Approved Professional Information for Medicines for Human Use:

APIXABAN 2,5 mg AUSTELL

APIXABAN 5 mg AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

APIXABAN 2,5 mg AUSTELL film-coated tablets

APIXABAN 5 mg AUSTELL film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

APIXABAN 2,5 mg AUSTELL film-coated tablets

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

Contains sugar: anhydrous lactose 50,50 mg.

APIXABAN 5 mg AUSTELL 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.

APIXABAN 2,5 mg AUSTELL 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.

APIXABAN 5 mg AUSTELL 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

APIXABAN AUSTELL 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)

APIXABAN AUSTELL 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 APIXABAN AUSTELL 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 APIXABAN AUSTELL is 5 mg taken orally twice daily.

Age, body weight, serum creatinine: In patients with at least 2 of the following characteristics, age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1,5 mg/dL (133 micromole/L), the recommended dose of APIXABAN AUSTELL 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 APIXABAN AUSTELL 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, APIXABAN AUSTELL is not recommended in these patients.

Hepatic impairment

APIXABAN AUSTELL 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).

APIXABAN AUSTELL 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 APIXABAN AUSTELL 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 APIXABAN AUSTELL (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 APIXABAN AUSTELL, discontinue warfarin or other VKA therapy and start APIXABAN AUSTELL when the INR is below 2,0.
When converting from APIXABAN AUSTELL to warfarin or other VKA therapy, continue APIXABAN AUSTELL for 48 hours after the first dose of warfarin or other VKA therapy.

Patients undergoing cardioversion

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

Surgery and invasive procedures

APIXABAN AUSTELL 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

APIXABAN AUSTELL can be taken with or without food.

If a dose is missed, the patient should take APIXABAN AUSTELL immediately and then continue with twice daily administration as before. For patients who are unable to swallow whole tablets. APIXABAN AUSTELL 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, APIXABAN AUSTELL may be crushed and suspended in 60 ml of water or D5W and promptly delivered through a nasogastric tube (see section 5.2).
Crushed APIXABAN AUSTELL 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.
- APIXABAN AUSTELL is not recommended in patients with severe renal disease (CrCl < 15 mL/min).
- APIXABAN AUSTELL is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- APIXABAN AUSTELL 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 APIXABAN AUSTELL 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. APIXABAN AUSTELL 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 APIXABAN AUSTELL. Standard anticoagulation tests cannot be used to monitor APIXABAN AUSTELL (see section 4.5).

Although treatment with APIXABAN AUSTELL 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 APIXABAN AUSTELL.

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 APIXABAN AUSTELL 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 APIXABAN AUSTELL (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 APIXABAN AUSTELL 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 APIXABAN AUSTELL have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of APIXABAN AUSTELL is not recommended in this setting.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including apixaban as in APIXABAN AUSTELL 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

APIXABAN AUSTELL 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 AUSTELL 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 AUSTELL should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (for cardioversion see section 4.2).

For patients undergoing catheter ablation for atrial fibrillation, APIXABAN AUSTELL treatment does

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

Temporary discontinuation

Discontinuing anticoagulants, including apixaban as in APIXABAN AUSTELL, 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 AUSTELL 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 ≥ 1,5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2,5 mg twice daily (see section 4.2).

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

Elderly patients

Increasing age may increase haemorrhagic risk (see section 5.2).
Also, the coadministration of apixaban as in APIXABAN AUSTELL 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 APIXABAN AUSTELL is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

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

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2 and 5.2).
Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1,5 x ULN were reportedly excluded in clinical studies. Therefore, APIXABAN AUSTELL should be used cautiously in this population (see section 5.2). Prior to initiating APIXABAN AUSTELL, liver function testing should be performed.

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

The use of APIXABAN AUSTELL 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 APIXABAN AUSTELL 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, APIXABAN AUSTELL should be used with caution;
- for the treatment of DVT and treatment of PE, APIXABAN AUSTELL 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

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

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg., amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for APIXABAN AUSTELL 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 APIXABAN AUSTELL 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 AUSTELL 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. APIXABAN AUSTELL 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. APIXABAN AUSTELL 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 sulfinpyrazone) or thrombolytic medicines. As such medicines increase the bleeding risk, co-administration of these with APIXABAN AUSTELL is not recommended (see section 4.4).

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban as in APIXABAN AUSTELL 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 (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 as in APIXABAN AUSTELL 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 APIXABAN AUSTELL 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

APIXABAN AUSTELL 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 APIXABAN AUSTELL.

Prevention of VTE: elective hip or knee replacement surgery			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Unknown**
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	--	--
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	--

Prevention of stroke and systemic embolism: NVAF			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Unknown**
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, Rectal haemorrhage, Gingival bleeding	Mouth haemorrhage, 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	--

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

4.9 Overdose

Overdose of APIXABAN AUSTELL 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 APIXABAN AUSTELL overdose or accidental ingestion.

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

have received apixaban. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

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

Haemodialysis decreased apixaban AUC by 14 % in subjects with end-stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 ≥ 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.

Distribution

Plasma protein binding in humans is approximately 87 %. The volume of distribution (Vss) is approximately 21 litres.

Biotransformation and elimination

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

APIXABAN 2,5 mg AUSTELL film-coated tablets:

Anhydrous lactose

Cellulose, microcrystalline (PH 102)

Croscarmellose sodium

Sodium lauryl sulfate

Magnesium stearate

Opadry II 32K520162 Yellow

Purified Water

APIXABAN 5 mg AUSTELL film-coated tablets:

Anhydrous lactose

Cellulose, microcrystalline (PH 102)

Croscarmellose sodium

Sodium lauryl sulfate

Magnesium stearate

Opadry II 32K540099 Pink

Purified Water

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

APIXABAN AUSTELL 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

APIXABAN 2,5 mg AUSTELL Film-coated tablets: 56/8.2/0421.419

APIXABAN 5 mg AUSTELL Film-coated tablets: 56/8.2/0422.420

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2023

10. DATE OF REVISION OF THE TEXT