PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ELIQMAK 2.5 (film coated tablet)

ELIQMAK 5 (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ELIQMAK 2.5: Each film coated tablet contains 2,5 mg apixaban.

ELIQMAK 5: Each film coated tablet contains 5 mg apixaban.

Contains sugar – lactose monohydrate

ELIQMAK 2.5: contains 50,25 mg lactose monohydrate.

ELIQMAK 5: contains 100,50 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

ELIQMAK 2.5: Yellow coloured, round, biconvex, film coated tablets, debossed “F51” on one side and plain on other side.

ELIQMAK 5: Pink coloured, capsule shaped, film coated tablets, debossed “F52” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of VTE: elective hip or knee replacement surgery.

ELIQMAK 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):

ELIQMAK is indicated to reduce the risk of stroke, systemic embolism and death in patients with non-valvular atrial fibrillation with one or more risk factors.

Treatment of VTE

ELIQMAK 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

Prevention of VTE: elective hip or knee replacement surgery

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

Special population

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 in patients with creatinine clearance < 15 ml/min and there are no data in patients undergoing dialysis, **ELIQMAK** is not recommended in these patients (see section 4.4)

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 **ELIQMAK** is not recommended in these patients.

Hepatic impairment:

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

ELIQMAK is not recommended in patients with severe hepatic impairment (see section 4.4).

Body weight:

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required (see section 5.1)

Prevention of stroke and systemic embolism: NVAF

See section 4.1

Paediatric and adolescent

The safety and efficacy of **ELIQMAK** in children below 18 have not been established.

Elderly

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required (see section 5.1)

Prevention of stroke and systemic embolism: NVAF

See section 4.1

Converting from or to parenteral anticoagulants

Switching from parenteral anticoagulants to **ELIQMAK** 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 any other VKA therapy to **ELIQMAK,** discontinue warfarin or other VKA therapy and start **ELIQMAK** when the INR is below 2,0.

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

Surgery and invasive procedures

ELIQMAK 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.

ELIQMAK can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2).
- **ELIQMAK** is not recommended in patients with severe renal disease (CrCl < 15 mL/min)
- **ELIQMAK** should not be administered with antiplatelet medicines other than aspirin (see section 4.4)
- 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 **ELIQMAK** are to be carefully observed for signs of bleeding. **ELIQMAK** 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. **ELIQMAK** 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 prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered. Reversal of **ELIQMAK** 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 **ELIQMAK**. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving **ELIQMAK**. Standard anticoagulation tests cannot be used to monitor **ELIQMAK** (see section 4.5).

Interaction with other medicines affecting haemostasis

The concomitant use of **ELIQMAK** 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 ELIQMAK following surgery (see section 4.5).

In patients with atria fibrillation and a condition that warrants chronic use of aspirin, **ELIQMAK** may be used with due regard to increased risk of major bleeding.

In a clinical study 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.

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 apixaban is not recommended

in this setting.

Patients with antiphospholipid syndrome

Treatment with 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 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.

Surgery and invasive procedures

ELIQMAK 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.

Temporary discontinuation

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

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines, such as **ELIQMAK**, 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 procedure is planned, **ELIQMAK** should be stopped 48 hours beforehand. Indwelling epidural or intrathecal catheters must be removed at least 6 hours prior to the first dose of

ELIQMAK. 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

Apixaban 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 apixaban 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).

Body weight

Low body weight (< 60 kg) may increase haemorrhagic risk (see section 5.2).

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

The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g.,

ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir). These medicines may increase apixaban exposure by 2-fold (see section 4.5).

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure.

Use with caution when co-administering ELIQMAK with strong inducers of both CYP3A4 and P-gp (see section 4.5).

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 stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE, apixaban should be used with caution;
- for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

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, **ELIQMAK** 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).

Special populations

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, ELIQMAK is not recommended in these patients (see section 4.2, Renal impairment, section 5.2, Renal impairment and section 4.3).

Prevention of stroke and systemic embolism: NVAF

ELIQMAK has not been studied in patients undergoing dialysis and is not recommended in these patients (see section 5.2).

Treatment of VTE

Because there is limited clinical experience in patients with creatinine clearance < 15 mL/min and no data in patients undergoing dialysis, ELIQMAK is not recommended in these patients (see sections 5.2 and 4.3).

Hepatic impairment

ELIQMAK is not recommended in patients with severe hepatic impairment (see section 5.2, Hepatic impairment and section 4.3).

ELIQMAK may be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see section 4.2, Hepatic impairment and section 5.2, Hepatic impairment).

Elderly patients

Increasing age may increase haemorrhagic risk (see section 5.2). Also, the co-administration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Information about excipients

ELIQMAK contains lactose. Patients with rare hereditary problems of galactose intolerance,

total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicines and other forms of interaction

Inhibitors of CYP3A4 and P-gp

Co-administration 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. Interaction with inhibitors of both Cytochrome P450 3A4 (CYP3A4) and p-glycoprotein (P-gp). The dose of **ELIQMAK** 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 AUC and a 1.3-fold increase in C_{max}. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. Clarithromycin (500 mg, twice a day), an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean apixaban AUC and C_{max} respectively.

Inducers of CYP3A4 and P-gp

Co administration 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, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such medicines, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp apixaban should be used with caution for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE. Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy maybe compromised (see section 4.4).

Anticoagulants, platelet aggregation inhibitors and NSAIDs

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) in Phase I studies did not show a relevant increase in template bleeding time, or further inhibition of platelet aggregation, compared to administration of the anti-platelet 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 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 clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

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

Medicines associated with serious bleeding are not recommended concomitantly with ELIQMAK, 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.

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, Interaction with other medicines affecting haemostasis).

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed 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 medicinal products 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 medicinal products 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

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, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen

Co administration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max}.

Atenolol

Co administration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

Activated charcoal

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established.

ELIQMAK is not recommended during pregnancy. Treatment may increase the risk of haemorrhage during pregnancy and delivery.

Breastfeeding

It is not known whether apixaban is excreted in human milk. A risk to newborn babies and infants cannot be excluded. **ELIQMAK** is not recommended for mothers who are breastfeeding their infants.

Fertility

Studies with animals dosed with apixaban have shown no effect on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were anaemia, haemorrhage, contusion, epistaxis, haematoma and nausea.

Tabulated summary of adverse reactions

Table 1: Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF):

System organ class	Frequent	Less frequent	Frequency unknown
Blood and lymphatic system disorders	Anaemia	Thrombocytopenia	
Immune system disorders		Hypersensitivity, allergic oedema, anaphylaxis,	Angioedema

		Pruritis	
Nervous system disorders		Brain haemorrhage*	
Eye disorders	Eye haemorrhage (including conjunctival haemorrhage)		
Vascular disorders	Haemorrhage, haematoma, hypotension (including postural hypotension)	Intra-abdominal haemorrhage	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis Respiratory tract haemorrhage	
Gastrointestinal disorders	Nausea Gastrointestinal haemorrhage Rectal haemorrhage gingival bleeding	Haemorrhoidal haemorrhage Mouth haemorrhage Haematochezia Retroperitoneal haemorrhage	

Hepatobiliary disorders	Gamma-glutamyl transferase increased	Liver function test abnormal, aspartate amino transferase increased, blood alkaline phosphate increased, blood bilirubin increased Alanine amino transferase increased	
Skin and subcutaneous tissue disorders		Skin rash Alopecia Erythema multiforme	
Musculoskeletal and connective tissue disorders		Muscle haemorrhage	
Renal and urinary disorders	Haematuria		
Reproductive system and breast disorders		Abnormal vaginal haemorrhage, urogenital haemorrhage	
General		Application site	

disorders and administration site conditions		bleeding	
Investigations		Occult blood positive	
Injury, poisoning and procedural complications	Contusion	Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage Traumatic haemorrhage	

Table 2: Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)

System organ	Frequent	Less frequent	Frequency

class			unknown
Blood and lymphatic system disorders	Anaemia Thrombocytopaenia		
Immune system disorders		Hypersensitivity, allergic oedema, anaphylaxis Pruritus	Angioedema
Nervous system disorders		Brain haemorrhage*	
Eye disorders		Eye haemorrhage (including conjunctival haemorrhage)	
Vascular disorders	Haemorrhage, haematoma,	hypotension (including postural hypotension)	Intra-abdominal haemorrhage
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis Respiratory tract haemorrhage	
Gastrointestinal disorders	Nausea Gastrointestinal haemorrhage Mouth	Haemorrhoidal haemorrhage Haematochezia	Retroperitoneal haemorrhage

	haemorrhage Rectal haemorrhage gingival bleeding		
Hepatobiliary disorders	Gamma-glutamyl transferase increased Alanine aminotransferase increased	Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphate increased, blood bilirubin increased	
Skin and subcutaneous tissue disorders	Skin rash	Alopecia	Erythema multiforme
Musculoskeletal and connective tissue disorders		Muscle haemorrhage	
Renal and urinary disorders	Haematuria		
Reproductive system and breast disorders	Abnormal vaginal haemorrhage, urogenital		

	haemorrhage		
General disorders and administration site conditions		Application site bleeding	
Investigations		Occult blood positive	
Injury, poisoning and procedural complications	Contusion	Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage Traumatic haemorrhage	

*The term ‘brain haemorrhage’ encompasses all intracranial or intraspinal haemorrhages (i.e. haemorrhagic stroke or putamen, cerebellar, intraventricular or subdural haemorrhages)

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 Med Safety APP (Medsafety X SAHPRA and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no antidote to **ELIQMAK**. Overdose of **ELIQMAK** may result in a higher risk of bleeding.

Administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of **ELIQMAK** reduced mean **ELIQMAK** AUC by 50 % and 27 %, respectively, and had no impact on C_{max}. Mean half-life of **ELIQMAK** decreased from 13,4 hours when **ELIQMAK** was administered alone to 5,3 hours and 4,9 hours, respectively, when activated charcoal was administered 2 and 6 hours after **ELIQMAK**. Thus, administration of activated charcoal may be useful in the management of **ELIQMAK** overdose or accidental ingestion.

Haemodialysis is unlikely to be an effective means of managing ELIQMAK 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. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

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-FXa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-FXa kits, however results differ across kits. Data from clinical studies are only available for the Rotachrom® Heparin chromogenic assay. Anti-FXa 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-FXa activity is approximately linear over a wide dose range of apixaban.

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 10mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and~30% CV, respectively.

Distribution

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

Biotransformation

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 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)

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 non-clinical studies, respectively.

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

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

In participants 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 participants 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:

The single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in participants with hepatic impairment. Changes in anti-Factor Xa activity and INR

were comparable between participants with mild to moderate hepatic impairment and healthy participants.

Gender:

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

Body weight:

Compared to apixaban exposure in participants 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 end points (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 – 50mg). 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 participants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose

Croscarmellose Sodium

Sodium lauryl sulfate

Povidone

Magnesium stearate

Instacoat Universal Yellow which contains:

- Hypromellose
- Triacetin
- Titanium dioxide
- Yellow iron oxide

Instacoat Universal Pink which contains:

- Hypromellose
- Triacetin
- Titanium dioxide
- Red Iron Oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for blister pack.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Tablets are packed in aluminium foil laminated on one side and laminated to clear PVC/PVdC on the other side. Pack sizes include 10, 20 and 14 tablets for apixaban 2.5 mg tablets and 20, 60, 14 and 56 tablets for apixaban 5 mg tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

ELIQMAK 2.5: 57/8.2/0020

ELIQMAK 5: 57/8.2/0021

9. DATE OF FIRST AUTHORISATION

ELIQMAK 2.5: 06 May 2025

ELIQMAK 5: 06 May 2025

10. DATE OF REVISION OF THE TEXT

06 May 2025



PM0306-01