# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Apixaban Hexal 5 mg, filmomhulde tabletten

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg apixaban.

Excipients with known effect
Each 5 mg film-coated tablet contains 96 mg lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Pink, oval, biconvex, film coated tablets, debossed with “AX” on one side and “5” on the other side, with a width of 5.0 – 5.7 mm and a length of 9.6 – 10.3 mm.

## 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≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

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

### 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 ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long-term.

*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)*
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 [Nationally Completed Name] immediately and then continue with twice daily intake as before.

*Switching*

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

*Switching from [Nationally Completed Name] to VKA therapy*
When converting patients from [Nationally Completed Name] to VKA therapy, administration of [Nationally Completed Name] should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of [Nationally Completed Name] with VKA therapy, an INR should be obtained prior to the next scheduled dose of [Nationally Completed Name]. Coadministration of [Nationally Completed Name] and VKA therapy should be continued until the INR is ≥ 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 ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 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*
[Nationally Completed Name] is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

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

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

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore [Nationally Completed Name] should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating [Nationally Completed Name], 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 [Nationally Completed Name] 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
[Nationally Completed Name] should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, [Nationally Completed Name] 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, [Nationally Completed Name] 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 [Nationally Completed Name] 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 drugs (NSAIDs), including acetylsalicylic acid.

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

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

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

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

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

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 ≥ 1.5 mg/dL (133

micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily (see section 4.2);

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

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 ≥ 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
[Nationally Completed Name] 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 film-coated 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 co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two medicinal products together, mean apixaban AUC and $C_{max}$ were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or $C_{max}$.

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

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

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

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

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

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

## 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

[Nationally Completed Name] 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 VTE 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 (≥ 1/10) common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) for NVAF and VTEt respectively.

**Table 2: Tabulated adverse reactions**

| **System organ class** | **Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)** | **Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)** |
|---|---|---|
| *Blood and lymphatic system disorders* | | |
| Anaemia | Common | Common |
| Thrombocytopenia | Uncommon | Common |
| *Immune system disorders* | | |
| Hypersensitivity, allergic oedema and Anaphylaxis | Uncommon | Uncommon |
| Pruritus | Uncommon | Uncommon* |
| *Nervous system disorders* | | |
| Brain haemorrhage† | Uncommon | Rare |
| Angioedema | Not known | Not known |
| *Eye disorders* | | |
| Eye haemorrhage (including conjunctival haemorrhage) | Common | Uncommon |
| *Vascular disorders* | | |
| Haemorrhage, haematoma | Common | Common |

| | | |
|---|---|---|
| Hypotension (including procedural hypotension) | Common | Uncommon |
| Intra-abdominal haemorrhage | Uncommon | Not known |
| *Respiratory, thoracic and mediastinal disorders* | | |
| Epistaxis | Common | Common |
| Haemoptysis | Uncommon | Uncommon |
| Respiratory tract haemorrhage | Rare | Rare |
| *Gastrointestinal disorders* | | |
| 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 |
| *Hepatobiliary disorders* | | |
| 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 |
| *Skin and subcutaneous tissue disorders* | | |
| Skin rash | Uncommon | Common |
| Alopecia | Uncommon | Uncommon |
| Erythema multiforme | Very rare | Not known |
| Cutaneous vasculitis | Not known | Not known |
| *Musculoskeletal and connective tissue disorders* | | |

| | | |
|---|---|---|
| Muscle haemorrhage | Rare | Uncommon |
| *Renal and urinary disorders* | | |
| Haematuria | Common | Common |
| Anticoagulant-related nephropathy | Not known | Not known |
| *Reproductive system and breast disorders* | | |
| Abnormal vaginal haemorrhage, urogenital haemorrhage | Uncommon | Common |
| *General disorders and administration site conditions* | | |
| Application site bleeding | Uncommon | Uncommon |
| *Investigations* | | |
| Occult blood positive | Uncommon | Uncommon |
| *Injury, poisoning and procedural complications* | | |
| Contusion | 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 |
| 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 (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 $C_{max}$. Mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

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

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

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® 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.

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

| | **Apix. $C_{max}$ (ng/mL)** | **Apix. $C_{min}$ (ng/mL)** | **Apix. anti-Factor Xa activity max (IU/mL)** | **Apix. anti-Factor Xa activity min (IU/mL)** |
|---|---|---|---|---|
| | Median [5th, 95th percentile] | | | |
| *Prevention of stroke and systemic embolism: NVAF* | | | | |
| 2.5 mg twice daily* | 123 [69, 221] | 79 [34, 162] | 1.8 [1.0, 3.3] | 1.2 [0.51, 2.4] |
| 5 mg twice daily | 171 [91, 321] | 103 [41, 230] | 2.6 [1.4, 4.8] | 1.5 [0.61, 3.4] |
| *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)* | | | | |
| 2.5 mg twice daily | 67 [30, 153] | 32 [11, 90] | 1.0 [0.46, 2.5] | 0.49 [0.17, 1.4] |
| 5 mg twice daily | 132 [59, 302] | 63 [22, 177] | 2.1 [0.91, 5.2] | 1.0 [0.33, 2.9] |
| 10 mg twice daily | 251 [111, 572] | 120 [41, 335] | 4.2 [1.8, 10.8] | 1.9 [0.64, 5.8] |

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

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

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 ≥ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥ 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 $CHADS_2$ score was 2.1, 18.9% of patients had prior stroke or TIA.

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

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

| | **Apixaban N = 9,120 n (%/yr)** | **Warfarin N = 9,081 n (%/yr)** | **Hazard ratio (95% CI)** | **p-value** |
|---|---|---|---|---|
| Stroke or systemic embolism | 212 (1.27) | 265 (1.60) | 0.79 (0.66, 0.95) | 0.0114 |
| Stroke | | | | |
| Ischaemic or unspecified | 162 (0.97) | 175 (1.05) | 0.92 (0.74, 1.13) | |
| Haemorrhagic | 40 (0.24) | 78 (0.47) | 0.51 (0.35, 0.75) | |
| Systemic embolism | 15 (0.09) | 17 (0.10) | 0.87 (0.44, 1.75) | |

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

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

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

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

| | **Apixaban N = 9,088 n (%/year)** | **Warfarin N = 9,052 n (%/year)** | **Hazard ratio (95% CI)** | **p-value** |
|---|---|---|---|---|
| Bleeding outcomes | | | | |

| | | | | |
|---|---|---|---|---|
| Major* | 327 (2.13) | 462 (3.09) | 0.69 (0.60, 0.80) | < 0.0001 |
| Fatal | 10 (0.06) | 37 (0.24) | | |
| Intracranial | 52 (0.33) | 122 (0.80) | | |
| Major + CRNM† | 613 (4.07) | 877 (6.01) | 0.68 (0.61, 0.75) | < 0.0001 |
| All | 2356 (18.1) | 3060 (25.8) | 0.71 (0.68, 0.75) | < 0.0001 |
| Other endpoints | | | | |
| All-cause death | 603 (3.52) | 669 (3.94) | 0.89 (0.80, 1.00) | 0.0465 |
| Myocardial infarction | 90 (0.53) | 102 (0.61) | 0.88 (0.66, 1.17) | |

* Major bleeding defined per International Society on Thrombosis and Haemostasis (ISTH) criteria.
† Clinically Relevant Non-Major

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

The efficacy results for prespecified subgroups, including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

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

The major bleeding results for prespecified subgroups including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the results for the overall population studied in the trial.

*AVERROES study*
In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomised to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], see section 4.2) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study active substance for a mean of 14 months. The mean age was 69.9 years, the mean $CHADS_2$ score was 2.0 and 13.6% of patients had prior stroke or TIA.

Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS2 score = 1 and physician did not recommend VKA (21.3%), patient could not be

relied on to adhere to VKA medicinal product instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

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

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

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

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

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

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

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

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

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

*Major bleeding defined per International Society on Thrombosis and 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 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≥ 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**

| | **Apixaban N = 2,609 n (%)** | **Enoxaparin/ Warfarin N = 2,635 n (%)** | **Relative risk (95% CI)** |
|---|---|---|---|
| VTE or VTE-related death | 59 (2.3) | 71 (2.7) | 0.84 (0.60, 1.18)* |
| DVT | 20 (0.7) | 33 (1.2) | |
| PE | 27 (1.0) | 23 (0.9) | |
| VTE-related death | 12 (0.4) | 15 (0.6) | |
| VTE or all-cause death | 84 (3.2) | 104 (4.0) | 0.82 (0.61, 1.08) |
| VTE or CV-related death | 61 (2.3) | 77 (2.9) | 0.80 (0.57, 1.11) |

| | | | |
|---|---|---|---|
| VTE, VTE-related death, or major bleeding | 73 (2.8) | 118 (4.5) | 0.62 (0.47, 0.83) |

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

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

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

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

| | **Apixaban N = 2,676 n (%)** | **Enoxaparin/ Warfarin N = 2,689 n (%)** | **Relative risk (95% CI)** |
|---|---|---|---|
| Major | 15 (0.6) | 49 (1.8) | 0.31 (0.17, 0.55) |
| Major + CRNM | 115 (4.3) | 261 (9.7) | 0.44 (0.36, 0.55) |
| Minor | 313 (11.7) | 505 (18.8) | 0.62 (0.54, 0.70) |
| All | 402 (15.0) | 676 (25.1) | 0.59 (0.53, 0.66) |

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

*AMPLIFY-EXT study*

In the AMPLIFY-EXT study a total of 2,482 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)¥ | 0.19 (0.11, 0.33)¥ |
| DVT* | 6 (0.7) | 7 (0.9) | 53 (6.4) | | |
| PE* | 7 (0.8) | 4 (0.5) | 13 (1.6) | | |
| All-cause death | 6 (0.7) | 3 (0.4) | 11 (1.3) | | |
| Recurrent VTE or VTE-related death | 14 (1.7) | 14 (1.7) | 73 (8.8) | 0.19 (0.11, 0.33) | 0.20 (0.11, 0.34) |
| Recurrent VTE or CV-related death | 14 (1.7) | 14 (1.7) | 76 (9.2) | 0.18 (0.10, 0.32) | 0.19 (0.11, 0.33) |
| Nonfatal DVT† | 6 (0.7) | 8 (1.0) | 53 (6.4) | 0.11 (0.05, 0.26) | 0.15 (0.07, 0.32) |
| Nonfatal PE† | 8 (1.0) | 4 (0.5) | 15 (1.8) | 0.51 (0.22, 1.21) | 0.27 (0.09, 0.80) |
| VTE-related death | 2 (0.2) | 3 (0.4) | 7 (0.8) | 0.28 (0.06, 1.37) | 0.45 (0.12, 1.71) |

¥ p-value < 0.0001

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

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

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

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

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

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

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

Paediatric population

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

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

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

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

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 monohydrate
Cellulose, microcrystalline
Croscarmellose sodium
Sodium laurylsulfate
Magnesium stearate

Film coat:
Hypromellose
Hydroxypropylcellulose
Macrogol 6000
Titanium dioxide (E171)
Iron oxide, red (E172)
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

NL/H/5035
Alu-PVC/PVdC blisters of 10, 12, 14, 20, 28, 30, 56, 60, 100, 168, 180 and 200 film-coated tablets.

Alu-PVC/PVdC perforated unit dose blisters of 20 x 1, 30 x 1, 60 x 1, 100 x 1, 168 x 1 and 180 x 1 film-coated tablets.
NL/5036/5037/5038
Alu-PVC/PVdC blisters of 10, 12, 14, 20, 28, 30, 56, 60, 100, 168, 180 and 200 film-coated tablets.
Alu-PVC/PVdC perforated unit dose blisters of 20 x 1, 60 x 1 100 x 1 and 168 x 1 film-coated tablets.

NL/H/5035/5037/5038
HDPE/PP bottles of 200 film-coated tablets

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

HEXAL AG
Industriestrasse 25
83607 Holzkirchen
Duitsland

## 8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 125882

## 9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 24 september 2021
Datum van laatste verlenging: 14 juli 2026

## 10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 4.8: 27 november 2025