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.

DATE OF APPROVAL: August 2016

Eliquis® apixaban

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This educational material is provided to further minimise the risk of bleeding and to guide healthcare professionals in managing that risk.

Patient Alert Card

A Patient Alert Card must be provided to each patient who is prescribed ELIQUIS® 2.5 mg or 5 mg, and the importance and consequences of anticoagulant therapy should be explained. The Patient Alert Card is included inside the ELIQUIS® 2.5 mg and 5 mg packs together with the package leaflet.

Specifically, the prescriber should talk to patients 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 physicians, dentists and pharmacists on the anticoagulant therapy and contains important contact information in the event of emergencies.

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

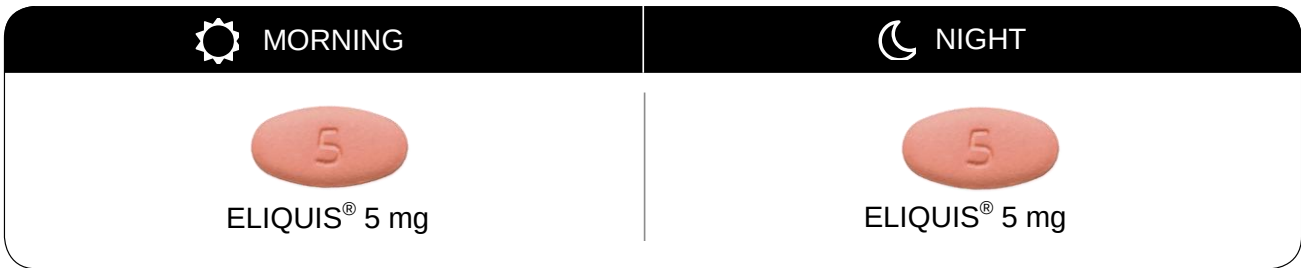
Therapeutic indication: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors[1, 2]

Risk factors for stroke in NVAF include prior stroke or transient ischaemic attack, age ≥75 years, hypertension, diabetes mellitus, and symptomatic heart failure (NYHA Class ≥II).

Dosing recommendations

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

Figure 1



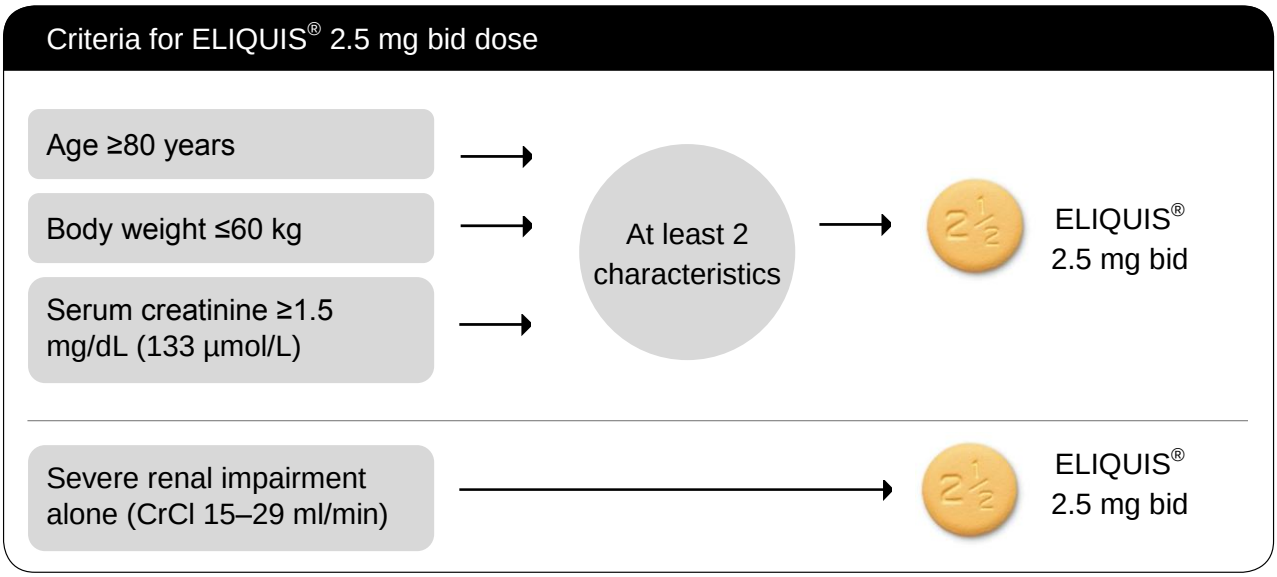
For patients who are unable to swallow whole tablets, ELIQUIS® tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, ELIQUIS® tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube. Crushed ELIQUIS® tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

Dose reduction

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

Patients with exclusive criteria of severe renal impairment (creatinine clearance [CrCl] 15–29 ml/min) should also receive ELIQUIS® 2.5 mg bid (Figure 2).

Figure 2



Missed dose

If a dose is missed, the patient should take ELIQUIS® immediately and then continue with bid intake as before.

Patients with renal impairment

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

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

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

Cardioversion

Patients can stay on ELIQUIS® while being cardioverted.

Patients with prosthetic heart valves

Safety and efficacy of ELIQUIS® have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of ELIQUIS® is not recommended in this setting.

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

Dosing recommendations

The recommended dose of ELIQUIS® for the treatment of acute DVT and treatment of PE is 10 mg taken orally bid for the first 7 days followed by 5 mg taken orally bid 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 (e.g. recent surgery, trauma, immobilisation).

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

When prevention of recurrent DVT and PE is indicated, the 2.5 mg bid dose should be initiated following completion of 6 months of treatment with ELIQUIS® 5 mg bid or with another anticoagulant, as indicated in Figure 3 and Table 1.

Figure 3

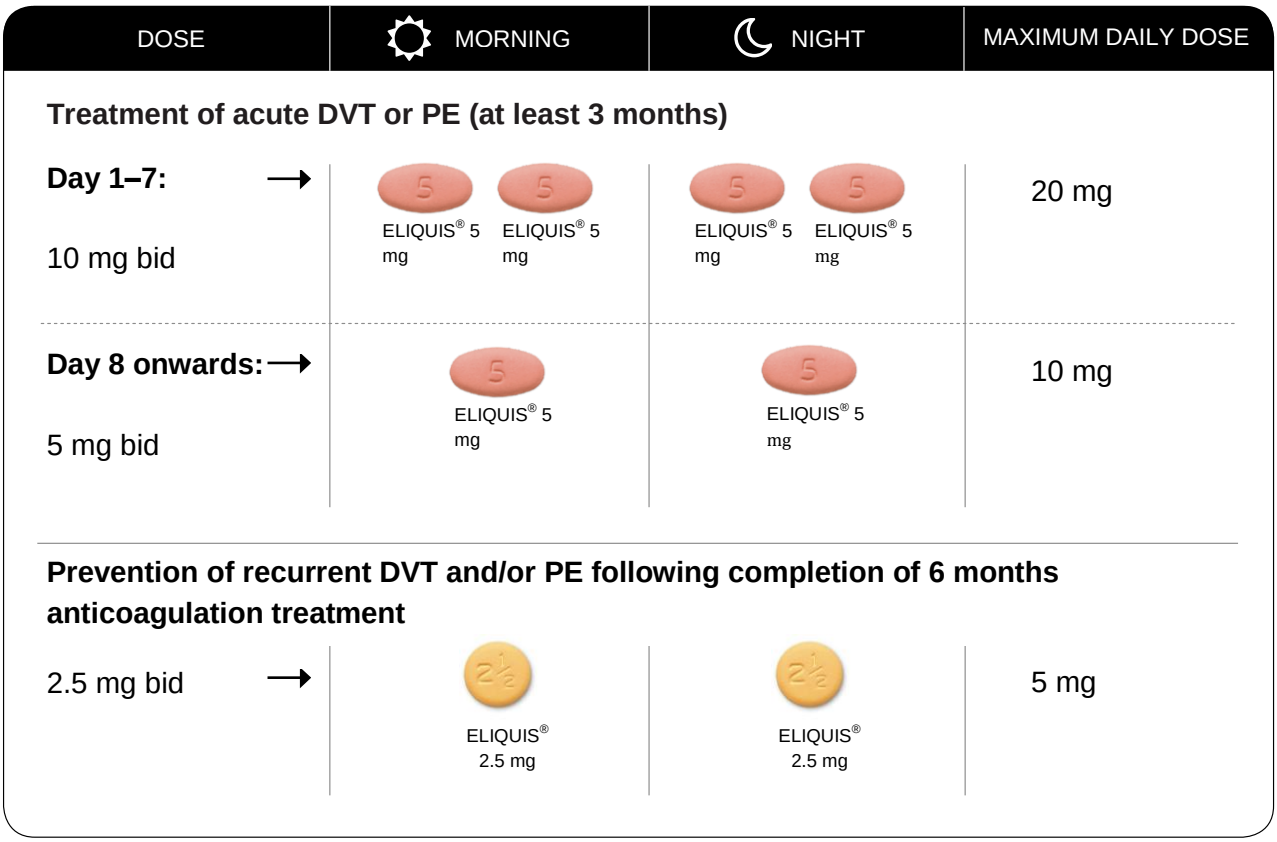


Table 1

	Dosing schedule	Maximum daily dose
Treatment of acute DVT or PE (at least 3 months)	10 mg bid for the first 7 days	20 mg
	followed by 5 mg bid	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of anticoagulation treatment for DVT or PE	2.5 mg bid	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 D5W, 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 D5W and immediately delivered through a nasogastric tube. Crushed ELIQUIS® tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

Missed dose

If a dose is missed, the patient should take ELIQUIS® immediately and then continue with bid intake as before.

Patients with renal impairment

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

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

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

Haemodynamically unstable PE patients or 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.

Patients with active cancer

Efficacy and safety of ELIQUIS® in the treatment of DVT, treatment of PE, and prevention of recurrent DVT and PE in patients with active cancer have not been established.

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

Dosing recommendations

The recommended dose of ELIQUIS® is 2.5 mg taken orally bid 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 D5W, 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 D5W and immediately delivered through a nasogastric tube. Crushed ELIQUIS® tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

Missed dose

If a dose is missed, the patient should take ELIQUIS® immediately and then continue with bid intake as before.

Patients with renal impairment

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

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

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

Switching to and from ELIQUIS®[1, 2]

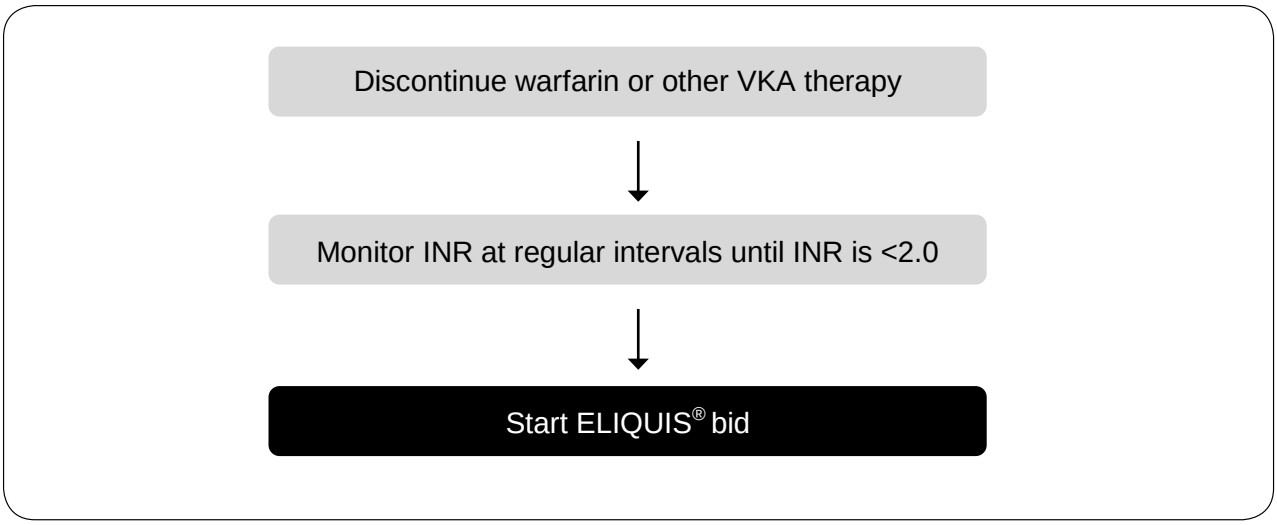
Switching treatment from parenteral anticoagulants to ELIQUIS® (and vice versa) can be done at the next scheduled dose.

These agents should not be administered simultaneously.

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

When converting patients from VKA therapy to ELIQUIS®, discontinue warfarin or other VKA therapy and start ELIQUIS® when the international normalised ratio (INR) is <2.0 (Figure 4).

Figure 4



Switching from ELIQUIS® to VKA therapy

When converting patients from ELIQUIS® to VKA therapy, continue administration of ELIQUIS® for at least 2 days after beginning VKA therapy. After 2 days of coadministration of ELIQUIS® with VKA therapy, obtain an INR prior to the next scheduled dose of ELIQUIS®. Continue coadministration of ELIQUIS® and VKA therapy until the INR is ≥2.0.

Populations potentially at higher risk of bleeding[1, 2]

Several sub-groups 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 if considered a significant risk factor for major bleeding	
• 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	The concomitant use of ELIQUIS® is **contraindicated**

Interactions with other medicinal products affecting haemostasis	
•	
Anticoagulants • Unfractionated heparins, low molecular weight heparins (e.g. enoxaparin), heparin derivatives (e.g. fondaparinux) • Oral anticoagulants (e.g. warfarin, rivaroxaban, dabigatran)	Concomitant treatment with ELIQUIS® and any other anticoagulant agent is **contraindicated**, except under the circumstances of switching therapy to or from ELIQUIS® or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter
Platelet aggregation inhibitors and NSAIDs • Acetylsalicylic acid (ASA) • Non-steroidal anti-inflammatory drugs (NSAIDs)	The concomitant use of ELIQUIS® with antiplatelet agents increases the risk of bleeding Care is to be taken if patients are treated concomitantly with NSAIDs, including ASA

- Medicinal products associated with serious bleeding are not recommended concomitantly with ELIQUIS®, such as: thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g. clopidogrel), dipyridamole, dextran and sulfinpyrazone.

Factors which may increase ELIQUIS® exposure/increase ELIQUIS® plasma levels	
Renal failure	*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 15–29 ml/min) should receive the lower dose of ELIQUIS® 2.5 mg bid • 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 bid
Elderly	• No dose adjustment required **Patients with NVAF** • No dose adjustment required except in combination with other factors
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 azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir)
Concomitant use with less potent inhibitors of CYP3A4 and/or P-gp	• No dose adjustment for ELIQUIS® is required when coadministered with, for example, diltiazem, naproxen, amiodarone, verapamil and quinidine

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 (e.g. 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, 3]

ELIQUIS® should be discontinued prior to elective surgery or invasive procedures 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.

Although treatment with ELIQUIS® does not require routine monitoring of exposure, a calibrated quantitative anti-FXa assay may be useful in exceptional situations where knowledge of ELIQUIS® exposure may help to inform clinical decisions, e.g. overdose and emergency surgery *(see section on use of coagulation tests).*

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 FXa inhibitor, its anticoagulant activity should abate within 24 to 48 hours of the last administered dose.

Discontinuation of ELIQUIS® prior to elective surgery	
Low risk of bleeding (procedures for which bleeding, if it occurs, will be minimal, non-critical in its location and/or easily controlled by simple mechanical haemostasis)	At least 24 hours prior to elective surgery or invasive procedures
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 (>4 half-lives)

Temporary discontinuation[1, 2]

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]

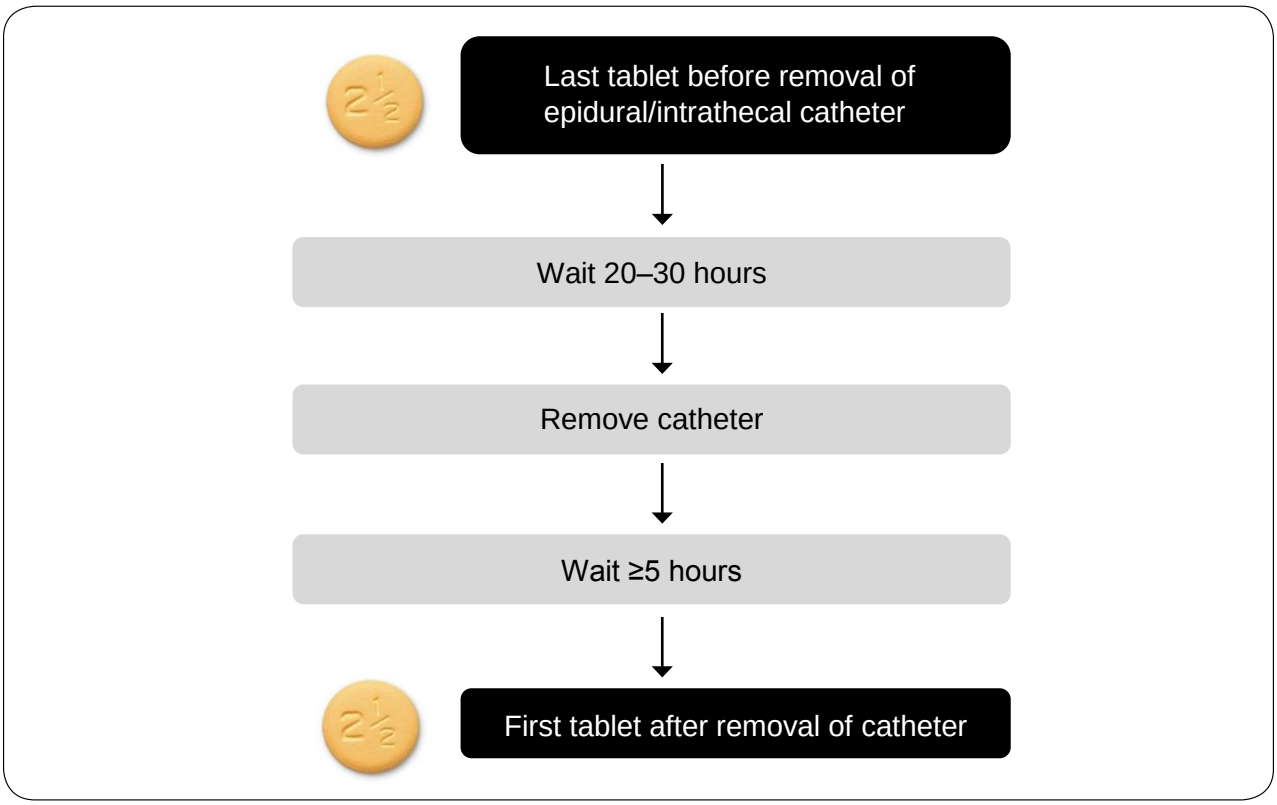
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. 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 (PK) characteristics of ELIQUIS®, a time interval of 20 to 30 hours (i.e., 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 (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary.

Figure 5



Management of overdose and haemorrhage[1, 2]

There is no antidote to ELIQUIS®. 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, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

In controlled clinical trials, orally-administered ELIQUIS® in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg bid for 7 days or 50 mg once daily (od) for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of ELIQUIS® reduced mean ELIQUIS® AUC by 50% and 27%, respectively, and had no impact on C_{max}. Mean half-life of ELIQUIS® 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.

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 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 4-factor PCC 30 minute 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.

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

Haemodialysis decreased ELIQUIS® 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]

Routine clinical monitoring is not required with ELIQUIS®. However, a calibrated quantitative anti-FXa assay may be useful in exceptional situations where knowledge of ELIQUIS® exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.

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

Anti-FXa assays

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

Table 2 shows the predicted steady state exposure and anti-FXa activity for each 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 2

Predicted ELIQUIS® steady-state exposure and anti-FXa activity				
	ELIQUIS® C_{max} (ng/mL)	ELIQUIS® C_{min} (ng/mL)	ELIQUIS® anti-FXa activity max (IU/mL)	ELIQUIS® anti-FXa activity min (IU/mL)
	Median [5^{th}, 95^{th} percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg bid	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 bid*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg bid	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 bid	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg bid	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg bid	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

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

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. 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: 669–676.

Prescribing Information

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

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 via:

ADR Reporting
The Medicines Authority
Post-Licensing Directorate
Sir Temi Zammit Buildings, Malta Life Sciences Park,
San Gwann SGN 3000, MaltaWebsite: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

Other Contact Information

For any suspected adverse reactions 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 (24-hour line).

For more information, please contact Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.
Local Representative: V.J. Salomone Pharma Ltd. Tel. +356 2122017

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