Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

ELIQUIS (apixaban) prescriber guide

This Prescriber Guide is not a substitute for the ELIQUIS® Summary of Product Characteristics (SmPC). Please consult the SmPC for full prescribing information. A digital version of the Prescriber Guide is available at the following website address: www.eliquis-edu.mt

This educational material is provided to further minimise the risk of bleeding that is associated with the use of ELIQUIS®, and to guide healthcare professionals in managing that risk.

Date of approval: [09 2024]

Date of internal approval: [09 2024]

Local approval number: 09 2024

Version: 12.0

Bristol Myers Squibb® | Pfizer

Eliquis® apixaban

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Patient alert card

A Patient Alert Card must be provided to each patient who is prescribed ELIQUIS®, and the importance and consequences of anticoagulant therapy should be explained. The Patient Alert Card is included inside all packs of ELIQUIS® (0.15 mg granules in capsules for opening; 0.5 mg coated granules packaged in 0.5 mg, 1.5 mg, and 2 mg sachets; 2.5 mg and 5 mg film-coated tablets) together with the package leaflet.

Specifically, the prescriber should talk to patients or caregivers about the importance of treatment compliance, the signs or symptoms of bleeding, and when to seek attention from a healthcare professional.

This Patient Alert Card provides information to healthcare professionals on the anticoagulant therapy and contains important contact information in the event of emergencies.

Patients or caregivers should be advised to carry the Patient Alert Card with them at all times and to show it to every healthcare professional involved in their care. They should also be reminded about the need to inform healthcare professionals involved in their care that they are taking ELIQUIS® if they require surgery or invasive procedures.

Adult therapeutic indication: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)[1,2]

Adult dosing recommendations

The recommended dose of ELIQUIS® is 5 mg taken orally twice daily with water, with or without food. Therapy should be continued long-term (Figure 1).

Figure 1

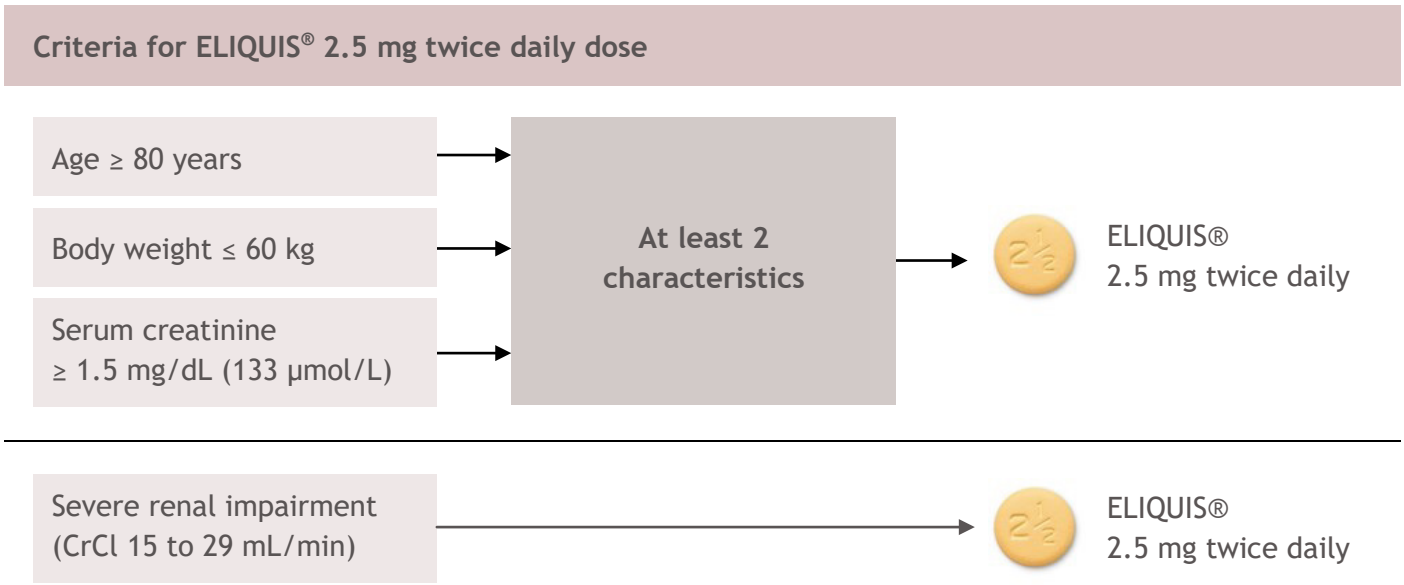
For patients who are unable to swallow whole tablets, ELIQUIS® tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, ELIQUIS® tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube. Crushed ELIQUIS® tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

Adult dose reduction

The recommended dose of Eliquis® is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5 mg/dL (133 µmol/L) (Figure 2).

In adult patients with NVAF and severe renal impairment (creatinine clearance [CrCl] 15 to 29 mL/min), for the prevention of stroke and systemic embolism, patients should receive the lower dose of ELIQUIS® 2.5 mg twice daily (Figure 2).

Figure 2



Adult missed dose

A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning. The patient should continue with the intake of the regular dose twice daily as recommended on the following day.

Adult patients with renal impairment

Renal impairment	
Dialysis	Not recommended
Renal failure (CrCl < 15 mL/min)	Not recommended
Severe renal impairment (CrCl 15 to 29 mL/min)	Dose reduction to 2.5 mg twice daily
Mild (CrCl 51 to 80 mL/min) or moderate (CrCl 30 to 50 mL/min) renal impairment	5 mg twice daily. No dose adjustment required unless the patient fulfils criteria for dose reduction to 2.5 mg twice daily based on age, body weight and/or serum creatinine (refer to Adult dose reduction section)

Adult patients with hepatic impairment

Hepatic impairment	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Contraindicated
Severe hepatic impairment	Not recommended
Mild or moderate hepatic impairment (Child Pugh A or B)	Use with caution No dose adjustment required

Prior to initiating ELIQUIS®, liver function testing should be performed. Patients with elevated liver enzymes alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) > 2x ULN or total bilirubin ≥ 1.5x ULN were excluded in clinical studies. Therefore, ELIQUIS® should be used with caution in this population.

Adult patients undergoing catheter ablation

ELIQUIS® can be continued in patients undergoing catheter ablation for atrial fibrillation.

Adult patients undergoing cardioversion

ELIQUIS® can be initiated or continued in NVAF adult patients who may require cardioversion.

For patients not previously treated with anticoagulants, exclusion of left atrial thrombus using an image-guided approach (eg transesophageal echocardiography [TEE] or computed tomographic scan [CT]) prior to cardioversion should be considered, in accordance with established medical guidelines. For patients in whom a prior intracardiac thrombus has been detected, established medical guidelines should be followed prior to cardioversion.

Patient status	Patient qualifies for dose reduction?	Dosing regimen
Initiating treatment with ELIQUIS®	No	5 mg twice daily for at least 2.5 days (5 single doses) before cardioversion
	Yes	2.5 mg twice daily for at least 2.5 days (5 single doses) before cardioversion
Insufficient time prior to cardioversion* to administer the expected twice daily regimen of 5 single doses of ELIQUIS® over 2.5 days	No	10 mg loading dose at least 2 hours before cardioversion, followed by 5 mg twice daily
	Yes	5 mg loading dose at least 2 hours before cardioversion, followed by 2.5 mg twice daily

* Physicians should consider checking for ventricular thrombus prior to cardioversion.

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

Adult therapeutic indication: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults[1,2]

Adult dosing recommendations

The recommended dose of ELIQUIS® for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily with water, with or without food.

As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (eg recent surgery, trauma, immobilisation).

The recommended dose of ELIQUIS® for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily with water, with or without food.

When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following the completion of 6 months of treatment with ELIQUIS® 5 mg twice daily or with another anticoagulant, as indicated in Figure 3.

Figure 3

Dosing schedule	Morning	Night	Daily dose
Treatment of acute DVT or PE (at least 3 months):			
Day 1-7: 10 mg twice daily →	 ELIQUIS® 5 mg, ELIQUIS® 5 mg	ELIQUIS® 5 mg, ELIQUIS® 5 mg	20 mg
Day 8 onwards: 5 mg twice daily →	 ELIQUIS® 5 mg	 ELIQUIS® 5 mg	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of anticoagulation treatment:			
2.5 mg twice daily →	 ELIQUIS® 2.5 mg	 ELIQUIS® 2.5 mg	5 mg

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

For patients who are unable to swallow whole tablets, ELIQUIS® tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, ELIQUIS® tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube. Crushed ELIQUIS® tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

Adult missed dose

A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning. The patient should continue with the intake of the regular dose twice daily as recommended on the following day.

Adult patients with renal impairment

Renal impairment	
Dialysis	Not recommended
Renal failure (CrCl < 15 mL/min)	Not recommended
Severe renal impairment (CrCl 15 to 29 mL/min)	Use with caution
Mild (CrCl 51–80 mL/min) or moderate (CrCl 30 to 50 mL/min) renal impairment	No dose adjustment required

Adult patients with hepatic impairment

Hepatic impairment	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Contraindicated
Severe hepatic impairment	Not recommended
Mild or moderate hepatic impairment (Child Pugh A or B)	Use with caution No dose adjustment required

Prior to initiating ELIQUIS®, liver function testing should be performed. Patients with elevated liver enzymes ALT/AST > 2x ULN or total bilirubin ≥ 1.5x ULN were excluded in clinical studies. Therefore, ELIQUIS® should be used with caution in this population.

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

ELIQUIS® is not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of ELIQUIS® has not been established in these clinical situations.

Adult patients with active cancer

Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events.

When ELIQUIS® is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made.

Adult Therapeutic indication: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery[1]

Adult dosing recommendations

The recommended dose of ELIQUIS® is 2.5 mg taken orally twice daily with water, with or without food. The initial dose should be taken 12 to 24 hours after surgery.

Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window.

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.

For patients who are unable to swallow whole tablets, ELIQUIS® tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, ELIQUIS® tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube. Crushed ELIQUIS® tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

Adult missed dose

A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning. The patient should continue with the intake of the regular dose twice daily as recommended on the following day.

Adult patients with renal impairment

Renal impairment	
Dialysis	Not recommended
Renal failure (CrCl < 15 mL/min)	Not recommended
Severe renal impairment (CrCl 15 to 29 mL/min)	Use with caution
Mild (CrCl 51–80 mL/min) or moderate (CrCl 30 to 50 mL/min) renal impairment	No dose adjustment required

Adult patients with hepatic impairment

Hepatic impairment	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Contraindicated
Severe hepatic impairment	Not recommended
Mild or moderate hepatic impairment (Child Pugh A or B)	Use with caution No dose adjustment required

Prior to initiating ELIQUIS®, liver function testing should be performed. Patients with elevated liver enzymes ALT/AST > 2x ULN or total bilirubin ≥ 1.5x ULN were excluded in clinical studies. Therefore, ELIQUIS® should be used cautiously in this population.

Paediatric therapeutic indication: Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age[1,2,3,4,5,6]

ELIQUIS® is not recommended for use in neonates and in paediatric patients aged 28 days to less than 18 years in indications other than treatment of VTE and prevention of recurrent VTE.

Paediatric dosing recommendations

ELIQUIS® treatment for paediatric patients from 28 days to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation therapy.

The recommended dose of ELIQUIS® is based on the patient's weight (Table 1). The dose should be adjusted according to weight tier as treatment progresses.

For weight not listed in the dosing table, no dosing recommendation can be provided.

Based on VTE treatment guidelines in the paediatric population, duration of overall therapy should be individualised after careful assessment of the treatment benefit and the risk for bleeding.

Table 1

ELIQUIS® dose recommendations for treatment of VTE and prevention of recurrent VTE in paediatric patients, by weight in kg

		Day 1-7		Day 8 and beyond	
Pharmaceutical forms	**Body weight**	**Dosing schedule**	**Maximum daily dose**	**Dosing schedule**	**Maximum daily dose**
Granules in capsules for opening 0.15 mg	4 to < 5 kg	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
Coated granules in sachet 0.5 mg, 1.5 mg, 2.0 mg	5 to < 6 kg	1.0 mg twice daily	2.0 mg	0.5 mg twice daily	1.0 mg
	6 to < 9 kg	2.0 mg twice daily	4.0 mg	1.0 mg twice daily	2.0 mg
	9 to < 12 kg	3.0 mg twice daily	6.0 mg	1.5 mg twice daily	3.0 mg
	12 to < 18 kg	4.0 mg twice daily	8.0 mg	2.0 mg twice daily	4.0 mg
	18 to < 25 kg	6.0 mg twice daily	12.0 mg	3.0 mg twice daily	6.0 mg
	25 to < 35 kg	8.0 mg twice daily	16.0 mg	4.0 mg twice daily	8.0 mg
Film-coated tablets 2.5 mg and 5.0 mg	> 35 kg	10.0 mg twice daily	20.0 mg	5.0 mg twice daily	10.0 mg

Paediatric missed dose

A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning. The patient should continue with the intake of the regular dose twice daily as recommended on the following day.

Paediatric patients with renal impairment

Based on adult data and limited data in paediatric patients, no dose adjustment is necessary in paediatric patients with mild to moderate renal impairment. ELIQUIS® is not recommended in paediatric patients with severe renal impairment. Paediatric patients with severe renal impairment have not been studied and therefore should not receive ELIQUIS®. In paediatric patients ≥ 2 years of age, severe renal impairment is defined as an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 body surface area (BSA). In Study CV185325, in patients less than 2 years of age, the thresholds defining severe renal impairment by sex and post-natal age are summarised in Table 2 below; each corresponds to an eGFR < 30 mL/min/1.73 m^2 BSA for patients ≥ 2 years of age.

Table 2

eGFR eligibility thresholds for study CV185325

Postnatal age (gender)	GFR reference range (mL/min/1.73 m^2)	Eligibility threshold for eGFR*
1 week (males and females)	41 ± 15	≥ 8
2–8 weeks (males and females)	66 ± 25	≥ 12
> 8 weeks to < 2 years (males and females)	96 ± 22	≥ 22
2–12 years (males and females)	133 ± 27	≥ 30
13–17 years (males)	140 ± 30	≥ 30
13–17 years (females)	126 ± 22	≥ 30

* Eligibility threshold for CV185325 study participation, where estimated glomerular filtration rate (eGFR) was calculated per the updated bedside Schwartz equation (Schwartz, GJ et al., CJASN 2009). This per protocol threshold corresponded to the eGFR below which a prospective patient was considered to have "inadequate renal function" that precluded participation in Study CV185325. Each threshold was defined as an eGFR < 30% of 1 standard deviation (SD) below the GFR reference range for age and gender. Threshold values for patients < 2 years of age correspond to an eGFR < 30 mL/min/1.73 m^2, the conventional definition of severe renal failure in patients > 2 years of age.

Paediatric patients with hepatic impairment

ELIQUIS® has not been studied in paediatric patients with hepatic impairment.

Prior to initiating ELIQUIS®, liver function testing should be performed.

Switching to and from ELIQUIS®[1,2,3,4,5,6]

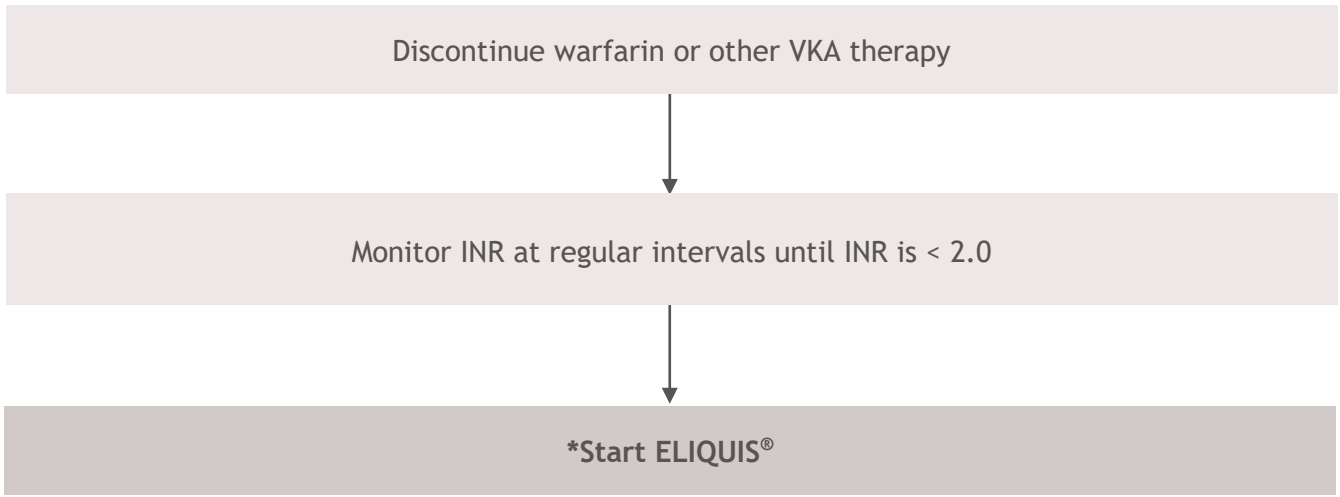
Switching treatment from parenteral anticoagulants to ELIQUIS® (and vice versa) can be done at the next scheduled dose.

These medicinal products should not be administered simultaneously.

Switching from vitamin K antagonist (VKA) therapy to ELIQUIS®

When converting patients (adult and paediatric) from VKA therapy to ELIQUIS®, warfarin or other VKA therapy should be discontinued and ELIQUIS® started when the international normalised ratio (INR) is < 2.0 (Figure 4).

Figure 4



* Refer to dosing recommendations per indication

Switching from ELIQUIS® to VKA therapy

No data are available for paediatric patients.

When converting adult patients from ELIQUIS® to VKA therapy, administration of ELIQUIS® should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of ELIQUIS® with VKA therapy, INR should be obtained prior to the next scheduled dose of ELIQUIS®. Coadministration of ELIQUIS® and VKA therapy should be continued until the INR is ≥ 2.0.

Populations potentially at higher risk of bleeding[1,2,3,4,5,6]

Several subgroups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. ELIQUIS® should be used with caution in conditions with an increased haemorrhagic risk. ELIQUIS® administration should be discontinued if severe haemorrhage occurs.

Lesion or condition considered a significant risk factor for major bleeding	
This includes: • Active clinically significant bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • 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	Circumstances where ELIQUIS® is **contraindicated**

Interactions with other medicinal products affecting haemostasis	
Anticoagulants • Unfractionated heparin (UFH), low molecular weight heparins (eg, enoxaparin, dalteparin), heparin derivatives (eg, fondaparinux) • Oral anticoagulants (eg, warfarin, rivaroxaban, dabigatran)	Due to an increased bleeding risk, concomitant treatment with ELIQUIS® and any other anticoagulant agent 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

Platelet aggregation inhibitors	The concomitant use of ELIQUIS® with antiplatelet agents increases the risk of bleeding ELIQUIS® should be used with caution when coadministered with selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs), non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA) and/or P2Y12 inhibitors (eg, clopidogrel) There is limited experience of coadministration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfinpyrazone) or thrombolytic agents. As such agents increase the bleeding risk, coadministration of these medicinal products with ELIQUIS® is not recommended
Factors which may increase ELIQUIS® exposure/increase ELIQUIS® plasma levels	
Renal impairment	*See sections on patients with renal impairment under dosing recommendations for each separate indication* • Use is not recommended in patients with CrCl < 15 mL/min or patients undergoing dialysis • No dose adjustment is required in patients with mild or moderate renal impairment **Patients with NVAF** • Patients with severe renal impairment (CrCl 15 to 29 mL/min) should receive the lower dose of ELIQUIS® 2.5 mg twice daily • Patients with serum creatinine ≥ 1.5 mg/dL (133 µmol/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of ELIQUIS® 2.5 mg twice daily
Elderly	• No dose adjustment required **Patients with NVAF** • No dose adjustment required except in combination with other factors

Adults with low body weight ≤ 60 kg	• No dose adjustment required
	Patients with NVAF • No dose adjustment required except in combination with other factors
Concomitant use with strong inhibitors of both CYP3A4 and P-gp	• ELIQUIS® is not recommended in patients receiving concomitant systemic treatment with, for example, azole-antimycotics (eg, ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (eg, ritonavir)
Concomitant use with agents not considered strong inhibitors of both CYP3A4 and P-gp	• No dose adjustment for ELIQUIS® is required when coadministered with, for example, amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine and verapamil

Factors which may reduce ELIQUIS® exposure/reduce ELIQUIS® plasma levels	
Concomitant use with strong inducers of both CYP3A4 and P-gp	• The concomitant use of ELIQUIS® with strong inducers of both CYP3A4 and P-gp (eg, rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in ELIQUIS® exposure and should be used with caution
	Treatment of DVT or PE • ELIQUIS® is not recommended

Surgery and invasive procedures[1,2,7]

ELIQUIS® should be discontinued prior to elective surgery or invasive procedures (excluding cardioversion or catheter ablation) with a risk of bleeding (see table below).

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.

In the event a patient treated with ELIQUIS® requires an elective procedure, such as surgery or an invasive procedure associated with an increased risk of bleeding, ELIQUIS® should be discontinued for a sufficient period of time prior to the procedure to reduce the risk of anticoagulant-related bleeding. The half-life of ELIQUIS® is approximately 12 hours. Given that ELIQUIS® is a reversible factor Xa inhibitor, its anticoagulant activity should abate within 24 to 48 hours from the last administered dose.

Discontinuation of ELIQUIS® prior to elective surgery/invasive procedure	
Low risk of bleeding (includes interventions for which bleeding, if it occurs, will be minimal, non-critical in its location and/or easily controlled)	At least **24 hours** prior to elective surgery or invasive procedure
Moderate or high risk of bleeding (includes interventions for which the probability of clinically significant bleeding cannot be excluded, or for which the risk of bleeding would be unacceptable)	At least **48 hours** prior to elective surgery or invasive procedures

Temporary discontinuation[1,2,3,4,5,6]

Discontinuing anticoagulants, including ELIQUIS®, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with ELIQUIS® must be temporarily discontinued for any reason, therapy should be restarted as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

Spinal/epidural anaesthesia or puncture[1]

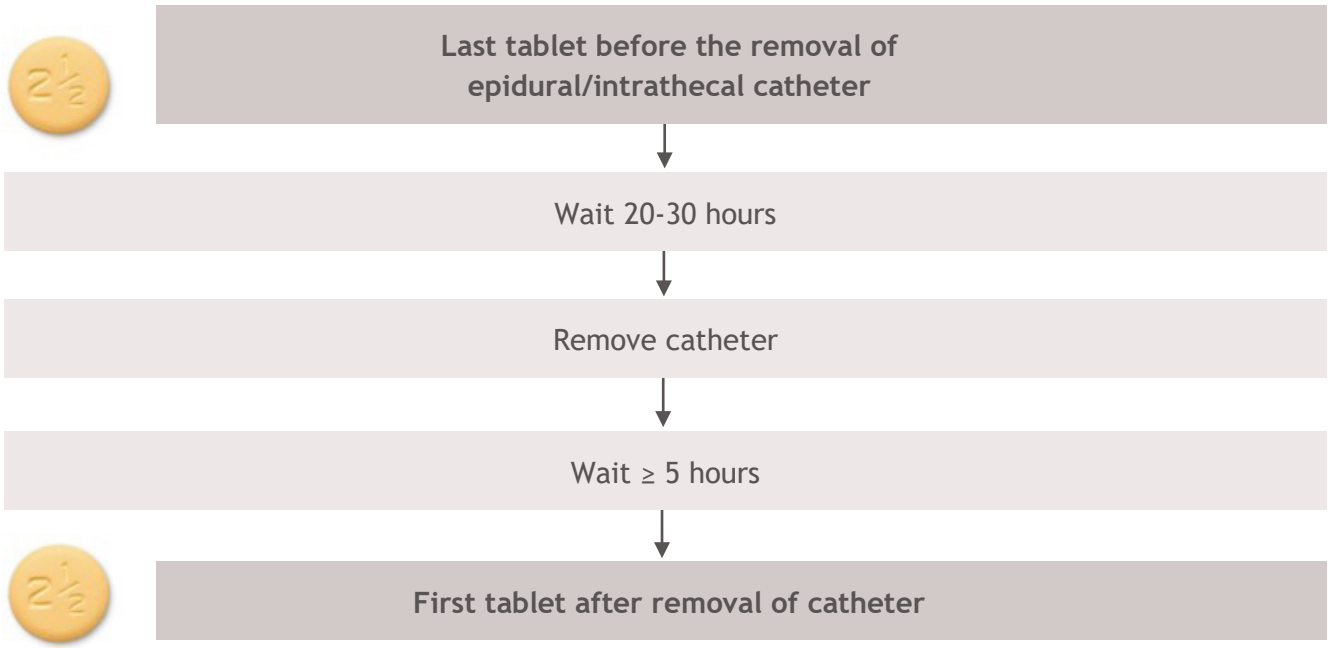
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma, which can result in long-term or permanent paralysis. Post-operative indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of ELIQUIS®.

Guidance on the use of ELIQUIS® in patients with indwelling intrathecal or epidural catheters

There is no clinical experience with the use of ELIQUIS® with indwelling intrathecal or epidural catheters. In case there is such need and based on the general pharmacokinetic characteristics of ELIQUIS®, a time interval of 20 to 30 hours (ie, 2 x half-life) between the last dose of ELIQUIS® and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of ELIQUIS® may be given at least 5 hours after catheter removal. As with all new anticoagulant drugs, experience with neuraxial blockade is limited and extreme caution is, therefore, recommended when using ELIQUIS® in the presence of neuraxial blockade (Figure 5).

Patients are to be frequently monitored for signs and symptoms of neurological impairment (eg, numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment are necessary.

Figure 5



No data are available on the timing of the placement or removal of neuraxial catheter in paediatric patients while on ELIQUIS®. In such cases, discontinue ELIQUIS® and consider a short acting parenteral anticoagulant.

Management of overdose and haemorrhage[1,2,3,4,5,6]

Overdose of ELIQUIS® may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued, and the source of bleeding investigated. The initiation of appropriate treatment, eg, surgical haemostasis, the transfusion of fresh frozen plasma, or the administration of a reversal agent for factor Xa inhibitors should be considered.

In controlled clinical studies, orally administered ELIQUIS® in healthy adult subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse reactions.

In health adult subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of ELIQUIS® reduced mean area under the curve (AUC) by 50% and 27%, respectively, and had no impact on Cmax. Mean half-life decreased from 13.4 hours when ELIQUIS® was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after ELIQUIS®. Thus, administration of activated charcoal may be useful in the management of ELIQUIS® overdose or accidental ingestion.

For situations in which reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors (andexanet alfa) is available for adults. Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered. Reversal of ELIQUIS® pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 30 minute 4-factor PCC infusion in healthy subjects. However, there is no clinical experience with the use of 4 factor PCC products to reverse bleeding in individuals who have received ELIQUIS®. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving ELIQUIS®. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of ELIQUIS® is not established in the paediatric population (refer to the summary of product characteristics of andexanet alfa). Transfusion of fresh frozen plasma, or administration of PCCs, or recombinant factor VIIa may also be considered.

Depending on local availability, consultation with a coagulation expert should be considered in case of major bleeding.

Haemodialysis decreased AUC by 14% in subjects with end-stage renal disease when a single dose of ELIQUIS® 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing ELIQUIS® overdose.

Use of coagulation tests[1,2,3,4,5,6]

Although treatment with ELIQUIS® does not require routine monitoring of exposure, a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of ELIQUIS® exposure may help to inform clinical decisions, eg, overdose and emergency surgery.

Prothrombin time (PT), INR and activated partial thromboplastin time (aPTT)

In adults, 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 ELIQUIS®. In the thrombin generation assay, ELIQUIS® reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Anti-Factor Xa (FXa) assays

ELIQUIS® also demonstrates anti-FXa activity (AXA) as evident by reduction in FXa enzyme activity in multiple commercial anti-FXa kits; however, results differ across kits. Data from adult clinical studies are only available for the Rotachrom® Heparin chromogenic assay. AXA activity exhibits a close direct linear relationship with ELIQUIS® plasma concentration, reaching maximum values at the time of ELIQUIS® peak plasma concentrations. The relationship between ELIQUIS® plasma concentration and AXA is approximately linear over a wide dose range of ELIQUIS®.

Table 3 shows the predicted steady state-exposure and AXA for each adult indication. In patients taking ELIQUIS® for the prevention of VTE following hip or knee replacement surgery, the results demonstrate a less than 1.6-fold fluctuation in peak-to-trough levels. In NVAF patients taking ELIQUIS® for the prevention of stroke and systemic embolism, the results demonstrate a less than 1.7-fold fluctuation in peak-to-trough levels. In patients taking ELIQUIS® for the treatment of DVT and PE or prevention of recurrent DVT and PE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

Table 3

Predicted ELIQUIS® steady-state exposure and anti-Factor Xa activity in adults				
	ELIQUIS® Cmax (ng/mL)	**ELIQUIS® Cmin (ng/mL)**	**ELIQUIS® AXA max (IU/mL)**	**ELIQUIS® AXA min (IU/mL)**
	Median [5th, 95th percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg twice daily	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg twice daily	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

* Dose adjusted population based on at least 2 of 3 dose reduction criteria as shown in Figure 2

Paediatric population

ELIQUIS® paediatric studies used the STA® Liquid Anti-Xa ELIQUIS® assay. Results from these studies indicate that the linear relationship between ELIQUIS® concentration and AXA is consistent with the previously documented relationship in adults. This lends support to the documented mechanism of action of ELIQUIS® as a selective inhibitor of FXa. Table 4 shows the predicted steady-state exposure and AXA for each paediatric indication.

Table 4

Predicted ELIQUIS® steady-state exposure and anti-Factor Xa activity in paediatric population				
	ELIQUIS® Cmaxss (ng/mL)	**ELIQUIS® Cminss (ng/mL)**	**ELIQUIS® AXA max (ng/mL)**	**ELIQUIS® AXA min (ng/mL)**
	Geometric mean [%CV]			
Weight tiers 9 to ≥ 35 kg in Study CV185155				
Exposures achieved using the paediatric dosing regimen were comparable to adults who received 2.5 mg twice daily	80.8 [16.8]	30.3 [22]	71.9 [17.3]	27.1 [22.2]
Weight tiers 6 to ≥ 35 kg in Study CV185362				
Exposures achieved using the paediatric dosing regimen were comparable to adults who received 5 mg twice daily	230 [39.5]	71.3 [61.3]	213 [41.7]	67.1 [30.2]

Weight tiers 6 to ≥ 35 kg in Study CV185325				
Exposures achieved using the paediatric dosing regimen were comparable to adults who received 5 mg twice daily	144 [36.9]	50 [54.5]	146 [40.2]	47.1 [57.2]

Prescribing Information

For the latest prescribing information, please refer to:
https://ec.europa.eu/health/documents/community-register/html/h691.htm

References

1. Bristol-Myers Squibb/Pfizer EEIG. ELIQUIS® 2.5 mg film-coated tablets Summary of Product Characteristics.
2. Bristol-Myers Squibb/Pfizer EEIG. ELIQUIS® 5 mg film-coated tablets Summary of Product Characteristics.
3. Bristol-Myers Squibb/Pfizer EEIG. ELIQUIS® 0.15 mg granules in capsules for opening Summary of Product Characteristics.
4. Bristol-Myers Squibb/Pfizer EEIG. ELIQUIS® 0.5 mg coated granule in sachet Summary of Product Characteristics.
5. Bristol-Myers Squibb/Pfizer EEIG. ELIQUIS® 1.5 mg coated granule in sachet Summary of Product Characteristics.
6. Bristol-Myers Squibb/Pfizer EEIG. ELIQUIS® 2 mg coated granule in sachet Summary of Product Characteristics.
7. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis. Archives of Cardiovascular Disease 2011;104:669–76.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Maltese Medicines Authority. Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at https://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000

E: postlicensing.medicinesauthority@gov.mt

Alternatively, you may also report such events promptly to Pfizer at Pfizer Hellas S.A., 243 Messoghion Ave. N.Psychiko, Athens GR-15451, Greece. Pfizer Hellas Pharmacovigilance Department contact details: +30 210 67 85 908 and +30 210 67 85 808 (24hour line), fax: +30 210 81 99 096, or via the webportal Pfizer's Adverse Event Reporting Portal (pfizersafetyreporting.com).

Other Contact Information

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Date of approval: [09 2024]

Date of internal approval: [09 2024]