

APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ELIQUIS[®] 2,5 mg (Film-coated Tablets)

ELIQUIS[®] 5 mg (Film-coated Tablets)

COMPOSITION:

Each film-coated tablet contains either 2,5 mg or 5 mg apixaban with the following inactive ingredients: anhydrous lactose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauryl sulphate. The film coating contains hypromellose, lactose monohydrate, titanium dioxide, triacetin, and yellow iron oxide (2,5 mg tablets) or red iron oxide (5 mg tablets).

ELIQUIS tablets contain lactose.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

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

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

Apixaban also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in the Rotachrom[®] Heparin chromogenic assay. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom[®] assay is within acceptable limits for use in a clinical laboratory. The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

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

Pharmacokinetic properties

Absorption

The absolute bioavailability of apixaban is approximately 50 % for doses up to 10 mg. Apixaban is absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses \geq 25 mg, apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20 % CV and ~30 % CV, respectively.

Distribution

Plasma protein binding in humans is approximately 87 %. The volume of distribution (V_{ss}) is approximately 21 litres.

Metabolism 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.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major medicine-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

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-FXa activity. (See DOSAGE AND

DIRECTIONS FOR USE, Prevention of stroke and systemic embolism: nonvalvular atrial fibrillation (NVAf)).

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 WARNINGS AND SPECIAL PRECAUTIONS, Hepatic impairment).

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-FXa activity and INR were 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 ELIQUIS in this population (see DOSAGE AND DIRECTIONS FOR USE, Hepatic impairment and WARNINGS AND SPECIAL PRECAUTIONS, Hepatic impairment).

Elderly

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32 % higher. (See DOSAGE AND DIRECTIONS FOR USE, Prevention of stroke and systemic embolism: NVAf).

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 DOSAGE AND DIRECTIONS FOR USE, Prevention of stroke and systemic embolism: NVAF).

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-FXa activity was best described by a linear model. The PK/PD relationship observed in patients who received apixaban in Phase 2 or Phase 3 clinical trials was consistent with that established in healthy subjects.

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 (see DOSAGE AND DIRECTIONS FOR USE, Renal impairment, PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Renal Impairment and CONTRAINDICATIONS).

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 (see PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Hepatic impairment and CONTRAINDICATIONS).

ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see DOSAGE AND DIRECTIONS FOR USE, Hepatic impairment and PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Hepatic impairment).

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), such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g., ritonavir). These medicines may increase ELIQUIS exposure by 2-fold (see INTERACTIONS).

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 (see INTERACTIONS).

Interaction with other medicines affecting haemostasis

The concomitant use of ELIQUIS with antiplatelet medicines increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin. **Other platelet aggregation inhibitors or other antithrombotic medicines are not recommended concomitantly with ELIQUIS following surgery (see INTERACTIONS).**

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. In a 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.

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

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

Paediatric use

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

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 ELIQUIS AUC and a 1,6 fold increase in mean apixaban C_{max} . (See WARNINGS AND SPECIAL PRECAUTIONS, Interaction with inhibitors of both Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)).

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. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1,4 fold increase in mean ELIQUIS AUC and a 1,3 fold increase in C_{max} . Naproxen (500 mg, single dose), an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1,5-fold and 1,6-fold increase in mean ELIQUIS AUC and C_{max} , respectively. 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, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54 % and 42 % decrease in mean ELIQUIS AUC and C_{max} , respectively. The concomitant use of ELIQUIS 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 (see WARNINGS AND SPECIAL PRECAUTIONS, Interaction with inducers of both CYP3A4 and P-gp).

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 (75 mg once daily) or with the combination of clopidogrel

75 mg and aspirin 162 mg once daily in Phase 1 studies did not show a relevant increase in bleeding time or further inhibition of platelet aggregation compared to administration of the antiplatelet agents without ELIQUIS. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of ELIQUIS alone. However the coadministration of ELIQUIS with clopidogrel, ticagrelor or other antiplatelet medicines, except aspirin, are not recommended due to the resulting associated increased risk of major bleeds (see CONTRAINDICATIONS).

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, sulfapyrazone, 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 WARNINGS AND SPECIAL PRECAUTIONS, Interaction with other medicinal products affecting haemostasis).

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 ($IC_{50} > 45 \mu M$) and weak inhibitory effect on the activity of CYP2C19 ($IC_{50} > 20 \mu M$) at concentrations that are significantly greater than peak plasma concentrations observed in patients. ELIQUIS did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to $20 \mu M$. 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, as described below, ELIQUIS did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin: Coadministration of ELIQUIS (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, ELIQUIS does not inhibit P-gp mediated substrate transport.

Naproxen: Coadministration of single doses of ELIQUIS (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 ELIQUIS (10 mg) and atenolol (100 mg) did not alter the pharmacokinetics of atenolol.

PREGNANCY AND LACTATION:

Safety has not been established.

Pregnancy

ELIQUIS is not recommended during pregnancy.

Lactation

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

ELIQUIS therapy is not recommended for mothers who are breastfeeding their infants.

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 \geq 80 years, body weight \leq 60 kg, or serum creatinine \geq 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 (see PHARMACOLOGICAL ACTION, Pharmacokinetic properties). 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 (see WARNINGS AND SPECIAL PRECAUTIONS, Renal impairment, Prevention of VTE: elective hip or knee replacement surgery and PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

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 (see WARNINGS AND SPECIAL PRECAUTIONS, Hepatic impairment and PHARMACOLOGICAL ACTION, Pharmacokinetic properties, 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 (see PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

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 (see PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

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

The safety of ELIQUIS has been evaluated in 5 924 patients exposed to ELIQUIS 2,5 mg twice daily undergoing major orthopaedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11 % of the patients treated with ELIQUIS 2,5 mg twice daily experienced adverse reactions.

Bleeding may occur during ELIQUIS therapy in the presence of associated risk factors such as organic lesions liable to bleed. 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 (see WARNINGS AND SPECIAL PRECAUTIONS, Haemorrhage risk).

Adverse reactions in the studies are listed in Table 1.

Table 1: Treatment-emergent adverse reactions in post-surgery orthopaedic patients

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)
<i>Blood and lymphatic system disorders</i>		
Anaemia (including	Thrombocytopenia	

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)
postoperative and haemorrhagic anaemia, and respective laboratory parameters)		
<i>Immune system disorders</i>		
		Hypersensitivity
<i>Eye disorders</i>		
		Ocular haemorrhage (including conjunctival haemorrhage)
<i>Vascular disorders</i>		
Haemorrhage (including haematoma, and vaginal and urethral haemorrhage)	Hypotension	
<i>Respiratory, thoracic and mediastinal disorders</i>		
	Epistaxis	Haemoptysis
<i>Gastrointestinal disorders</i>		
Nausea	Gastrointestinal haemorrhage (including haematemesis and melaena), haematochesia	Rectal haemorrhage, gingival bleeding
<i>Hepatobiliary disorders</i>		
	Increased transaminases (including increased alanine aminotransferase and increased aspartate aminotransferase, increased gamma-glutamyltransferase, abnormal	

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)
	liver function test, increased blood alkaline phosphatase, increased blood bilirubin	
<i>Musculoskeletal and connective tissue disorders</i>		
		Muscle haemorrhage
<i>Renal and urinary disorders</i>		
	Haematuria (including respective laboratory parameters)	
<i>Injury, poisoning and procedural complications</i>		
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	

Prevention of stroke and systemic embolism: NVAf

The safety of ELIQUIS has been evaluated in clinical studies, including 11 284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients to 2,5 mg twice daily. The ELIQUIS exposures were > 12 months for 9 375 patients and > 24 months for 3 369 patients.

Adverse reactions are listed in Table 2.

Table 2: Treatment-emergent adverse reactions in NVAF patients

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)
<i>Immune system disorders</i>		
	Hypersensitivity (including medicine hypersensitivity such as skin rash and anaphylactic reaction such as allergic oedema)	
<i>Nervous system disorders</i>		
	Brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)	
<i>Eye disorders</i>		
Eye haemorrhage (including conjunctival haemorrhage)		
<i>Vascular disorders</i>		
Other haemorrhage, haematoma	Intra-abdominal haemorrhage	
<i>Respiratory, thoracic and mediastinal disorders</i>		
Epistaxis	Haemoptysis	Respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage, and pharyngeal

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)
		haemorrhage)
<i>Gastrointestinal disorders</i>		
Gastrointestinal haemorrhage (including haematemesis and melaena), rectal haemorrhage, gingival bleeding	Haemorrhoidal haemorrhage, haematochesia, mouth haemorrhage	Retroperitoneal haemorrhage
<i>Renal and urinary disorders</i>		
Haematuria		
<i>Reproductive system and breast disorders</i>		
	Abnormal vaginal haemorrhage, urogenital haemorrhage	
<i>General disorders and administration site conditions</i>		
	Application site bleeding	
<i>Investigations</i>		
	Occult blood positive	
<i>Injury, poisoning and procedural complications</i>		
Contusion	Traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage	

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.

IDENTIFICATION:

ELIQUIS 2,5 mg: Yellow, round, biconvex film-coated tablets with “893” debossed on one side and “2½”

on the other side.

ELIQUIS 5 mg: Pink, oval shaped, biconvex film-coated tablets with “894” debossed on one side and “5” on the other side.

PRESENTATION:

ELIQUIS 2,5 mg: Cartons containing clear PVC/PVDC/silver aluminium blisters of 10 film-coated tablets (1 blister of 10 film-coated tablets each), 20 film-coated tablets (2 blisters of 10 film-coated tablets each) or 60 film-coated tablets (6 blisters of 10 film-coated tablets each).

ELIQUIS 5 mg: Cartons containing clear PVC/PVDC/silver aluminium blisters of 20 film-coated tablets (2 blisters of 10 film-coated tablets each), 60 film-coated tablets (6 blisters of 10 film-coated tablets each) or 14 film-coated tablets (1 blister of 14 film-coated tablets each) or 56 film-coated tablets (4 blisters of 14 film-coated tablets each).

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Do not remove blister from carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ELIQUIS 2,5 mg: 47/8.2/0463

ELIQUIS 5 mg: 47/8.2/0464

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton

Pfizer Laboratories (Pty) Ltd
Eliquis 2,5 mg and 5 mg Film-coated Tablets
Final Approved Package Insert – 20 March 2018

2196

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 20 March 2018

Rotachrom® is a registered trademark of Diagnostica Stago.

ELIQUIS® is a registered trademark of Bristol-Myers Squibb.

Manufacturer: Bristol-Myers Squibb Manufacturing Company, Humacao, Puerto Rico

BOTSWANA: S2

ELIQUIS 2,5 mg Reg. No.: BOT 1402582C (60's)

ELIQUIS 5 mg Reg. No.: BOT1402583D (60's)

NAMIBIA: S2

ELIQUIS 2,5 mg Reg. No.: 13/8.2/0212

ELIQUIS 5 mg Reg. No.: 13/8.2/0213

ZIMBABWE: PP10

ELIQUIS 2,5 mg Reg. No.: 2014/10.2/4896

ELIQUIS 5 mg Reg. No.: 2014/10.2/4897