PROFESSIONAL INFORMATION FOR XARPIX 2,5 / XARPIX 5

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

XARPIX 2,5 mg (Film-coated tablets)

XARPIX 5 mg (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each film-coated tablet of XARPIX 5 contains 5 mg of apixaban.

Excipients with known effect:

Each film-coated tablet of XARPIX 2,5 contains 50,50 mg lactose monohydrate.

Each film-coated tablet of XARPIX 5 contains 101,00 mg lactose monohydrate.

For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

XARPIX 2,5 (Film coated tablets)

Yellow, round, biconvex, film coated tablet, debossed AX on one side and 2,5 on the other side; diameter 5,7 – 6,5 mm; thickness 2,7 – 3,8 mm.

XARPIX 5 (Film coated tablets)

Pink, oval, biconvex, film coated tablet, debossed AX on one side and 5 on the other side; width 5,0 – 5,7 mm; length 9,6 – 10,3 mm; thickness 3,3 – 4,3 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prevention of VTE: elective hip or knee replacement surgery

XARPIX 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)

XARPIX 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.

Treatment of VTE

XARPIX is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE.

4.2 Posology and method of administration

Posology

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

Prevention of VTE: elective hip or knee replacement surgery

The recommended dose of XARPIX 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 XARPIX 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 micromol/L), the recommended dose of XARPIX is 2,5 mg twice daily.

Treatment of DVT and PE

The recommended dose of XARPIX is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

Prevention of recurrent DVT and PE

The recommended dose of XARPIX is 2,5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.

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 section 4.2 Prevention of stroke and systemic embolism: NVAF, Recommended dosage, Age, body weight, serum creatinine.

Treatment of VTE

No dose adjustment required (see section 5.2).

Converting from or to parenteral anticoagulants

In general, switching treatment from parenteral anticoagulants to XARPIX (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 XARPIX, discontinue warfarin or other VKA therapy and start XARPIX when the INR is below 2,0.

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

Patients undergoing cardioversion

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

For patients not previously treated with anticoagulants, at least 5 doses of XARPIX 5 mg twice daily (2,5 mg twice daily in patients who qualify for a dose reduction) should be given before cardioversion to ensure adequate anticoagulation.

If cardioversion is required before 5 doses of XARPIX 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.

Confirmation should be sought prior to cardioversion that the patient has taken XARPIX as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

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, XARPIX 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. Because there is no clinical experience in patients with creatinine clearance < 15 mL/min, a dosing recommendation cannot be provided.

There are no data in patients undergoing dialysis, therefore, XARPIX is not recommended in these patients (see section 5.2).

Treatment of VTE

No dose adjustment is necessary in patients with mild, moderate or serve (creatinine clearance 15 – 29 mL/min) renal impairment. Because there is limited clinical experience in patients with creatinine clearance < 15 mL/min and no data in patients undergoing dialysis, XARPIX is not recommended in these patients (see section 5,2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see section 4.4 and section 5.2) therefore XARPIX may be used with caution.

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

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 the recommended dose section 4.2, Prevention of stroke and systemic embolism: NVAF, Recommended dosage, Age, body weight, serum creatine.

Treatment of VTE

No dose adjustment required (see section 5.2).

Paediatric and adolescent

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

Method of administration

Oral use

XARPIX can be taken with or without food.

For patients who are unable to swallow whole tablets, XARPIX tablets 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, XARPIX tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube (see section 5.2).

Crushed XARPIX tablets 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.
- Active clinically significant bleeding.
- Severe renal disease (CrCl < 15 mL/min)
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2).

- Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agents other than aspirin, including antiplatelet medicines 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).
- Patients with antiphospholipid syndrome (APS) with persistent positivity for all three antiphospholipid antibodies (patients with triple positive APS),

4.4. Special warnings and precautions for use

Haemorrhage risk

Patients taking XARPIX are to be carefully observed for signs of bleeding. XARPIX 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. XARPIX 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. Reversal of XARPIX pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, has been demonstrated after administration of 4-factor PCCs in healthy subjects. However, there is no clinical experience with the use of 4-factor PCC medicines to reverse bleeding in individuals who have received XARPIX. There is currently no experience with the use of recombinant factor VIIa in individuals receiving XARPIX. Standard anticoagulation tests cannot be used to monitor XARPIX (see section 4.4)

Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see section 5.1).

A medicine to reverse the anti-factor Xa activity of apixaban is not available.

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 XARPIX 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 aspirin.

Other platelet aggregation inhibitors or other antithrombotic medicines are not recommended concomitantly with XARPIX following surgery (see section 4.5).

In patients with atrial fibrillation and conditions that warrants chronic use of antiplatelet therapy such as aspirin, XARPIX may be used with due regard to increased risk of major bleeding.

Use of thrombolytic medicines for the treatment of acute ischemic stroke

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

Patients with prosthetic heart valves

Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of XARPIX 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, as evidence regarding safety and efficacy, including the benefit/harm balance of apixaban in patients with APS, is inconclusive/incomplete. There is some evidence that treatment with apixaban may be associated with an increased risk of recurrent arterial thrombotic events in patients with APS compared to treatment of these patients with warfarin, a vitamin K antagonist. 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

XARPIX should be discontinued 48 to 72 hours prior to elective surgery or invasive procedures such as neuraxial regional anaesthesia. This includes interventions for which the probability of clinically significant bleeding cannot be excluded, the risk of bleeding would be unacceptable, 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, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

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

Temporary discontinuation of XARPIX

Discontinue XARPIX, in the presence of active bleeding, elective surgery, or invasive procedures that place patients at an increased risk of haemorrhage. Restart XARPIX therapy 12 – 24 hours after the danger of haemorrhage has ceased.

Spinal/epidural anaesthesia or puncture

Prevention of VTE: elective hip or knee replacement surgery

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines, such as XARPIX, for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which

can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicines affecting haemostasis. When an indwelling epidural or intrathecal catheter is planned, XARPIX should be stopped 48 hours beforehand. Indwelling epidural or intrathecal catheters must be removed at least 6 hours prior to the first dose of XARPIX. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, the medical practitioner should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Treatment of VTE

XARPIX 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 XARPIX is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made (see also section 4.3).

Patients with renal impairment

Prevention of VTE: elective hip or knee replacement surgery

There is limited clinical experience in patients with creatinine clearance < 15 ml/min and there are no data in patients undergoing dialysis, XARPIX is not recommended in these patients (see sections 4.2 and 5.2).

Prevention of stroke and systemic embolism: NVAF

XARPIX has not been studied in patients undergoing dialysis and is not recommended in these patients.

Elderly patients

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

Also the coadministration of XARPIX with aspirin 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

XARPIX is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

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

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

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

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

XARPIX can be administered with caution 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 XARPIX exposure by 2-fold (see section 4.5) or greater in the presence of additional factors that increase XARPIX exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp.

The concomitant use of XARPIX 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 XARPIX exposure. Use caution when co-administering XARPIX with strong inducers of both CYP3A4 and P-gp (see section 4.5).

Hip fracture surgery

Apixaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, XARPIX is not recommended in these patients.

Laboratory parameters

Clotting tests [e.g., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)] are affected as expected by the mechanism of action of apixaban. Changes observed in

these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see section 5.1). These parameters should not be used to monitor XARPIX therapy.

Paediatric use

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

XARPIX film-coated tablets contain lactose.

Patient with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. {Quantity of lactose is below the threshold for diabetes warning.}

4.5. Interaction with other medicines and other forms of interaction

Effects of other medicines on XARPIX

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} (see section 4.4)·

The dose of XARPIX must not exceed 2,5 mg twice daily when used with these medicines.

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 co-administered with medicines 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 AUG 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 AUG 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 AUG 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, phenobarbitone or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for XARPIX is required during concomitant therapy with such medicines, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution (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 co-administered with aspirin 325 mg once a day.
Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and aspirin 162 mg once daily, or with prasugrel (60 mg followed by 10 mg

once daily) did 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. However, the coadministration of XARPIX with clopidogrel, ticagrelor or other antiplatelet medicines, except aspirin, are not recommended due to the resulting associated increased risk of major bleeds (see section 4.4).

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.
There may be individuals with a more pronounced pharmacodynamic response when antiplatelet medicines are co-administered with apixaban. XARPIX should be used with caution when co-administered with SSRIs/SNRIs, NSAIDs (including aspirin) and/or P2Y12 inhibitors because these medicines typically increase the bleeding risk (see section 4.4).

Medicines associated with serious bleeding are not recommended with XARPIX, such as unfractionated heparins and heparin derivatives (including low molecular weight heparins (LMWH)), FXa inhibiting oligosaccharides (e.g. fondaparinux), direct thrombin II inhibitors (e.g., desirudin), thrombolytic agents, GPIIb/IIIa receptor antagonists, dipyridamole, dextran, sulfinpyrazone, vitamin K antagonists, and other oral anticoagulants. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section 4.4).

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. 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 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 co-administered 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, 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 AUG 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), 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), did not alter the pharmacokinetics of atenolol.

Activated charcoal

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

4.6 Pregnancy and lactation

Safety has not been established.

Pregnancy

XARPIX is not recommended during pregnancy.

Treatment may increase the risk of haemorrhage during pregnancy and delivery.

Lactation

It is unknown whether apixaban or its metabolites are excreted in human milk. A risk to newborns and infants cannot be excluded.

XARPIX therapy is not recommended for mothers who are breastfeeding.

Fertility

Fertility: Animal studies dosed with apixaban have shown no effect on fertility.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

System organ class	***Frequent***	***Less Frequent***	***Frequency Unknown***
Blood and the lymphatic system disorders:	Anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)	Thrombocytopenia	
Immune system disorders:		Hypersensitivity (including medicine hypersensitivity as skin rash and anaphylactic reaction such as allergic oedema), pruritus	Angioedema
Nervous system disorders:		Brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)	

Eye disorders:	Eye haemorrhage (including conjunctival haemorrhage)		
Vascular disorders:	haemorrhage (including haematoma, vaginal and urethral haemorrhage)	Hypotension (including procedural hypotension), intra-abdominal haemorrhage	
Respiratory, thoracic and mediastinal disorders:	Epistaxis	Haemoptysis, respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage, and pharyngeal haemorrhage)	
Gastrointestinal disorders:	Nausea, gastrointestinal haemorrhage (including haematemesis and melaena), rectal	Haemorrhoidal haemorrhage, haematochesia, mouth haemorrhage, retroperitoneal haemorrhage	

	haemorrhage, gingival bleeding		
Hepatobiliary disorders:		Increased transaminases (including increased alanine aminotransferase and increased aspartate aminotransferase, increased gamma-glutamyltransferase, abnormal liver function test, increased blood alkaline phosphatase, increased blood bilirubin	
Skin and subcutaneous tissue disorders:		Skin rash, alopecia, erythema multiforme	Cutaneous vasculitis
Musculoskeletal and connective tissue disorders:		Muscle haemorrhage	

Renal and urinary disorders:	Haematuria (including respective laboratory parameters)		
Reproductive system disorders:		Abnormal vaginal haemorrhage, urogenital haemorrhage	
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	

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicines is important. It allows continued monitoring of the benefit/risk balance of the medicines. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse drug reaction and quality problem reporting form**", found online under SAHPRA's publications: https//www.sahpra.org.za/documents/adverse-drug-reactions-and-quality-problem-reporting-form/.

Suspected adverse reactions can also be reported directly to the HCR via https://pvi1j.solutions.iqvia.com or adverse.event.sac@sandoz.com.

4.9. Overdose

There is no antidote to XARPIX. Overdose of XARPIX 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 should be considered.

Administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available (see section 4.4). Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered.

Reversal of XARPIX pharmacodynamic effects
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.

Haemodialysis is unlikely to be an effective means of managing XARPIX overdose.

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 8.2 Anticoagulants

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors

ATC code: B01AF02

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-Factor Xa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-Factor Xa kits, however results differ across kits. Data from clinical studies are only available for the Rotachrom® Heparin chromogenic assay. Anti-Factor Xa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-Factor Xa activity is approximately linear over a wide dose range of apixaban. The dose-and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clothing tests.

5.2. Pharmacokinetic properties

Absorption:

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

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

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water exposure was comparable to exposure after oral administration of 2 whole 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets with 30 g of applesauce the C_{max} and AUC were 21 % and 16 % lower, respectively, when compared to administration of 2 whole 5 mg tablets.

Following administration of a crushed 5 mg apixaban tablet suspended in 60 mL of D5W and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical trials involving healthy subjects receiving a single oral 5 mg apixaban tablet dose.

Distribution:

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

Biotransformation and Elimination:

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional

contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours. 0-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).

Special populations

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

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36 % when a single dose of apixaban 5 mg was administered immediately after haemodialysis,

compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14 % in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 ml/min. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment:

Apixaban has not been studied in patients with severe hepatic impairment or active hepatobiliary disease. Apixaban is not recommended in patients with severe hepatic impairment (see section 4.4).

In a study comparing subjects with mild and moderate hepatic impairment (classified as Child Pugh A and B, respectively) to healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with mild or moderate hepatic impairment. Changes in anti-factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment. However, caution is advised when using XARPIX in this population (see section 4.2 and 4.4). No dose adjustment is required in patients with mild to moderate hepatic impairment.

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 (see section 4.2).

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:

Lactose monohydrate

Cellulose, microcrystalline

Croscarmellose sodium

Sodium laurylsulfate

Magnesium stearate

Hypromellose (type 2910)

Hydroxypropylcellulose

Macrogols 6000

Titanium dioxide (E171)

Iron oxide, yellow (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep blisters enclosed in cardboard carton until required for use.

6.5. Nature and contents of container

XARPIX 2,5 and 5 mg film-coated tablets are packed into PVC/PVDC (transparent)/ Aluminium blisters.

Blister consist of:

- Forming foil: Plastic thermoformable foil (PVC, polyethylene, polyvinyliden chloride (inner))
- Lidding foil: Hard tempered aluminium foil (Protective lacquer, aluminium, PVC based heatseal lacquer (inner))

Blisters are packed together with the leaflet into the cardboard carton.

Pack sizes:

The available pack sizes are 60’s and 100’s.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

XARPIX 2,5: 56/8.2/0627.625

XARPIX 5: 56/8.2/0628.626

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.

[1]Company Reg. No.: 1990/001979/07