angioedema	Not known	Not known	Not known
<i>Nervous system disorders</i>			
Brain haemorrhage <sup>†</sup>	Not known	Uncommon	Rare

<b>System organ class</b>	<b>Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)</b>	<b>Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors (NVAf)</b>	<b>Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)</b>
<i>Eye disorders</i>			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
<i>Vascular disorders</i>			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon
Intra-abdominal haemorrhage	Not known	Uncommon	Not known
<i>Respiratory, thoracic and mediastinal disorders</i>			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	Not known	Rare	Rare
<i>Gastrointestinal disorders</i>			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidal haemorrhage	Not known	Uncommon	Uncommon
Mouth haemorrhage	Not known	Uncommon	Common
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	Not known	Rare	Not known
<i>Hepatobiliary disorders</i>			
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon
Gamma-glutamyltransferase increased	Uncommon	Common	Common
Alanine aminotransferase increased	Uncommon	Uncommon	Common
<i>Skin and subcutaneous tissue disorders</i>			
Skin rash	Not known	Uncommon	Common
Alopecia	Rare	Uncommon	Uncommon
Erythema multiforme	Not known	Very rare	Not known
Cutaneous vasculitis	Not known	Not known	Not known
<i>Musculoskeletal and connective tissue disorders</i>			
Muscle haemorrhage	Rare	Rare	Uncommon
<i>Renal and urinary disorders</i>			
Haematuria	Uncommon	Common	Common
<i>Reproductive system and breast disorders</i>			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common
<i>General disorders and administration site conditions</i>			
Application site bleeding	Not known	Uncommon	Uncommon

<b>System organ class</b>	<b>Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)</b>	<b>Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors (NVAf)</b>	<b>Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)</b>
<i>Investigations</i>			
Occult blood positive	Not known	Uncommon	Uncommon
<i>Injury, poisoning and procedural complications</i>			
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	Uncommon
Traumatic haemorrhage	Not known	Uncommon	Uncommon

\* 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).

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).

#### 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.

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

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

For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available (see section 4.4). Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered. Reversal of apixaban pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 4-factor PCC 30 minute infusion in healthy subjects. However, there is no clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received apixaban. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

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

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.

## **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). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-Factor Xa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-Factor Xa kits, however results differ across kits. Data from clinical studies are only available for the Rotachrom<sup>®</sup> 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.

Table 3 below shows the predicted steady state exposure and anti-Factor Xa activity for each indication. In patients taking apixaban for the prevention of VTE following hip or knee replacement surgery, the results demonstrate a less than 1.6-fold fluctuation in peak-to-trough levels. In 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.

<b>Table 3: Predicted apixaban steady-state exposure and anti-Factor Xa activity</b>				
	<b>Apix. C<sub>max</sub> (ng/mL)</b>	<b>Apix. C<sub>min</sub> (ng/mL)</b>	<b>Apix. anti-Factor Xa activity max (IU/mL)</b>	<b>Apix. anti-Factor Xa activity min (IU/mL)</b>
Median [5th, 95th Percentile]				
<i>Prevention of VTE: elective hip or knee replacement surgery</i>				
2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
<i>Prevention of stroke and systemic embolism: NVAf</i>				
2.5 mg 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]
<i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)</i>				
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.

#### 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 ( $\leq 60$  kg), 1,495 patients (743 in the apixaban group) with BMI  $\geq 33$  kg/m<sup>2</sup>, and 415 patients (203 in the apixaban group) with moderate renal impairment.

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

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

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal DVT, non-fatal PE, and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 4).



**Table 4: Efficacy results from pivotal phase III studies**

Study	ADVANCE-3 (hip)			ADVANCE-2 (knee)		
	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	27/1,949 1.39%	74/1,917 3.86%	< 0.0001	147/976 15.06%	243/997 24.37%	<0.0001
Event rate						
Relative risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Major VTE						
Number of events/subjects	10/2,199 0.45%	25/2,195 1.14%	0.0107	13/1,195 1.09%	26/1,199 2.17%	0.0373
Event rate						
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 clinically relevant non-major (CRNM) bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 5). All the bleeding criteria included surgical site bleeding.

**Table 5: 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
<b>Treatment Period<sup>1</sup></b>				
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%)
<b>Post-surgery treatment period<sup>2</sup></b>				
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

<sup>1</sup> Includes events occurring after first dose of enoxaparin (pre-surgery)

<sup>2</sup> 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 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  $\geq$  75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class  $\geq$  II)

ARISTOTLE study

In the ARISTOTLE study a total of 18,201 patients were 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<sub>2</sub> 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 6) compared with warfarin.

Table 6: Efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study

	<b>Apixaban N=9,120 n (%/yr)</b>	<b>Warfarin N=9,081 n (%/yr)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
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 7). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

**Table 7: Secondary endpoints in patients with atrial fibrillation in the ARISTOTLE study**

	<b>Apixaban N = 9,088 n (%/year)</b>	<b>Warfarin N = 9,052 n (%/year)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
<b>Bleeding outcomes</b>				
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
<b>Other endpoints</b>				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66, 1.17)	

\* Major bleeding defined per 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<sub>2</sub> score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

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

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

#### AVERROES study

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were 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<sub>2</sub> score was 2.0 and 13.6% of patients had prior stroke or TIA.

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

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

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

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism (see Table 8) compared to ASA.

**Table 8: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study**

	<b>Apixaban N = 2,807 n (%/year)</b>	<b>ASA N = 2,791 n (%/year)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
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 9).

**Table 9: Bleeding events in patients with atrial fibrillation in the AVERROES study**

	<b>Apixaban N = 2,798 n(%/year)</b>	<b>ASA N = 2,780 n (%/year)</b>	<b>Hazard ratio (95%CI)</b>	<b>p-value</b>
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 4,614 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 CHA2DS2-VASc score > 2, and 47% had a HAS-BLED score > 3. For patients randomised to VKA, the proportion of time in therapeutic range (TTR) (INR 2-3) was 56%, with 32% of time below TTR and 12% above TTR.

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

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

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

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

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

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

#### Patients undergoing cardioversion

EMANATE, an open-label, multi-center study, enrolled 1500 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 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 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 $\geq$  2) and warfarin (target INR range 2.0-3.0) orally for 6 months.

The mean age was 56.9 years and 89.8% of 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 10).

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

	<b>Apixaban N=2,609 n (%)</b>	<b>Enoxaparin/Warfarin in N=2,635 n (%)</b>	<b>Relative risk (95% CI)</b>
VTE or VTE-related death	59 (2.3)	71 (2.7)	0.84 (0.60, 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 11).

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

	<b>Apixaban N=2,676 n (%)</b>	<b>Enoxaparin/ Warfarin N=2,689 n (%)</b>	<b>Relative risk (95% CI)</b>
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55)
Major + CRNM	115 (4.3)	261 (9.7)	0.44 (0.36, 0.55)

	<b>Apixaban</b> N=2,676 n (%)	<b>Enoxaparin/ Warfarin</b> N=2,689 n (%)	<b>Relative risk</b> (95% CI)
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 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 12).

**Table 12: Efficacy results in the AMPLIFY-EXT study**

	<b>Apixaban</b>	<b>Apixaban</b>	<b>Placebo</b> (N=829)	<b>Relative risk (95% CI)</b>	
	<b>2.5 mg</b> (N=840)	<b>5.0 mg</b> (N=813)		<b>Apix 2.5 mg</b> <b>vs. placebo</b>	<b>Apix 5.0 mg</b> <b>vs. placebo</b>
	n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15, 0.40) <sup>‡</sup>	0.19 (0.11, 0.33) <sup>‡</sup>
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 <sup>†</sup>	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)
Nonfatal PE <sup>†</sup>	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)

<sup>‡</sup>p-value < 0.0001

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

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

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

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see Table 13).

**Table 13: Bleeding results in the AMPLIFY-EXT study**

	Apixaban	Apixaban	Placebo (N=826)	Relative risk (95% CI)	
	2.5 mg (N=840)	5.0 mg (N=811)		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

There is no authorised paediatric indication (see section 4.2).

#### 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  $\geq 1$  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 14). 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 14: Apixaban dosing in the PREVAPIX-ALL study**

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



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

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

*Prevention of thromboembolism (TE) in 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 15). 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 15: Apixaban dosing in the SAXOPHONE study**

Weight Range	Dose schedule
6 to < 9 kg	1 mg twice daily
9 to < 12 kg	1.5 mg twice daily
12 to < 18 kg	2 mg twice daily
18 to < 25 kg	3 mg twice daily
25 to < 35 kg	4 mg twice daily
≥ 35 kg	5 mg twice daily

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

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

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

## 5.2 Pharmacokinetic properties

### Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or  $C_{max}$  at the 10 mg dose. Apixaban can be taken with or without food.

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

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

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

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

### Biotransformation and elimination

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

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

O-demethylation and hydroxylation at the 3-oxopiperidiny 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.

### 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.

### Gender

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

### Ethnic origin and race

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

### Body weight

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

### Pharmacokinetic/pharmacodynamic relationship

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

## **5.3 Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-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  
Cellulose, microcrystalline  
Croscarmellose sodium  
Sodium laurilsulfate  
Magnesium stearate

Film coat:

Hypromellose  
Lactose monohydrate  
Titanium dioxide (E171)  
Triacetin  
Iron oxide yellow (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 condition.

**6.5 Nature and contents of container**

PVC/PVdC-Aluminium blisters are available in 10, 14, 20, 28, 56, 60, 100, 112, 168, and 200 film-coated tablets.

PVC/PVdC-Aluminium blisters are available in perforated unit dose blisters of 10 x 1, 20 x 1, 28 x 1, 56 x 1, 60 x 1, 100 x 1 and 168 x 1 film-coated tablet.

HDPE bottle with polypropylene child resistant/continues threaded closure containing 60, 100, 168, 180, 200 and 1,000 film-coated tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

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

**7. MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6<sup>a</sup> Planta,  
Barcelona, 08039  
Spain

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/001  
EU/1/20/1458/003  
EU/1/20/1458/004  
EU/1/20/1458/006

EU/1/20/1458/008  
EU/1/20/1458/010  
EU/1/20/1458/012  
EU/1/20/1458/014  
EU/1/20/1458/041  
EU/1/20/1458/043

EU/1/20/1458/002  
EU/1/20/1458/005  
EU/1/20/1458/007  
EU/1/20/1458/009  
EU/1/20/1458/011  
EU/1/20/1458/013  
EU/1/20/1458/042

EU/1/20/1458/015  
EU/1/20/1458/016  
EU/1/20/1458/017  
EU/1/20/1458/018  
EU/1/20/1458/019  
EU/1/20/1458/020

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 23 July 2020

#### **10. DATE OF REVISION OF THE TEXT**

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

## 1. NAME OF THE MEDICINAL PRODUCT

Apixaban Accord 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 103.95 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 shaped, approximate 9.8 mm in length, 5.2 mm in width, biconvex, film-coated tablet debossed with "IU2" on one side and plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

### 4.2 Posology and method of administration

#### Posology

#### Prevention of stroke and systemic embolism in 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  $\geq 80$  years, body weight  $\leq 60$  kg, or serum creatinine  $\geq 1.5$  mg/dL (133 micromole/L).

Therapy should be continued long-term.

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

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).

Missed dose

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

Switching

Switching treatment from parenteral anticoagulants to Apixaban Accord (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 Apixaban Accord*

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

*Switching from Apixaban Accord to VKA therapy*

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

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

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

- for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (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  $\geq 1.5$  mg/dL (133 micromole/L) associated with age  $\geq 80$  years or body weight  $\leq 60$  kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2).

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

- for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (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).

#### Hepatic impairment

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

#### Body weight

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).

#### Gender

No dose adjustment required (see section 5.2).

#### Patients undergoing catheter ablation (NVAF)

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

#### Patients undergoing cardioversion

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

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

For patients initiating treatment with apixaban, 5 mg 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, 5.1).

#### *Paediatric population*

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

#### Method of administration

##### Oral use

Apixaban Accord should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Apixaban Accord 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, Apixaban Accord 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 Apixaban Accord 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, 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).

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

#### 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 medicinal products (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 Accord.

In a clinical study of patients with atrial fibrillation, concomitant use of acetylsalicylic acid (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 (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).

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

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

#### Patients with prosthetic heart valves

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

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-

glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Surgery and invasive procedures

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.

#### 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

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  $\geq 1.5$  mg/dL (133 micromole/L) associated with age  $\geq 80$  years or body weight  $\leq 60$  kg should receive the lower dose of 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).

### 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

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  $\geq$  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)

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

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

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

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

- for the prevention of stroke and systemic embolism in patients with 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.

### 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

Apixaban Accord 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).

#### Other concomitant therapies

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

#### Effect of apixaban on other medicinal products

*In vitro* apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 ( $IC_{50} > 45 \mu M$ ) and weak inhibitory effect on the activity of CYP2C19 ( $IC_{50} > 20 \mu M$ ) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to  $20 \mu M$ . Therefore, apixaban is not expected to alter the metabolic clearance of coadministered medicinal products that are 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).

## **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**

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

#### **4.8 Undesirable effects**

##### Summary of the safety profile

The safety of apixaban has been investigated in 4 Phase III clinical studies including more than 15,000 patients: more than 11,000 patients in NVAf studies and more than 4,000 patients in the VTEt treatment (VTEt) studies, for an average total exposure of 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 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 ( $\geq 1/10$ ) common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data) for NVAf and VTEt respectively.

**Table 2: Tabulated adverse reactions**

<b>System organ class</b>	<b>Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors (NVAf)</b>	<b>Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)</b>
<i>Blood and lymphatic system disorders</i>		
Anaemia	Common	Common
Thrombocytopenia	Uncommon	Common
<i>Immune system disorders</i>		
Hypersensitivity, allergic oedema and anaphylaxis	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon*
Angioedema	Not known	Not known
<i>Nervous system disorders</i>		
Brain haemorrhage <sup>†</sup>	Uncommon	Rare
<i>Eye disorders</i>		

<b>System organ class</b>	<b>Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors (NVAf)</b>	<b>Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)</b>
Eye haemorrhage (including conjunctival haemorrhage)	Common	Uncommon
<i>Vascular disorders</i>		
Haemorrhage, haematoma	Common	Common
Hypotension (including procedural hypotension)	Common	Uncommon
Intra-abdominal haemorrhage	Uncommon	Not known
<i>Respiratory, thoracic and mediastinal disorders</i>		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Respiratory tract haemorrhage	Rare	Rare
<i>Gastrointestinal disorders</i>		
Nausea	Common	Common
Gastrointestinal haemorrhage	Common	Common
Haemorrhoidal haemorrhage	Uncommon	Uncommon
Mouth haemorrhage	Uncommon	Common
Haematochezia	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Common	Common
Retroperitoneal haemorrhage	Rare	Not known
<i>Hepatobiliary disorders</i>		
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon
Gamma-glutamyltransferase increased	Common	Common
Alanine aminotransferase increased	Uncommon	Common
<i>Skin and subcutaneous tissue disorders</i>		
Skin rash	Uncommon	Common
Alopecia	Uncommon	Uncommon
Erythema multiforme	Very rare	Not known
Cutaneous vasculitis	Not known	Not known
<i>Musculoskeletal and connective tissue disorders</i>		
Muscle haemorrhage	Rare	Uncommon
<i>Renal and urinary disorders</i>		
Haematuria	Common	Common
<i>Reproductive system and breast disorders</i>		
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Common
<i>General disorders and administration site conditions</i>		
Application site bleeding	Uncommon	Uncommon
<i>Investigations</i>		
Occult blood positive	Uncommon	Uncommon
<i>Injury, poisoning and procedural complications</i>		
Contusion	Common	Common
Post procedural haemorrhage (including post procedural	Uncommon	Uncommon



<b>System organ class</b>	<b>Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors (NVAf)</b>	<b>Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)</b>
haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage		
Traumatic haemorrhage	Uncommon	Uncommon

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

† The term “Brain haemorrhage” encompasses all intracranial or intraspinal haemorrhages (ie., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).

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).

#### 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.

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

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

For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available (see section 4.4). Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered. Reversal of apixaban pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 4-factor PCC 30 minute infusion in healthy subjects. However, there is no clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received apixaban. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

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

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.

## **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). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-Factor Xa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-Factor Xa kits, however results differ across kits. Data from clinical studies are only available for the Rotachrom<sup>®</sup> 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.

Table 3 below shows the predicted steady state exposure and anti-Factor Xa activity. 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.

<b>Table 3: Predicted apixaban steady-state exposure and anti-Factor Xa activity</b>				
	<b>Apix. C<sub>max</sub> (ng/mL)</b>	<b>Apix. C<sub>min</sub> (ng/mL)</b>	<b>Apix. anti-Factor Xa activity max (IU/mL)</b>	<b>Apix. anti-Factor Xa activity min (IU/mL)</b>
	Median [5th, 95th Percentile]			
<i>Prevention of stroke and systemic embolism: NVAF</i>				
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]
<i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)</i>				
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.

#### Clinical efficacy and safety

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

A total of 23,799 patients were 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  $\geq$  75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class  $\geq$  II)

##### *ARISTOTLE study*

In the ARISTOTLE study a total of 18,201 patients were 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<sub>2</sub> 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 4) compared with warfarin.

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

	<b>Apixaban N=9,120 n (%/yr)</b>	<b>Warfarin N=9,081 n (%/yr)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
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 5). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

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

	<b>Apixaban N = 9,088 n (%/year)</b>	<b>Warfarin N = 9,052 n (%/year)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
<b>Bleeding outcomes</b>				
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	2,356 (18.1)	3,060 (25.8)	0.71 (0.68, 0.75)	< 0.0001
<b>Other endpoints</b>				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66, 1.17)	

\* Major bleeding defined per 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<sub>2</sub> score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

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

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

### AVERROES study

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were 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<sub>2</sub> score was 2.0 and 13.6% of patients had prior stroke or TIA.

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

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

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

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

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

	<b>Apixaban N = 2,807 n (%/year)</b>	<b>ASA N = 2,791 n (%/year)</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
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 7).

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

	<b>Apixaban N = 2,798 n(%/year)</b>	<b>ASA N = 2,780 n (%/year)</b>	<b>Hazard ratio (95%CI)</b>	<b>p-value</b>
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 patients with NVAF who had ACS (43%) and/or underwent PCI (56%). All patients received background therapy with a P2Y<sub>12</sub> 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<sub>2</sub>DS<sub>2</sub>-VASc score > 2, and 47% had a HAS-BLED score > 3. For patients randomised to VKA, the proportion of time in therapeutic range (TTR) (INR 2-3) was 56%, with 32% of time below TTR and 12% above TTR.

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

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

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

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

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

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

#### Patients undergoing cardioversion

EMANATE, an open-label, multi-center study, enrolled 1500 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 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 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  $INR \geq 2$ ) and warfarin (target INR range 2.0-3.0) orally for 6 months.

The mean age was 56.9 years and 89.8% of 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 8).

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

	<b>Apixaban N=2,609 n (%)</b>	<b>Enoxaparin/ warfarin N=2,635 n (%)</b>	<b>Relative risk (95% CI)</b>
VTE or VTE-related death	59 (2.3)	71 (2.7)	0.84 (0.60, 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 9).

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

	<b>Apixaban N=2,676 n (%)</b>	<b>Enoxaparin/ warfarin N=2,689 n (%)</b>	<b>Relative risk (95% CI)</b>
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55)
Major + CRNM	115 (4.3)	261 (9.7)	0.44 (0.36, 0.55)
Minor	313 (11.7)	505 (18.8)	0.62 (0.54, 0.70)
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 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 10).

**Table 10: 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) <sup>‡</sup>	0.19 (0.11, 0.33) <sup>‡</sup>
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 <sup>†</sup>	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)
Nonfatal PE <sup>†</sup>	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)

<sup>‡</sup>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)

<sup>†</sup> Individual subjects could experience more than one event and be represented in both classifications

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

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see Table 11).

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

	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

There is no authorised paediatric indication (see section 4.2).

#### 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  $\geq 1$  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 12). Apixaban was provided as a 2.5 mg tablet, 0.5 mg tablet, or 0.4 mg/mL oral solution. The median duration of exposure in the apixaban arm was 25 days.

**Table 12: Apixaban dosing in the PREVAPIX-ALL study**

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

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

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

epistaxis. Minor bleeding events occurred in 37 patients in the apixaban arm (14.5%) and 20 patients (7.8%) in the standard of care arm.

*Prevention of thromboembolism (TE) in 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 13). Apixaban was provided as a 5 mg tablet, 0.5 mg tablet, or 0.4 mg/mL oral solution. The mean duration of exposure in the apixaban arm was 331 days.

**Table 13: Apixaban dosing in the SAXOPHONE study**

Weight Range	Dose schedule
6 to < 9 kg	1 mg twice daily
9 to < 12 kg	1.5 mg twice daily
12 to < 18 kg	2 mg twice daily
18 to < 25 kg	3 mg twice daily
25 to < 35 kg	4 mg twice daily
≥ 35 kg	5 mg twice daily

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

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

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

## 5.2 Pharmacokinetic properties

### Absorption

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

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

#### Biotransformation and elimination

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

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

O-demethylation and hydroxylation at the 3-oxopiperidinyll 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.

#### 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.

#### Gender

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

### Ethnic origin and race

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

### Body weight

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

### Pharmacokinetic/pharmacodynamic relationship

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

## **5.3 Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-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  
Cellulose, microcrystalline  
Croscarmellose sodium  
Sodium laurilsulfate  
Magnesium stearate

#### Film coat:

Hypromellose  
Lactose monohydrate  
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 condition.

### **6.5 Nature and contents of container**

PVC/PVdC-Aluminium blisters are available in 10, 14, 20, 28, 56, 60, 100, 112, 168, and 200 film-coated tablets.

PVC/PVdC-Aluminium blisters are available in perforated unit dose blisters of 10 x 1, 20 x 1, 28 x 1, 56 x 1, 60 x 1, 100 x 1 and 168 x 1 film-coated tablet.

HDPE bottle with polypropylene child resistant/continues threaded closure containing 60, 100, 168, 180, 200 and 1,000 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

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

## **7. MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6<sup>a</sup> Planta,  
Barcelona, 08039  
Spain

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/021  
EU/1/20/1458/023  
EU/1/20/1458/024  
EU/1/20/1458/026  
EU/1/20/1458/028  
EU/1/20/1458/030  
EU/1/20/1458/032  
EU/1/20/1458/034  
EU/1/20/1458/044  
EU/1/20/1458/046

EU/1/20/1458/022  
EU/1/20/1458/025  
EU/1/20/1458/027  
EU/1/20/1458/029  
EU/1/20/1458/031  
EU/1/20/1458/033

EU/1/20/1458/045

EU/1/20/1458/035

EU/1/20/1458/036

EU/1/20/1458/037

EU/1/20/1458/038

EU/1/20/1458/039

EU/1/20/1458/040

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 23 July 2020

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://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

LABORATORI FUNDACIÓ DAU  
C/ C, 12-14 Pol. Ind. Zona Franca, Barcelona,  
08040 Barcelona, Spain

Accord Healthcare Polska Sp. z.o.o.  
ul.Lutomierska 50,  
95-200, Pabianice,  
Poland

Pharmadox Healthcare Limited  
KW20A Kordin Industrial Park,  
Paola PLA 3000, Malta

Accord Healthcare single member S.A.  
64th Km National Road Athens, Lamia,  
Schimatari, 32009,  
Greece

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 Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe apixaban are provided with the following educational material:

- Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

Key Elements of the Prescriber Guide:

- Details of populations potentially at higher risk of bleeding
- Recommended doses and guidance on the posology for different indications
- Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
- Guidance regarding switching from or to Apixaban Accord treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider
  - Importance of treatment compliance
  - Necessity to carry the Patient alert card with them at all times
  - The need to inform Health Care Professionals that they are taking Apixaban Accord if they need to have any surgery or invasive procedure.

Key Elements of the Patient Alert 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 alert card with them at all times
- The need to inform Health Care Professionals that they are taking Apixaban Accord 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 OF UNIT PACK 2.5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 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**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

10 film-coated tablets  
14 film-coated tablets  
20 film-coated tablets  
28 film-coated tablets  
56 film-coated tablets  
60 film-coated tablets  
100 film-coated tablets  
112 film-coated tablets  
168 film-coated tablets  
200 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6<sup>a</sup> Planta,  
Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/001  
EU/1/20/1458/003  
EU/1/20/1458/004  
EU/1/20/1458/006  
EU/1/20/1458/008  
EU/1/20/1458/010  
EU/1/20/1458/012  
EU/1/20/1458/014  
EU/1/20/1458/041  
EU/1/20/1458/043

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Apixaban Accord 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 FOR UNIT PACK 2.5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 2.5 mg tablets

apixaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR UNIT PACK 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 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. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

10 film-coated tablets  
14 film-coated tablets  
20 film-coated tablets  
28 film-coated tablets  
56 film-coated tablets  
60 film-coated tablets  
100 film-coated tablets  
112 film-coated tablets  
168 film-coated tablets  
200 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

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Edifici Est, 6<sup>a</sup> Planta,  
Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

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EU/1/20/1458/026  
EU/1/20/1458/028  
EU/1/20/1458/030  
EU/1/20/1458/032  
EU/1/20/1458/034  
EU/1/20/1458/044  
EU/1/20/1458/046

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Apixaban Accord 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 FOR UNIT PACKS 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 5 mg tablets

apixaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF UNIT PACK CONTAINING SINGLE-UNIT-DOSE BLISTERS 2.5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 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**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet  
10 x 1 film-coated tablet  
20 x 1 film-coated tablet  
28 x 1 film-coated tablet  
56 x 1 film-coated tablet  
60 x 1 film-coated tablet  
100 x 1 film-coated tablet  
168 x 1 film-coated tablet

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6ª Planta,  
Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/002  
EU/1/20/1458/005  
EU/1/20/1458/007  
EU/1/20/1458/009  
EU/1/20/1458/011  
EU/1/20/1458/013  
EU/1/20/1458/042

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Apixaban Accord 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**

**SINGLE-UNIT-DOSE BLISTERS 2.5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 2.5 mg tablets

apixaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF UNIT PACK CONTAINING SINGLE-UNIT-DOSE BLISTERS 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 5 mg film-coated tablets  
apixaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 5 mg apixaban.

**3. LIST OF EXCIPIENTS**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

10 x 1 film-coated tablet

20 x 1 film-coated tablet

28 x 1 film-coated tablet

56 x 1 film-coated tablet

60 x 1 film-coated tablet

100 x 1 film-coated tablet

168 x 1 film-coated tablet

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

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Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

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EU/1/20/1458/025  
EU/1/20/1458/027  
EU/1/20/1458/029  
EU/1/20/1458/031  
EU/1/20/1458/033  
EU/1/20/1458/045

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Apixaban Accord 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**

**SINGLE-UNIT-DOSE BLISTERS 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 5 mg tablets

apixaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF BOTTLE PACK 2.5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 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**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet  
60 film-coated tablets  
100 film-coated tablets  
168 film-coated tablets  
180 film-coated tablets  
200 film-coated tablets  
1,000 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

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World Trade Center, Moll de Barcelona s/n,  
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Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/015  
EU/1/20/1458/016  
EU/1/20/1458/017  
EU/1/20/1458/018  
EU/1/20/1458/019  
EU/1/20/1458/020

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Apixaban Accord 2.5 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**

**LABEL FOR BOTTLE PACK 2.5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 2.5 mg tablets  
apixaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 2.5 mg apixaban.

**3. LIST OF EXCIPIENTS**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet  
60 film-coated tablets  
100 film-coated tablets  
168 film-coated tablets  
180 film-coated tablets  
200 film-coated tablets  
1,000 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6a Planta,  
Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/015  
EU/1/20/1458/016  
EU/1/20/1458/017  
EU/1/20/1458/018  
EU/1/20/1458/019  
EU/1/20/1458/020

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF BOTTLE PACK 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 5 mg film-coated tablets  
apixaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 5 mg apixaban.

**3. LIST OF EXCIPIENTS**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet  
60 film-coated tablets  
100 film-coated tablets  
168 film-coated tablets  
180 film-coated tablets  
200 film-coated tablets  
1,000 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6ª Planta,  
Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/035  
EU/1/20/1458/036  
EU/1/20/1458/037  
EU/1/20/1458/038  
EU/1/20/1458/039  
EU/1/20/1458/040

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Apixaban Accord 5 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**

**LABEL FOR BOTTLE PACK 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Apixaban Accord 5 mg tablets  
apixaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 5 mg apixaban.

**3. LIST OF EXCIPIENTS**

Contain lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

60 film-coated tablets  
100 film-coated tablets  
168 film-coated tablets  
180 film-coated tablets  
200 film-coated tablets  
1,000 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
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**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona s/n,  
Edifici Est, 6a Planta,  
Barcelona, 08039  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1458/035  
EU/1/20/1458/036  
EU/1/20/1458/037  
EU/1/20/1458/038  
EU/1/20/1458/039  
EU/1/20/1458/040

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

## PATIENT ALERT CARD

### Apixaban Accord (apixaban) Patient Alert Card

Carry this card with you at all times

Show this card to your pharmacist, dentist and any other healthcare professionals that treat you.

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

Please complete this section or ask your doctor to do it

Name:

Birth Date:

Indication:

Dose: mg twice daily

Doctor's Name:

Doctor's telephone:

#### Information for patients

- Take Apixaban Accord regularly as instructed. If you miss a dose, take it as soon as you remember and continue to follow your dosing schedule.
- Do not stop taking Apixaban Accord without talking to your doctor, as you are at risk of suffering from a stroke or other complications.
- Apixaban Accord helps to thin your blood. However, this may increase your 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 need surgery or any invasive procedure, inform your doctor that you are taking Apixaban Accord.

#### Information for healthcare professionals

- Apixaban Accord (apixaban) is an oral anticoagulant acting by direct selective inhibition of factor Xa.
- Apixaban Accord may increase the risk of bleeding. In case of major bleeding events, it should be stopped immediately.
- Treatment with Apixaban Accord 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.

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### Apixaban Accord 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 Apixaban Accord is and what it is used for
2. What you need to know before you take Apixaban Accord
3. How to take Apixaban Accord
4. Possible side effects
5. How to store Apixaban Accord
6. Contents of the pack and other information

#### 1. What Apixaban Accord is and what it is used for

Apixaban Accord 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.

Apixaban Accord 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.

#### 2. What you need to know before you take Apixaban Accord

**Do not take Apixaban Accord 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 Apixaban Accord

- 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 under 18 years of age.

### Other medicines and Apixaban Accord

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 Apixaban Accord and some may decrease its effects. Your doctor will decide, if you should be treated with Apixaban Accord when taking these medicines and how closely you should be monitored.

The following medicines may increase the effects of Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord 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**

Apixaban Accord has not been shown to impair your ability to drive or use machine.

### **Apixaban Accord 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 Apixaban Accord**

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. Apixaban Accord 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 Apixaban Accord. 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 or with the convex side of a spoon on a plate.
- 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 or the spoon and plate 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 Apixaban Accord tablet mixed in 60 mL of water or 5% glucose in water, through a nasogastric tube.

**Take Apixaban Accord as recommended for the following:**

To prevent blood clots from forming after hip or knee replacement operations.

The recommended dose is one tablet of Apixaban Accord 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 Apixaban Accord **5 mg** twice a day.

The recommended dose is one tablet of Apixaban Accord **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 Apixaban Accord **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 Apixaban Accord **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 Apixaban Accord **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.

**Your doctor might change your anticoagulant treatment as follows:**

*- Changing from Apixaban Accord to anticoagulant medicines*

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

*- Changing from anticoagulant medicines to Apixaban Accord*

Stop taking the anticoagulant medicines. Start treatment with Apixaban Accord 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 Apixaban Accord*

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



- *Changing from Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord .

### **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 Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord**

- Take the dose as soon as you remember and:
  - take the next dose of Apixaban Accord at the usual time
  - then continue as normal.

**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 Apixaban Accord**

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. Apixaban Accord 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 Apixaban Accord 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

The following side effects are known if you take Apixaban Accord 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.

The following side effects are known if you take Apixaban Accord 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.

### **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 Apixaban Accord**

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 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 Apixaban Accord contains

- The active substance is apixaban. Each tablet contains 2.5 mg of apixaban.
- The other ingredients are:
  - Tablet core: **Lactose (see section 2)**, cellulose microcrystalline, croscarmellose sodium, sodium laurilsulfate, magnesium stearate
  - Film coat: **Lactose monohydrate (see section 2)**, hypromellose, titanium dioxide (E171), triacetin, iron oxide yellow (E172)

### What Apixaban Accord looks like and contents of the pack

The film-coated tablets are yellow, round shaped, biconvex, film coated tablet debossed with “IU1” on one side and plain on the other side.

PVC/PVdC-Aluminium blisters are available in 10, 14, 20, 28, 56, 60, 100, 112, 168, and 200 film-coated tablets.

PVC/PVdC-Aluminium blisters are available in perforated unit dose blisters of 10 x 1, 20 x 1, 28 x 1, 56 x 1, 60 x 1, 100 x 1 and 168 x 1 film-coated tablet.

HDPE bottle with polypropylene child resistant/continues threaded closure containing 60, 100, 168, 180, 200 and 1,000 film-coated tablets.

Not all pack sizes may be marketed.

### Patient Alert Card: handling information

Inside the Apixaban Accordpack together with the package leaflet you will find a Patient Alert Card or your doctor might give you a similar card.

This Patient Alert Card includes information that will be helpful to you and alert other doctors that you are taking Apixaban Accord. **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 and Manufacturer**

#### **Marketing Authorisation Holder**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona, s/n,  
Edifici Est, 6<sup>a</sup> Planta,  
08039 Barcelona,  
Spain

#### **Manufacturer**

LABORATORI FUNDACIÓ DAU  
C/ C, 12-14 Pol. Ind. Zona Franca, Barcelona,  
08040 Barcelona, Spain

Accord Healthcare Polska Sp. z.o.o.  
ul.Lutomierska 50,  
95-200, Pabianice,  
Poland

Pharmadox Healthcare Limited  
KW20A Kordin Industrial Park,  
Paola PLA 3000, Malta

Accord Healthcare single member S.A.  
64th Km National Road Athens, Lamia,  
Schimatari, 32009,  
Greece

**This leaflet was last revised in**

#### **Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

## Package leaflet: Information for the user

### Apixaban Accord 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

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6. Contents of the pack and other information

#### 1. What Apixaban Accord is and what it is used for

Apixaban Accord 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.

Apixaban Accord 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.

#### 2. What you need to know before you take Apixaban Accord

**Do not take Apixaban Accord 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.
- 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

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.

Take special care with Apixaban Accord

- 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.

## Children and adolescents

This medicine is not recommended in children and adolescents under 18 years of age.

## Other medicines and Apixaban Accord

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 Apixaban Accord and some may decrease its effects. Your doctor will decide, if you should be treated with Apixaban Accord when taking these medicines and how closely you should be monitored.

The following medicines may increase the effects of Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord 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**

Apixaban Accord has not been shown to impair your ability to drive or use machines.

### **Apixaban Accord 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 Apixaban Accord**

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. Apixaban Accord 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 Apixaban Accord. 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 or with the convex side of a spoon on a plate.
- 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 (or the spoon and plate) 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 Apixaban Accord tablet mixed in 60 mL of water or 5% glucose in water, through a nasogastric tube.

### **Take Apixaban Accord as recommended for the following:**

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 Apixaban Accord **5 mg** twice a day.

The recommended dose is one tablet of Apixaban Accord **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 Apixaban Accord **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 Apixaban Accord **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 Apixaban Accord **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.

#### **Your doctor might change your anticoagulant treatment as follows:**

##### *- Changing from Apixaban Accord to anticoagulant medicines*

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

##### *- Changing from anticoagulant medicines to Apixaban Accord*

Stop taking the anticoagulant medicines. Start treatment with Apixaban Accord 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 Apixaban Accord*

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

##### *- Changing from Apixaban Accord 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 Apixaban Accord 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 Apixaban Accord.

#### **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 Apixaban Accord than you should**

**Tell your doctor immediately** if you have taken more than the prescribed dose of Apixaban Accord. Take the medicine pack with you, even if there are no tablets left.

If you take more Apixaban Accord 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 Apixaban Accord**

- Take the dose as soon as you remember and:
  - take the next dose of Apixaban Accord at the usual time
  - then continue as normal.

**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 Apixaban Accord**

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.

The following side effects are known if you take Apixaban Accord 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.

The following side effects are known if you take Apixaban Accord 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 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.

#### **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 Apixaban Accord**

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 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 Apixaban Accord contains

- The active substance is apixaban. Each tablet contains 5 mg of apixaban.
- The other ingredients are:
  - Tablet core: **Lactose (see section 2)**, cellulose microcrystalline, croscarmellose sodium, sodium laurilsulfate, magnesium stearate
  - Film coat: **Lactose monohydrate (see section 2)**, hypromellose, titanium dioxide (E171), triacetin, iron oxide red (E172)

### What Apixaban Accord looks like and contents of the pack

The film-coated tablets are pink, oval shaped, biconvex, film coated tablet debossed with “IU2” on one side and plain on other side.

PVC/PVdC-Aluminium blisters are available in 10, 14, 20, 28, 56, 60, 100, 112, 168, and 200 film-coated tablets.

PVC/PVdC-Aluminium blisters are available in perforated unit dose blisters of 10 x 1, 20 x 1, 28 x 1, 56 x 1, 60 x 1, 100 x 1 and 168 x 1 film-coated tablet.

HDPE bottle with polypropylene child resistant/continues threaded closure containing 60, 100, 168, 180, 200 and 1,000 film-coated tablets.

Not all pack sizes may be marketed.

### Patient Alert Card: handling information

Inside the Apixaban Accord pack together with the package leaflet you will find a Patient Alert Card or your doctor might give you a similar card.

This Patient Alert Card includes information that will be helpful to you and alert other doctors that you are taking Apixaban Accord. **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 and Manufacturer

#### Marketing Authorisation Holder

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**This leaflet was last revised in****Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>