Eliquis®
apixaban
2.5mg, 5mg

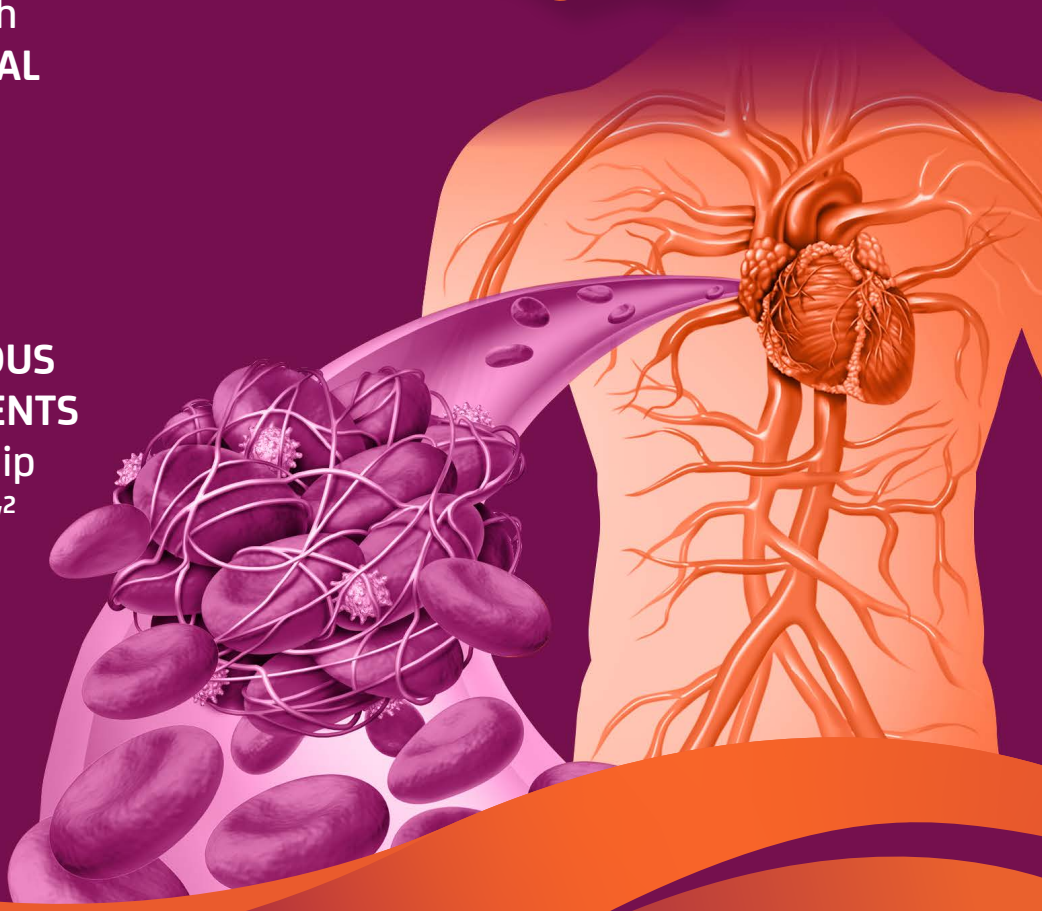
Eliquis® is the #1 NOAC*1 GLOBALLY

Choose Eliquis®

for your patients with
NON-VALVULAR ATRIAL FIBRILLATION[2]

&

for the
PREVENTION OF VENOUS THROMBOEMBOLIC EVENTS
in elective knee and hip replacement surgery[2]



* Data from IMS MIDAS (Standard Units divided by recommended administration of each NOAC within 24 hours. Timeframe Q2 2020 to Q1 2021).

REFERENCES:
1. Data on file, IMS MIDAS, Patient treatment days prescribed Q1 2021 MAT.
2. ELIQUIS® Package Insert, Approved 20 March 2018.

LICENCE HOLDER: Pfizer Laboratories (Pty) Ltd. Reg. No. 1954/000781/07. 85 Bute Lane, Sandton, 2196, South Africa. Tel. No: 0860 PFIZER (734937). Please refer to detailed package insert for full prescribing information. PP-ELI-ZAF-0334

Pfizer

S4 **ELIQUIS®** 2,5 mg and 5 mg (Film-coated Tablets). Each film-coated tablet contains either 2,5 mg or 5 mg apixaban. Reg. no's: 47/8.2/0463 / 47/8.2/0464. **PHARMACOLOGICAL CLASSIFICATION:** A 8.2 Anticoagulants. **INDICATIONS: Prevention of VTE: elective hip or knee replacement surgery:** ELIQUIS 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):** ELIQUIS 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. **CONTRAINDICATIONS:** Hypersensitivity to the active substance (apixaban) or to any of the excipients. Clinically significant active bleeding. ELIQUIS is not recommended in patients with severe renal disease (CrCl < 15 ml/min). ELIQUIS is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. ELIQUIS should not be administered with antiplatelet medicines other than aspirin (see WARNINGS AND SPECIAL PRECAUTIONS). **WARNINGS AND SPECIAL PRECAUTIONS: Haemorrhage risk:** Patients taking ELIQUIS are to be carefully observed for signs of bleeding. ELIQUIS 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. ELIQUIS administration should be discontinued if severe haemorrhage occurs (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT). 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 with the use of recombinant factor VIIa in individuals receiving ELIQUIS. Standard anticoagulation tests cannot be used to monitor ELIQUIS (see INTERACTIONS). **There is no reversal medication for ELIQUIS. Temporary discontinuation of ELIQUIS:** Discontinue ELIQUIS, in the presence of active bleeding, elective surgery, or invasive procedures that place patients at an increased risk of haemorrhage. Restart ELIQUIS 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 in patients with creatinine clearance < 15 ml/min and there are no data in patients undergoing dialysis, ELIQUIS is not recommended in these patients. ***Prevention of stroke and systemic embolism: NVAF:*** ELIQUIS has not been studied in patients undergoing dialysis and is not recommended in these patients. **Hepatic impairment:** ELIQUIS is not recommended in patients with severe hepatic impairment. ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). **Interaction with inhibitors of both Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp):** ELIQUIS 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). These medicines may increase ELIQUIS exposure by 2-fold. **Interaction with inducers of both CYP3A4 and P-gp:** The concomitant use of ELIQUIS 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 apixaban exposure. Use caution when coadministering ELIQUIS with strong inducers of both CYP3A4 and P-gp. **Interaction with other medicines affecting haemostasis:** The concomitant use of ELIQUIS with antiplatelet medicines increases the risk of bleeding. **Other platelet aggregation inhibitors or other antithrombotic medicines are not recommended concomitantly with ELIQUIS following surgery.** In patients with atrial fibrillation and a condition that warrants chronic use of aspirin, ELIQUIS may be used with due regard to increased risk of major bleeding. **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 ELIQUIS, 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, ELIQUIS should be stopped 48 hours beforehand. Indwelling epidural or intrathecal catheters must be removed at least 6 hours prior to the first dose of ELIQUIS. 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:** Safety and efficacy has not been established hence, ELIQUIS is not recommended. **Paediatric use:** The efficacy and safety of ELIQUIS in children below age 18 have not been established. **Effects on ability to drive and to use machines:** ELIQUIS has no or negligible influence on the ability to drive and use machines. **Lactose intolerance:** As ELIQUIS contains lactose, patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ELIQUIS. Lactose may also have an effect on the glycaemic control of patients with diabetes mellitus. **INTERACTIONS: Effect of other medicines on ELIQUIS: Inhibitors of CYP3A4 and P-gp:** Coadministration of ELIQUIS with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean ELIQUI S AUC and a 1,6-fold increase in mean apixaban C_{max}. The dose of ELIQUIS 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) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for ELIQUIS is required when coadministered with less potent inhibitors of CYP3A4 and/or P-gp. **Inducers of CYP3A4 and P-gp:** Coadministration of ELIQUIS with rifampicin, and with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to reduced ELIQUIS plasma concentrations. No dose adjustment for ELIQUIS is required during concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be coadministered with caution. **Anticoagulants, platelet aggregation inhibitors, and NSAIDs:** After combined administration of enoxaparin (40 mg single dose) with ELIQUIS (5 mg single dose), an additive effect on anti-FXa activity was observed. Pharmacokinetic or pharmacodynamic interactions were not evident in healthy subjects when ELIQUIS was coadministered with aspirin 325 mg once a day. ELIQUIS coadministered with clopidogrel, ticagrelor or other antiplatelet medicines, except aspirin, are not recommended due to the resulting associated increased risk of major bleeds. Naproxen (500 mg), an inhibitor of P-gp, led to a 1,5-fold and 1,6-fold increase in mean ELIQUIS AUC and C_{max}, in healthy subjects, respectively. Corresponding increases in clotting tests were observed for ELIQUIS. No clinically relevant prolongation of bleeding time was observed after concomitant administration of ELIQUIS and naproxen. ELIQUIS should be used with caution when coadministered with NSAIDs (including aspirin) because these medicinal products typically increase the bleeding risk. Medicines associated with serious bleeding are not recommended concomitantly with ELIQUIS, 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. **Other concomitant therapies:** No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when ELIQUIS was coadministered with atenolol or famotidine. Coadministration of ELIQUIS 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of ELIQUIS. Following administration of the two medicines together, mean ELIQUIS AUC and C_{max} were 15 % and 18 % lower than when administered alone. The administration of ELIQUIS 10 mg with famotidine 40 mg had no effect on ELIQUIS AUC or C_{max}. Clotting tests (e.g., PT, INR, and aPTT) are affected as expected by the mechanism of action of ELIQUIS (see PHARMACOLOGICAL ACTION, Pharmacodynamic properties, Mechanism of action). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see PHARMACOLOGICAL ACTION, Pharmacodynamic properties). These parameters should not be used to monitor ELIQUIS therapy. **Paediatric population:** Interaction studies have only been performed in adults. **Effect of ELIQUIS on other medicines:** *In vitro* ELIQUIS 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. ELIQUIS did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 µM. Therefore, ELIQUIS is not expected to alter the metabolic clearance of coadministered medicines that are metabolised by these enzymes. ELIQUIS is not a significant inhibitor of P-gp. In studies conducted in healthy subjects, ELIQUIS did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol. **PREGNANCY AND LACTATION:** Safety has not been established and ELIQUIS is not recommended. **DOSAGE AND DIRECTIONS FOR USE:** ELIQUIS can be taken with or without food. If a dose is missed, the patient should take ELIQUIS 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 ELIQUIS 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 ELIQUIS 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 ELIQUIS 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. Because there is limited clinical experience in patients with creatinine clearance < 15 ml/min and there are no data in patients undergoing dialysis, ELIQUIS is not recommended in these patients. ***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 DOSAGE AND DIRECTIONS FOR USE, 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, ELIQUIS is not recommended in these patients. **Hepatic impairment:** ELIQUIS 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. ELIQUIS is not recommended in patients with severe hepatic impairment (see WARNINGS AND SPECIAL PRECAUTIONS, Hepatic impairment and PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Hepatic impairment). **Body weight:** ***Prevention of VTE: elective hip or knee replacement surgery:*** No dose adjustment required. ***Prevention of stroke and systemic embolism: NVAF:*** See DOSAGE AND DIRECTIONS FOR USE, Prevention of stroke and systemic embolism: NVAF. **Paediatric and adolescent:** The efficacy and safety of ELIQUIS in children below age 18 have not been established. No data are available. **Elderly:** ***Prevention of VTE: elective hip or knee replacement surgery:*** No dose adjustment required. ***Prevention of stroke and systemic embolism: NVAF:*** See DOSAGE AND DIRECTIONS FOR USE, Prevention of stroke and systemic embolism: NVAF. **Converting from or to parenteral anticoagulants:** In general, switching treatment from parenteral anticoagulants to ELIQUIS (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 ELIQUIS, discontinue warfarin or other VKA therapy and start ELIQUIS when the INR is below 2,0. When converting from ELIQUIS to warfarin or other VKA therapy, continue ELIQUIS for 48 hours after the first dose of warfarin or other VKA therapy. **Surgery and invasive procedures:** ELIQUIS 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. **SIDE EFFECTS: Clinical experience: Prevention of VTE: elective hip or knee replacement surgery:** Common adverse reactions were anaemia, haemorrhage, contusion, and nausea. The use of ELIQUIS may be associated with an increased risk of occult or overt bleeding from any tissue or organ. **Common treatment-emergent adverse reactions in post-surgery orthopaedic patients:** ***Blood and lymphatic system disorders:*** Anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters). ***Vascular disorders:*** Haemorrhage (including haematoma, and vaginal and urethral haemorrhage). ***Gastrointestinal disorders:*** Nausea. ***Injury, poisoning and procedural complications:*** Contusion. **Common treatment-emergent adverse reactions in NVAF patients:** ***Eye disorders:*** Eye haemorrhage (including conjunctival haemorrhage). ***Vascular disorders:*** Other haemorrhage, haematoma. ***Respiratory, thoracic and mediastinal disorders:*** Epistaxis. ***Gastrointestinal disorders:*** Gastrointestinal haemorrhage (including haematemesis and melaena), rectal haemorrhage, gingival bleeding. ***Renal and urinary disorders:*** Haematuria. ***Injury, poisoning and procedural complications:*** Contusion. **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:** There is no antidote to ELIQUIS. Overdose of ELIQUIS may result in a higher risk of bleeding. Treatment should be symptomatic and supportive. **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:** Pfizer Laboratories (Pty) Ltd. Reg. No.: 1954/000781/07. 85 Bute Lane, Sandton, 2196, South Africa. Tel. No.: 0860 PFIZER (734937). PI Ref.: 20/03/2018. **BOTSWANA:** S2 **ELIQUIS®** 2,5 mg, Reg. No.: BOT 1402582C (60's); S2 **ELIQUIS®** 5 mg, Reg. No.: BOT 1402583D (60's). **NAMIBIA:** S2 **ELIQUIS®** 2,5 mg, Reg. No.: 13/8.2/0212; S2 **ELIQUIS®** 5 mg, Reg. No.: 13/8.2/0213. **ZIMBABWE:** PP10 **ELIQUIS®** 2,5 mg, Reg. No.: 2014/10.2/4896; PP10 **ELIQUIS®** 5 mg, Reg. No.: 2014/10.2/4897. Please refer to detailed package insert for complete prescribing information. PP-ELI-ZAF-0272.

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Tel. No: 0860 PFIZER (734937). Please refer to detailed package insert for full prescribing information. PP-ELI-ZAF-0334

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