

**Approved Professional Information for Medicines for Human Use: PIXECLOT**

**SCHEDULING STATUS**

S4

**1. NAME OF THE MEDICINE**

PIXECLOT 2,5 mg film-coated tablets

PIXECLOT 5 mg film-coated tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

PIXECLOT 2,5 mg film-coated tablets

Each film-coated tablet contains 2,5 mg apixaban.

Contains sugar: anhydrous lactose 50,50 mg.

PIXECLOT 5 mg Film-coated Tablets

Each film-coated tablet contains 5 mg apixaban.

Contains sugar: anhydrous lactose 101,0 mg.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablets.

PIXECLOT 2,5 mg film-coated tablets

Yellow, round shaped, approximate 6,00 mm in diameter, biconvex, film-coated tablet debossed with "IU1" on one side and plain on the other side.

PIXECLOT 5 mg film-coated tablets

Pink, oval shaped, approximate 9,8 mm in length, 5,2 mm in width, biconvex, film coated tablet debossed with "IU2" on one side and plain on other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

*Prevention of VTE: elective hip or knee replacement surgery*

PIXECLOT is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

*Prevention of stroke and systemic embolism: nonvalvular atrial fibrillation (NVAF)*

PIXECLOT is also indicated to reduce the risk of stroke, systemic embolism, and death in patients with nonvalvular atrial fibrillation with one or more risk factors.

### **4.2 Posology and method of administration**

#### **Posology**

#### **Recommended dosage**

*Prevention of VTE: elective hip or knee replacement surgery*

The recommended dose of PIXECLOT is 2,5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

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

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

*Prevention of stroke and systemic embolism: NVAF*

The recommended dose of PIXECLOT is 5 mg taken orally twice daily.

*Age, body weight, serum creatinine:* In patients with at least 2 of the following characteristics, age  $\geq$  80 years, body weight  $\leq$  60 kg, or serum creatinine  $\geq$  1,5 mg/dL (133 micromole/L), the recommended dose of PIXECLOT is 2,5 mg twice daily.

#### **Special populations**

## **Renal impairment**

### ***Prevention of VTE: elective hip or knee replacement surgery***

In surgical patients no dose adjustment is necessary in patients with mild, moderate or severe (creatinine clearance 15 - 29 mL/min) renal impairment (see section 5.2). There is limited clinical experience in patients with creatinine clearance < 15 mL/min and there are no data in patients undergoing dialysis, therefore PIXECLOT is not recommended in these patients (see section 4.4 and section 5.2).

### ***Prevention of stroke and systemic embolism: NVAf***

In patients with AF no dose adjustment is recommended in patients with creatinine clearance 15 to 29 mL/min, except as described under section 4.2., Prevention of stroke and systemic embolism: NVAf. There is no clinical experience in patients with creatinine clearance < 15 mL/min, therefore a dosing recommendation cannot be provided.

There are no data in patients undergoing dialysis, therefore, PIXECLOT is not recommended in these patients.

## **Hepatic impairment**

PIXECLOT may 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 section 4.4 and section 5.2).

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

## **Body weight**

### ***Prevention of VTE: elective hip or knee replacement surgery***

No dose adjustment required (see section 5.2).

***Prevention of stroke and systemic embolism: NVAF***

See Posology, Prevention of stroke and systemic embolism: NVAF.

**Elderly**

***Prevention of VTE: elective hip or knee replacement surgery***

No dose adjustment required (see section 5.2).

***Prevention of stroke and systemic embolism: NVAF***

See Posology, Prevention of stroke and systemic embolism: NVAF.

**Paediatric population**

The efficacy and safety of PIXECLOT in children below age 18 have not been established. No data are available.

**Converting from or to parenteral anticoagulants**

In general, switching treatment from parenteral anticoagulants to PIXECLOT (and vice versa) can be done at the next scheduled dose.

**Converting from or to warfarin or other vitamin K antagonists (VKA)**

When converting patients from warfarin or other VKA therapy to PIXECLOT, discontinue warfarin or other VKA therapy and start PIXECLOT when the INR is below 2,0.

When converting from PIXECLOT to warfarin or other VKA therapy, continue PIXECLOT for 48 hours after the first dose of warfarin or other VKA therapy.

**Patients undergoing cardioversion**

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

**Surgery and invasive procedures**

PIXECLOT should be discontinued 2 to 3 days prior to elective surgery or invasive procedures such as neuraxial regional anaesthesia. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

### **Method of administration**

PIXECLOT can be taken with or without food.

If a dose is missed, the patient should take PIXECLOT immediately and then continue with twice daily administration as before. For patients who are unable to swallow whole tablets. PIXECLOT may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally (see section 5.2). Alternatively, PIXECLOT may be crushed and suspended in 60 ml of water or D5W and promptly delivered through a nasogastric tube (see section 5.2).

Crushed PIXECLOT are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

### **4.3 Contraindications**

- Hypersensitivity to the active substance (apixaban) or to any of the excipients listed in section 6.1.
- Clinically significant active bleeding.
- PIXECLOT is not recommended in patients with severe renal disease (CrCl < 15 mL/min).
- PIXECLOT is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- PIXECLOT should not be administered with antiplatelet medicines other than aspirin (see section 4.4).
- 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**

Patients taking PIXECLOT are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage such as congenital or acquired bleeding disorders; active ulcerative gastrointestinal disease; bacterial endocarditis; thrombocytopenia; platelet disorders; history of haemorrhagic stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery. PIXECLOT administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9).

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 or the transfusion of fresh frozen plasma, should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving PIXECLOT. Standard anticoagulation tests cannot be used to monitor PIXECLOT (see section 4.5).

Although treatment with PIXECLOT 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. There is no reversal medication for PIXECLOT.

### **Interaction with other medicines affecting haemostasis**

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of PIXECLOT with antiplatelet medicines 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 (ASA).

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

In a clinical study of patients with atrial fibrillation, concomitant use of ASA is reported to have increased the major bleeding risk on apixaban as in PIXECLOT 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.

### **Patients with prosthetic heart valves**

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

### **Patients with antiphospholipid syndrome**

Direct acting Oral Anticoagulants (DOACs) including apixaban as in PIXECLOT are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In 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**

PIXECLOT 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.

PIXECLOT 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.

PIXECLOT 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, PIXECLOT treatment does not need to be interrupted (see sections 4.2, 4.3 and 4.5).

### **Temporary discontinuation**

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

### **Patients with renal impairment**

For the prevention of stroke and systemic embolism in patients with NVAf, patients with severe renal impairment (creatinine clearance 15 - 29 mL/min), and patients with serum creatinine  $\geq 1,5$  mg/dL (133 micromole/L) associated with age  $\geq 80$  years or body weight  $\leq 60$  kg should receive the lower dose of apixaban 2,5 mg twice daily (see section 4.2).

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

### **Elderly patients**

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

Also, the coadministration of apixaban as in PIXECLOT 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 as in PIXECLOT is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

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

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2 and 5.2).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin  $\geq$  1,5 x ULN were reportedly excluded in clinical studies. Therefore, PIXECLOT should be used cautiously in this population (see section 5.2). Prior to initiating PIXECLOT, liver function testing should be performed.

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

The use of PIXECLOT 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 medicines 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 as in PIXECLOT 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 reportedly observed with coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

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

- for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAf and for the prevention of recurrent DVT and PE, PIXECLOT should be used with caution;
- for the treatment of DVT and treatment of PE, PIXECLOT 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.

### **Excipient lactose**

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

### **Excipient sodium**

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

## **4.5 Interaction with other medicines and other forms of interaction**

### **Inhibitors of CYP3A4 and P-gp**

Coadministration of apixaban as in PIXECLOT 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 PIXECLOT is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) (see section 4.4).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg., amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for PIXECLOT is required when coadministered with medicine 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 PIXECLOT 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 PIXECLOT is required during concomitant therapy with such medicines, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp 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. PIXECLOT 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 reportedly not show a relevant increase in template bleeding time, or further inhibition of platelet aggregation, compared to administration of the antiplatelet medicines 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 medicines are coadministered with apixaban. PIXECLOT should be used with caution when coadministered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicines 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 sulfapyrazone) or thrombolytic medicines. As such medicines increase the bleeding risk, co-administration of these with PIXECLOT is not recommended (see section 4.4).

### **Other concomitant therapies**

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban as in PIXECLOT 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 medicines 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 medicines**

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

In studies conducted in healthy subjects, as described below, it was reported that 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 reportedly do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Treatment may increase the risk of haemorrhage during pregnancy and delivery. As a precautionary measure, it is preferable to avoid the use of PIXECLOT during pregnancy.

#### **Breastfeeding**

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

#### **Fertility**

Studies in animals dosed with apixaban have reportedly shown no effect on fertility.

### **4.7 Effects on ability to drive and use machines**

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

#### 4.8 Undesirable effects

##### a) Summary of the safety profile

The safety of apixaban has reportedly been investigated in 4 Phase III clinical studies including more than 15000 patients: more than 11000 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 NVAf studies, the overall incidence of adverse reactions is reportedly 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 reportedly 15,6 % in the apixaban vs enoxaparin/warfarin study and 13,3 % in the apixaban vs placebo study.

**b) Tabulated list of adverse reactions**

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with apixaban as in PIXECLOT.

<b>Prevention of VTE: elective hip or knee replacement surgery</b>			
<b>System Organ</b>	<b>Frequency</b>		
<b>Class</b>	<b>Frequent</b>	<b>Less Frequent</b>	<b>Unknown</b>
Blood and lymphatic system disorders	Anaemia	Thrombocytopenia	--
Immune system disorders	--	Hypersensitivity, Allergic oedema and anaphylaxis, Pruritus	Angioedema
Nervous system disorders	--	Brain haemorrhage†	--
Eye disorders	--	Eye haemorrhage (including conjunctival haemorrhage)	--
Vascular disorders	Haemorrhage, Haematoma	Hypotension (including procedural hypotension)	Intra-abdominal haemorrhage

Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis, Respiratory tract haemorrhage	--
Gastrointestinal disorders	Nausea, Gastrointestinal haemorrhage, Mouth haemorrhage, Rectal haemorrhage, Gingival bleeding	Haemorrhoidal haemorrhage, Haematochezia	Retroperitoneal haemorrhage
Hepatobiliary disorders	Gamma-glutamyltransferase increased, Alanine aminotransferase increased	Liver function test abnormal, aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased.	--
Skin and subcutaneous tissue disorders	Skin rash	Alopecia	--
Musculoskeletal and connective tissue disorders	--	Muscle haemorrhage	--
Renal and urinary disorders	Haematuria	--	--
Reproductive system and breast disorders	Abnormal vaginal haemorrhage, Urogenital haemorrhage	--	--

*Handwritten signature*

General disorders and administration site conditions	--	Application site bleeding	--
Investigations	--	Occult blood positive	--
Injury, poisoning and procedural complications	Contusion	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, Traumatic haemorrhage	--

<b>Prevention of stroke and systemic embolism: NVAf</b>			
<b>System Organ</b>	<b>Frequency</b>		
<b>Class</b>	<b>Frequent</b>	<b>Less Frequent</b>	<b>Unknown</b>
Blood and lymphatic system disorders	Anaemia	Thrombocytopenia	--
Immune system disorders	--	Hypersensitivity, Allergic oedema and anaphylaxis, Pruritus	Angioedema
Nervous system disorders	--	Brain haemorrhage†	--
Eye disorders	Eye haemorrhage (including conjunctival haemorrhage)	--	--
Vascular disorders	Haemorrhage, Haematoma, Hypotension (including procedural hypotension)	Intra-abdominal haemorrhage	--
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis, Respiratory tract haemorrhage	--
Gastrointestinal disorders	Nausea,	Mouth haemorrhage,	--

	Gastrointestinal haemorrhage, Rectal haemorrhage, Gingival bleeding	Haemorrhoidal haemorrhage, Haematochezia, Retroperitoneal haemorrhage	
Hepatobiliary disorders	Gamma-glutamyltransferase increased	Liver function test abnormal, aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Alanine aminotransferase increased	--
Skin and subcutaneous tissue disorders	--	Skin rash, Alopecia	--
Musculoskeletal and connective tissue disorders	--	Muscle haemorrhage	--
Renal and urinary disorders	Haematuria	--	--
Reproductive system and breast disorders	--	Abnormal vaginal haemorrhage, Urogenital haemorrhage	--
General disorders and administration site conditions	--	Application site bleeding	--
Investigations	--	Occult blood positive	--

Injury, poisoning and procedural complications	Contusion	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, Traumatic haemorrhage	--
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† 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 as in PIXECLOT 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 section 4.4).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting

Austell Pharmaceuticals (Pty) Ltd, 560419-20, PIXECLOT, Film-coated tablets and 2,5 mg & 5 mg

Form”, found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>

#### 4.9 Overdose

Overdose of PIXECLOT 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) reportedly 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 reportedly 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 as in PIXECLOT 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

Austell Pharmaceuticals (Pty) Ltd, 560419-20, PIXECLOT, Film-coated tablets and 2,5 mg & 5 mg 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**

Pharmacological Classification/ Category and Class: A 8.2 Anticoagulants.

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors

ATC Code: B01AF02

Apixaban is an inhibitor of coagulation factor Xa (FXa). Apixaban Inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development.

The pharmacodynamic effects of apixaban are reflective of the mechanism of action. As a result of FXa Inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin time (aPTI). However, changes observed in these clotting tests are not suitable for assessing the effects of apixaban.

Apixaban also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in the Rotachrom® Heparin chromogenic assay. The relationship between apixaban plasma

concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom assay is within acceptable limits for use in a clinical laboratory.

The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom anti-FXa assay may be useful in situations where knowledge of apixaban exposure may help to inform clinical decisions.

## **5.2 Pharmacokinetic properties**

### **Absorption**

The absolute bioavailability of apixaban is approximately 50 % for doses up to 10 mg.

Apixaban is absorbed with maximum concentrations ( $C_{max}$ ) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or  $C_{max}$  at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses  $\geq$  25 mg, apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of  $\sim$ 20 % CV and  $\sim$ 30 % CV, respectively.

### **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 reportedly 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 medicine-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,

Austell Pharmaceuticals (Pty) Ltd, 560419-20, PIXECLOT, Film-coated tablets and 2,5 mg & 5 mg 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-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 by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **PIXECLOT 2,5 mg film-coated tablets:**

Anhydrous lactose

Cellulose, microcrystalline (PH 102)

Croscarmellose sodium

Sodium lauryl sulfate

Magnesium stearate

Readycoat Universal Yellow 42H0190519

Readycoat Universal Yellow 42H0190519:

Hydroxy Propyl Methyl Cellulose E-15

Lactose monohydrate

Titanium dioxide

Triacetin

Iron oxide yellow

#### **PIXECLOT 5 mg film-coated tablets:**

Anhydrous lactose

Cellulose, microcrystalline (PH 102)

Croscarmellose sodium

Sodium lauryl sulfate

Magnesium stearate

Readycoat Universal Pink 42H0183723

Readycoat Universal Pink 42H0183723:

Hydroxy Propyl Methyl Cellulose E-15

Lactose monohydrate

Titanium dioxide

Triacetin

Iron oxide red

## **6.2 Incompatibilities**

Not Applicable

## **6.3 Shelf life**

36 months

## **6.4 Special precautions for storage**

Store at or below 25 °C.

Store in original packaging until required for use.

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

PIXECLOT film-coated tablets are packed in clear PVC/PVDC-Alu blisters and/or white opaque HDPE bottles.

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

Not all pack sizes may be marketed.

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

No special requirements.

#### **7. HOLDER OF CERTIFICATE OF REGISTRATION**

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

#### **8. REGISTRATION NUMBERS**

PIXECLOT 2,5 mg Film-coated tablets: 56/8.2/0419

PIXECLOT 5 mg Film-coated tablets: 56/8.2/0420

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

10 October 2023

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