

APIXATOR 2.5 and 5

1. Generic Name

Apixaban Tablets 2.5 mg and 5 mg.

2. Qualitative and quantitative composition

APIXATOR 2.5

Each Film coated tablet contains:

Apixaban 2.5 mg

Colours: Yellow oxide of iron and Titanium Dioxide I.P.

Excipientsq.s.

The excipients are Anhydrous Lactose, Croscarmellose Sodium, Microcrystalline Cellulose, Dioxide, Magnesium stearate, Sodium Lauryl Sulphate, Opadry Yellow, Purified water.

APIXATOR 5

Each Film coated tablet contains:

Apixaban 5 mg

Colours: Red Oxide of iron and Titanium Dioxide I.P.

Excipientsq.s.

The excipients are Anhydrous Lactose, Croscarmellose Sodium, Microcrystalline Cellulose, Dioxide, Magnesium stearate, Sodium Lauryl Sulphate, Opadry Pink, Purified water.

3. Dosage form and strength

Dosage Form: Film coated tablets

Strength: 2.5 mg and 5 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), including those with one or more risk factors, such as prior stroke or transient ischemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary Embolism (PE), and prevention of Recurrent DVT and PE in adult patients.

4.2 Posology and method of administration

Posology

As Directed by the physician.

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.

Missed dose

If a dose is missed, the patient should take Apixaban 5 mg Film-coated Tablets immediately and then continue with twice daily intake as before.

Elderly

VTEt – No dose adjustment required.

NVAf – No dose adjustment required, unless criteria for dose reduction are met

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

-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.

In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply

-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

Hepatic impairment

Apixaban 5 mg Film-coated Tablets is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

It is not recommended in patients with severe hepatic impairment.

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.

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) $>2 \times$ ULN or total bilirubin $\geq 1.5 \times$ ULN were excluded in clinical studies. Therefore Apixaban 5 mg Film-coated Tablets should be used with caution in this population. Prior to initiating Apixaban 5 mg Film-coated Tablets, liver function testing should be performed.

Body weight

VTET - No dose adjustment required.

NVAF - No dose adjustment required, unless criteria for dose reduction are met.

Gender

No dose adjustment required.

Patients undergoing catheter ablation (NVAF)

Patients can continue apixaban use while undergoing catheter ablation.

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. 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.

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. The administration of the loading dose should be given at least 2 hours before cardioversion.

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.

Paediatric population

The safety and efficacy of Apixaban 5 mg Film-coated Tablets in children and adolescents below age 18 have not been established. No data are available.

Method of administration

Oral use

Apixaban 5 mg Film-coated Tablets should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Apixaban 5 mg Film-coated 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. Alternatively, Apixaban 5 mg Film-coated Tablets may be crushed and suspended in 60 ml of water or G5W and immediately delivered through a nasogastric tube. Crushed Apixaban 5 mg Film-coated Tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

4.3 Contraindications

- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- 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, 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.

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. 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. 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.

The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding.

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.

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 5 mg Film-coated Tablets.

In a reported 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 reported clinical study, there was limited (2.1%) use of concomitant dual antiplatelet therapy.

A reported 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.

In a reported 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.

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 patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted.

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.

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

Elderly patients

Increasing age may increase haemorrhagic risk. 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.

Patients with hepatic impairment

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). Patients with elevated liver enzymes ALT/AST $> 2 \times$ ULN or total bilirubin $\geq 1.5 \times$ ULN were excluded in clinical studies. Therefore apixaban should be used cautiously in this population. 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 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 reported 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:

- 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.

4.5 Drugs interactions

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).

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.

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.

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.

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

Other concomitant therapies

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

Effect of apixaban on other medicinal products

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

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

Digoxin

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

Naproxen

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

Atenolol

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

Activated charcoal

Administration of activated charcoal reduces apixaban exposure.

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. 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. 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.

4.7 Effects on ability to drive and use machines

Apixaban 5 mg Film-coated Tablets 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.

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

In the reported 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.

Tabulated list of adverse reactions

Table 1 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 1:

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*
Angioedema	Not known	Not known
Nervous system disorders		
Brain haemorrhage†	Uncommon	Rare
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
Gastrointestinal haemorrhage	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	Uncommon
Skin and subcutaneous tissue disorders		
Skin rash	Uncommon	Common
Alopecia	Unommon	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
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.

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 any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

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. 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 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.

5.2 Pharmacodynamic properties

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 \geq II)

ARISTOTLE Study

In the reported 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%], or warfarin (target INR range 2.0-3.0), patients were exposed to study active substance for a mean of 20 months. The mean age was 69.1 years, the mean CHADS2 score was 2.1, 18.9% of patients had prior stroke or TIA.

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

Table 2:

	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 3:

	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 CHADS2 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 CHADS2 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 reported AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomized to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study active substance for a mean of 14 months. The mean age was 69.9 years, the mean CHADS2 score was 2.0 and 13.6% of patients had prior stroke or TIA.

Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), 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 compared to ASA.

Table 4:

	Apixaban N = 2,807	ASA N = 2,791	Hazard Ratio (95% CI)	p-value
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	n (%/year)	n (%/year)		
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

Table 5:

	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) or at least 2 hours after a 10 mg loading dose (or a 5 mg loading dose in selected patients) 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 reported 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.

Table 6:

	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].

Table 7:

	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 reported 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.

Table 8:

	Apixaban	Apixaban	Placebo	Relative risk (95% CL)	
	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.

Table 9:

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

The European Medicines Agency has deferred the obligation to submit the results of studies with apixaban in one or more subsets of the paediatric population in venous and arterial embolism and thrombosis.

5.3 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 ~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-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-FXa activity.

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36% when a single dose of apixaban 5 mg was administered immediately after 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 reported 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-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 – 50 mg). The relationship between apixaban plasma concentration and anti-Factor Xa activity was best described.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

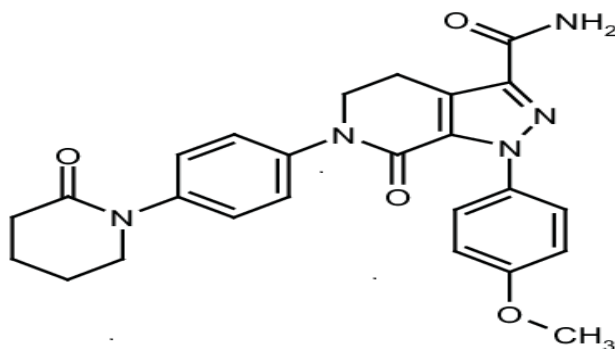
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-foetal development and juvenile toxicity.

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.

7. Description

Apixaban Apixaban is a pyrazolopyridine that is 7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide. Its empirical formula is C₂₅H₂₅N₅O₄ and its structural formula is:



Apixaban is a White to pale yellow crystalline powder with a molecular weight of 459.497.

Apixaban Tablets 2.5 mg

Apixaban Tablets 2.5 mg is a Yellow colored, round shaped, biconvex, beveled edge film coated tablet debossed with "H6" on one side and plain on the other side.

Apixaban Tablets 5 mg

Apixaban Tablets 5 mg is a Pink colored, oval Shaped, biconvex, beveled edge film-coated tablets having "H5" debossed on one side and plain on other side.

APIXATOR 2.5

The excipients are Anhydrous Lactose, Croscarmellose Sodium, Microcrystalline Cellulose, Dioxide, Magnesium stearate, Sodium Lauryl Sulphate, Opadry Yellow, Purified water

APIXATOR 5

The excipients are Anhydrous Lactose, Croscarmellose Sodium, Microcrystalline Cellulose, Dioxide, Magnesium stearate, Sodium Lauryl Sulphate, Opadry Pink, Purified water

8. Pharmaceutical particulars

8.1. Incompatibilities

None stated

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

Apixaban Tablets 2.5 mg and 5 mg Available in 10 BLISTER STRIPS OF 10 TABLETS EACH

8.4. Storage and handing instructions

STORE AT A TEMPERATURE NOT EXCEEDING 30°C.

9. Patient counselling information

Apixaban Tablets 2.5 and 5 mg film-coated tablets

APIXATOR

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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What APIXATOR is and what it is used for

9.2. What you need to know before you take APIXATOR

9.3. How to take APIXATOR

9.4. Possible side effects

9.5. How to store APIXATOR

9.6. Contents of the pack and other information

9.1. What APIXATOR is and what it is used for

APIXATOR 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.

APIXATOR is used in adults:

It is used for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf), including those with one or more risk factors, such as prior stroke or transient ischemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary Embolism (PE), and prevention of Recurrent DVT and PE in adult patients.

9.2. What you need to know before you take APIXATOR

Do not take APIXATOR if:

- you are allergic to Apixaban or any of the other ingredients of this medicine.
- 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

Take special care with APIXATOR

- 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 APIXATOR

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

The following medicines may increase the effects of Apixaban 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 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 APIXATOR 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 APIXATOR 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

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

9.3. How to take APIXABAN

Dose

Swallow the tablet with a drink of water. APIXATOR 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 APIXATOR. The tablet may be crushed and mixed with water, or 5% glucose in water, or apple juice or apple puree, immediately before you take it.

Instructions for crushing:

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

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

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

The recommended dose is **one tablet** of Apixaban **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 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 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 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 to anticoagulant medicines

Stop taking Apixaban. 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

Stop taking the anticoagulant medicines. Start treatment with Apixaban 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.

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

- Changing from Apixaban 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 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.

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 than you should Tell your doctor immediately

if you have taken more than the prescribed dose of Apixaban. Take the medicine pack with you, even if there are no tablets left. If you take more Apixaban 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

Take the dose as soon as you remember and:

- take the next dose of Apixaban 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

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

9.4. 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 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.

- 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 any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5. How to store APIXATOR

STORE AT A TEMPERATURE NOT EXCEEDING 30°C.

9.6. Contents of the pack and other information

The active substance in APIXATOR is Apixaban.

APIXATOR 2.5

The excipients are Anhydrous Lactose, Croscarmellose Sodium, Microcrystalline Cellulose, Dioxide, Magnesium stearate, Sodium Lauryl Sulphate, Opadry Yellow, Purified water.

APIXATOR 5

The excipients are Anhydrous Lactose, Croscarmellose Sodium, Microcrystalline Cellulose, Dioxide, Magnesium stearate, Sodium Lauryl Sulphate, Opadry Pink, Purified water.

Apixaban Tablets 2.5 mg and 5 mg Available in 10 BLISTER STRIPS OF 10 TABLETS EACH.

10. Details of Manufacturer

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10,

East District, Gangtok. Sikkim-737 135

11. Details of permission or licence number with date

Mfg Lic No.: M/563/2010 issued on 06/12/2021

12. Date of revision

NA

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/APIXABAN 2.5 and 5 mg/ Sep 2022/01/PI