Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EPLIPIX 2,5 (film-coated tablets)

EPLIPIX 5 (film-coated tablets)

2. QUALITATIVE AND QUANTITAIVE COMPOSITION

Each **EPLIPIX 2,5** film coated tablet contains:

Apixaban 2,5 mg

Contains sugar: lactose monohydrate 38,7 mg per tablet.

Each **EPLIPIX 5** film coated tablet contains:

Apixaban 5 mg

Contains sugar: lactose monohydrate 77,4 mg per tablet.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

EPLIPIX 2,5

Light yellow to yellow coloured round shaped film coated tablets debossed with “A1” on one side and plain on the other side.

EPLIPIX 5

Light pink to pink coloured oval shaped film coated tablets debossed with “A3” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of venous thromboembolic events (VTE): elective hip or knee replacement surgery

EPLIPIX is indicated for the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.

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

EPLIPIX is also indicated to reduce the risk of stroke, systemic embolism and death in patients with NVAF with one or more risk factors.

4.2 Posology and method of administration

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

Recommended dosage

Prevention of VTE: elective hip or knee replacement surgery

The recommended dose of **EPLIPIX** 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 **EPLIPIX** 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 **EPLIPIX** is 2,5 mg twice daily.

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). Because, there is limited clinical experience reported in patients with creatinine clearance < 15 ml/min and there are no data reported in patients undergoing dialysis, **EPLIPIX** is not recommended in these patients (see sections 4.4 and 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. Because, there is no clinical experience reported in patients with creatinine clearance < 15 ml/min, a dosing recommendation cannot be provided.

There are no data reported in patients undergoing dialysis, therefore, **EPLIPIX** is not recommended in these patients.

Hepatic impairment

EPLIPIX 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 sections 4.4 and 5.2).

EPLIPIX is not recommended in patients with severe hepatic impairment (see sections 4.4 and 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 section 4.2, Prevention of stroke and systemic embolism: NVAF.

Paediatric and adolescent

The efficacy and safety of **EPLIPIX** in children below age 18 have not been reported. No data are available.

Elderly

Prevention of VTE: elective hip or knee ·replacement surgery

No dose adjustment required (see section 5.2)

Converting from or to parenteral anticoagulants

In general, switching treatment from parenteral anticoagulants to **EPLIPIX** (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 **EPLIPIX**, discontinue warfarin or other VKA therapy and start **EPLIPIX** when the international normalised ratio (INR) is below 2,0.

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

Patients undergoing cardioversion

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

For patients not previously treated with anticoagulants, at least 5 doses of **EPLIPIX** 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 **EPLIPIX** 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 **EPLIPIX** as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Surgery and invasive procedures

EPLIPIX 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:

For oral use. **EPLIPIX** can be taken with or without food.

For patients who are unable to swallow whole tablets, **EPLIPIX** 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, 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 EPLIPIX 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.
- **EPLIPIX** is not recommended in patients with severe renal disease (CrCI <15 m/min).
- **EPLIPIX** is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- **EPLIPIX** should not be administered with antiplatelet medicines other than aspirin (see section 4.4).
- **EPLIPIX** is not recommended in patients with anti-phospholipid syndrome (APS) with persistent positivity for all three anti-phospholipid antibodies (patients with triple positive APS).
- 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 medicine e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy, when UFH is given at doses

necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation.

4.4 Special warnings and precautions for use

Haemorrhage risk

Patients taking **EPLIPIX** are to be carefully observed for signs of bleeding. **EPLIPIX** 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. **EPLIPIX** administration should be discontinued if severe haemorrhage occurs (see section 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 recombinant factor VIIa may be considered. However, there is currently no experience reported with the use of recombinant factor VIIa in individuals receiving **EPLIPIX**. Standard anticoagulation tests cannot be used to monitor **EPLIPIX** (see section 4.5).

There is no reversal medication for EPLIPIX.

Temporary discontinuation of EPLIPIX

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

Renal impairment

Prevention of VTE: elective hip or knee replacement surgery

Because there is limited clinical experience reported in patients with creatinine clearance < 15 ml/min and there are no data reported in patients undergoing dialysis, **EPLIPIX** is not recommended in these patients (see sections 4.2, 4.3 and 5.2).

Prevention of stroke and systemic embolism: NVAF

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

Hepatic impairment

EPLIPIX is not recommended in patients with severe hepatic impairment (see sections 4.3 and 5.2).

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

EPLIPIX may 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 alanine aminotransferase/aspartate aminotransferase (ALT/AST) > 2 x upper limit of normal (ULN) or total bilirubin ≥ 1,5 x ULN were excluded in reported clinical trials. Therefore, **EPLIPIX** should be used cautiously in this population. Prior to initiating **EPLIPIX**, liver function testing should be performed.

Interaction with inhibitors of both Cytochrome P450 3A4 (CY3A4) and P-glycoprotein (P-gp)

EPLIPIX can be administered with caution in patients receiving concomitant systemic treatment with strong inhibitors of both Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g., ritonavir). These medicines may increase **EPLIPIX** exposure by 2-fold (see section

4.5), or greater in the presence of additional factors that increase **EPLIPIX** exposure (e.g. severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of **EPLIPIX** with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may lead to a ~50 % reduction in **EPLIPIX** exposure. In a reported clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with co-administration of **EPLIPIX** with strong inducers of both CYP3A4 and P-gp compared with using **EPLIPIX** 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.

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 **EPLIPIX** with antiplatelet medicines increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory medicines (NSAIDs), including aspirin. **Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with EPLIPIX** (see section 4.3).

In a reported clinical trial of patients with atrial fibrillation, concomitant use of aspirin increased the major bleeding risk on apixaban from 1,8 % per year to 3,4 % per year and increased the bleeding risk on warfarin from 2,7 % per year to 4,6 % per year.

Patients with prosthetic heart valves

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

Patients with antiphospholipid syndrome

Treatment of patients with established APS is not recommended 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 the 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 and vitamin K anatagonist.

Surgery and invasive procedures

EPLIPIX 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.

EPLIPIX 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.

EPLIPIX 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, **EPLIPIX** treatment does not need to be interrupted.

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 **EPLIPIX**, 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, **EPLIPIX** should be stopped 48 hours beforehand. Indwelling epidural or intrathecal catheters must be removed at least 6 hours prior to the first dose of apixaban. 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.

Hip fracture surgery

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

Paediatric use

The efficacy and safety of **EPLIPIX** in children below age 18 have not been reported. No data are available.

Elderly patients

Increasing age may increase haemorrhagic risk. Also, the co-administration of **EPLIPIX** 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.

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.

Lactose intolerance

EPLIPIX contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take **EPLIPIX.**

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on EPLIPIX

Inhibitors of CYP3A4 and P-gp

Co-administration of **EPLIPIX** with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, have reported a 2-fold increase in mean **EPLIPIX** AUC and a 1,6 fold increase in mean **EPLIPIX** maximum plasma concentration (C_{max}) (see section 4.4).

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

Active substances that are not considered strong inhibitors of both CYP3A4 and P-gp (e.g., diltiazem, naproxen, amiodarone, verapamil, quinidine, clarithromycin, fluconazole) are expected to increase **EPLIPIX** plasma concentration to a lesser extent. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, has reported a 1,4 fold increase in mean **EPLIPIX** 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, has reported a 1,5 fold and 1,6-fold·increase in mean **EPLIPIX** AUC and C_{max} respectively. No dose adjustment for **EPLIPIX** is required when co-administered with less potent inhibitors of CYP3A4 and/or P-gp.

Inducers of CYP3A4 and p-gp

Co-administration of **EPLIPIX** with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54 % and 42 % decrease in mean **EPLIPIX** AUC and C_{max}, respectively. The concomitant use of **EPLIPIX** with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to reduced **EPLIPIX** plasma concentrations.

No dose adjustment for **EPLIPIX** is required during concomitant therapy with such medicines, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp **EPLIPIX** should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF.

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 **EPLIPIX** (5 mg single dose), an additive effect on anti-Factor Xa activity was reported.

Pharmacokinetic or pharmacodynamic interactions were not reportedly evident in healthy subjects when apixaban was co-administered with aspirin 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once daily) 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) in reported phase 1 studies did not show a relevant increase in 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 co-administration of apixaban with clopidogrel, ticagrelor or other antiplatelet medicines except aspirin) are not recommended due to the resulting associated increased risk of major bleeds (see section 4.3).

Naproxen (500 mg), an inhibitor of P-gp, led to 1,5 fold and 1,6-fold increase in mean apixaban AUC and C_{max}, in healthy subjects, respectively. Corresponding increases in clotting tests were reported for apixaban. No clinically relevant prolongation of bleeding time was reported after concomitant administration of apixaban and naproxen.

EPLIPIX should be used with caution when co-administered with NSAIDs (including aspirin) because these medicines typically increase the bleeding risk.

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet medicines are co-administered with apixaban. **EPLIPIX** should be used with caution when co-administered with SSRIs/SNRIs or NSAIDs, aspirin and/or P2Y12 inhibitors because these medicines typically increase the bleeding risk.

Medicines associated with serious bleeding are not recommended concomitantly with **EPLIPIX**, 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 medicines, GPIIb/IIIa receptor antagonists, dipyridamole, dextran, sulfinpyrazone, vitamin K antagonists, and other oral anticoagulants.

Other concomitant therapies

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

Clotting tests (e.g., PT, INR, and aPTT) are affected as expected by the mechanism of action of **EPLIPIX**. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. These parameters should not be used to monitor **EPLIPIX** therapy.

Effect of EPLIPIX on other medicines

Reported *in vitro* apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6; CYP2B6, CYP2C8, CYP2C9, CYPD206 or CYP3A4 (IC50 > 45 µM) and weak inhibitory effect on the activity of CYP2C19 (IC_{50} > 20 µM) at concentrations that are significantly greater than peak plasma concentrations reported in patients. Apixaban did not induce CYP1A2, CYP286, 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. **EPLIPIX** is not a significant inhibitor of P-gp.

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

Digoxin**:** Co-administration 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, **EPLIPIX** does not inhibit P-gp mediated substrate transport.

Naproxen**:** Co-administration of single doses of apixaban (10 mg) and naproxen (500 mg) did not have any effect on the naproxen AUC or C_{max}.

Atenolol**:** Co-administration 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 **EPLIPIX** exposure.

Paediatric population

Interaction studies have only been reported in adults.

4.6 Fertility, pregnancy and lactation

Safety has not been established.

Pregnancy

EPLIPIX is not recommended during pregnancy.

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

Breastfeeding

It is unknown whether **EPLIPIX** or its metabolites are excreted in human milk. A risk to newborns and infants cannot be excluded. **EPLIPIX** therapy is not recommended for mothers who are breastfeeding their infants.

Fertility

No effect on fertility has been reported in animals.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical experience

In the reported VTEp studies, in total, 11% of the patients treated with apixaban 2,5 mg twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with apixaban was 10 % in the apixaban vs enoxaparin reported studies.

In the reported NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24,3 % in the apixaban vs warfarin study and 9,6 % in the apixaban vs acetylsalicylic acid reported study. In the apixaban vs warfarin reported 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 reported VTEt studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15,6 % in the apixaban vs enoxaparin/warfarin reported study and 13,3 % in the apixaban vs placebo study.

Frequent adverse reactions were haemorrhage, contusion, epistaxis, and haematoma.

The use of EPLIPIX may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding (see sections 4.4 and 5.1).

System Organ Class	**Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)**	**Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)**
Blood and lymphatic system disorders		
Anaemia	Frequent	Frequent
Thrombocytopenia	Less frequent	Less frequent
Immune system disorders		
Hypersensitivity, allergic oedema and Anaphylaxis	Less frequent	Less frequent
Pruritus	Less frequent	Less frequent
Angioedema	Frequency unknown	Frequency unknown

Nervous system disorders		
Brain haemorrhage†	Frequency unknown	Less frequent
Eye disorders		
Eye haemorrhage (including conjunctival haemorrhage)	Less frequent	Frequent
Vascular disorders		
Haemorrhage, haematoma	Frequent	Frequent
Hypotension (including procedural hypotension)	Less frequent	Frequent
Intra-abdominal haemorrhage	Frequency unknown	Less frequent
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Less frequent	Frequent
Haemoptysis	Less frequent	Less frequent
Respiratory tract haemorrhage	Frequency unknown	Less frequent
Gastrointestinal disorders		
Nausea	Frequent	Frequent
Gastrointestinal haemorrhage	Less frequent	Frequent
Haemorrhoidal haemorrhage	Frequency unknown	Less frequent
Mouth haemorrhage	Frequency unknown	Less frequent
Haematochezia	Less frequent	Less frequent
Rectal haemorrhage, gingival bleeding	Less frequent	Frequent

Retroperitoneal haemorrhage	Frequency unknown	Less frequent
Hepatobiliary disorders		
Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Less frequent	Less frequent
Gamma-glutamyltransferase increased	Less frequent	Frequent
Alanine aminotransferase increased	Less frequent	Less frequent
Skin and subcutaneous tissue disorders		
Skin rash	Frequency unknown	Less frequent
Alopecia	Less frequent	Less frequent
Musculoskeletal and connective tissue disorders		
Muscle haemorrhage	Less frequent	Less frequent
Renal and urinary disorders		
Haematuria	Less frequent	Frequent
Reproductive system and breast disorders		
Abnormal vaginal haemorrhage, urogenital haemorrhage	Less frequent	Less frequent
General disorders and administration site conditions		
Application site bleeding	Frequency unknown	Less frequent
Investigations		

Occult blood positive	Frequency unknown	Less frequent
Injury, poisoning and procedural complications		
Contusion	Frequent	Frequent
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	Less frequent	Less frequent
Traumatic haemorrhage	Frequency unknown	Less frequent

† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (i.e. haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).

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. Health care providers 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

There is no antidote to **EPLIPIX.** Overdose of **EPLIPIX** may result in a higher risk of bleeding. 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 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 (aPTT). However, changes reported 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 reported 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, e.g. overdose and emergency surgery.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of apixaban is reported as approximately 50 % for doses up to 10 mg. Apixaban is reported to be 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 reported to 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 reported as approximately 87 %. The volume of distribution (Vss) is reported as 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 reported in clinical and nonclinical studies, respectively.

Apixaban has reported 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 drug-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).

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 (see section 4.2).

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was reported to be increased by 36 % when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that reported in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, was reported to decrease 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 reported 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-FXa activity and INR were reported to be comparable between subjects with mild to moderate hepatic impairment and healthy subjects. No dose adjustment is required in patients with mild or moderate hepatic impairment. However, given the limited number of subjects studied, caution is advised when using apixaban in this population (see sections 4.2 and 4.4).

Elderly

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

Gender

Exposure to apixaban was reported as approximately 18 % higher in females than in males.

Ethnic origin and race

The results across reported phase I studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black 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 reported in patients was consistent with that established in healthy subjects.

5.3 Preclinical safety data

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

The major reported effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the reported toxicity studies little to no increase of bleeding tendency was found. However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Croscarmellose sodium

Lactose monohydrate

Microcrystalline cellulose PH 101, PH102

Magnesium stearate

Povidone

Sodium lauryl sulphate

Film-coating

Opadry II Yellow (EPLIPIX 2,5):

Hypromellose

Lactose monohydrate

Titanium dioxide

Triacetin

Iron oxide yellow

Opadry II Pink (EPLIPIX 2,5):

Hypromellose

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.

6.5 Nature and contents of container

60 tablets or 180 tablets are packed in a round, opaque white/off-white HDPE bottle closed with a child-resistance closure with a heat seal and pulp liner for induction seal with a polyester coil.

10 tablets (for **EPLIPIX 2,5**) and 7 tablets (for **EPLIPIX 5**) are packed in a clear PVC film laminated with PVDC coat and aluminium foil with heat seal lacquer coating foil as lidding material.

6.6 Special precautions for disposal and other handling

No special requirement

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

EPLIPIX 2,5: 55/8.2/0549

EPLIPIX 5: 55/8.2/0550

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 November 2023

10. DATE OF REVISON OF THE TEXT

28 November 2023