Treating Every Stage of VTE with ELIQUIS™

ESC 2019 Guidelines: NOACs as the first choice for anticoagulation for patients with PE[1]

Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE (Class I, Level C)*

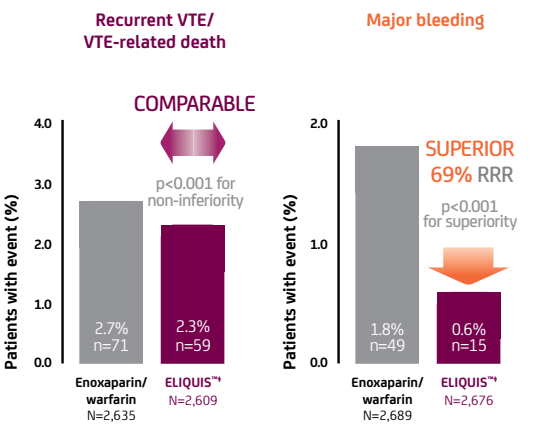
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC, a **NOAC is recommended in preference to a VKA** (Class I, Level A)*†

Therapeutic anticoagulation **for at least 3 months** is recommended for all patients with PE (Class I, Level A)

If extended oral anticoagulation is decided after PE in a patient without cancer, a **reduced dose of the NOACs (apixaban 2.5 mg BID or rivaroxaban 10 mg QD) should be considered after 6 months** of therapeutic anticoagulation (Class IIa, Level A)

Start and stay with ELIQUIS™ for the treatment and prevention of recurrent DVT/PE

AMPLIFY[2]: Treatment of DVT/PE

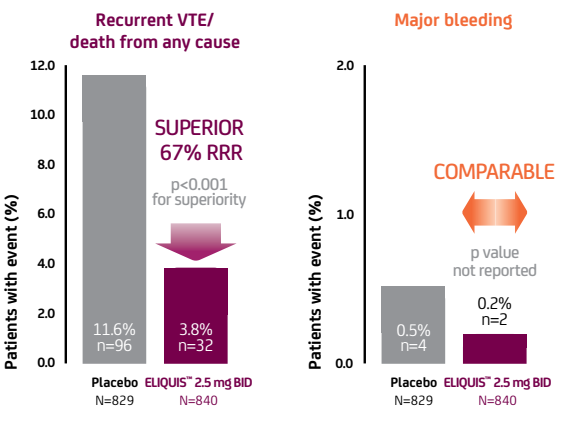


Primary efficacy endpoint
RR=0.84 (95% CI: 0.60–1.18)

Primary safety endpoint
RR=0.31 (95% CI: 0.17–0.55)

Adapted from Agnelli et al. 2013[2]

AMPLIFY-EXT[3]: Prevention of recurrent DVT/PE[§]



Primary efficacy endpoint
RR=0.33 (95% CI: 0.22–0.48)

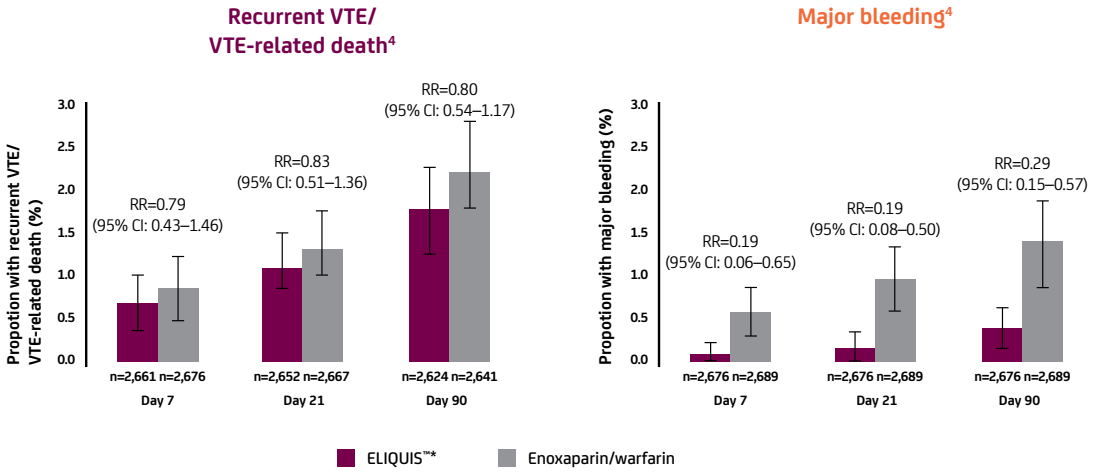
Primary safety endpoint
RR=0.49 (95% CI: 0.09–2.64)

Adapted from Agnelli et al. 2013[3]

* In patients with intermediate- or low-risk PE[1]
† NOACs are not recommended in patients with severe renal impairment, during pregnancy and lactation, and in patients with the antiphospholipid antibody syndrome (Class III, Level C).[1]
‡ ELIQUIS™ 10 mg BID for 7 days followed by 5 mg BID for 6 months[2]
§ While ELIQUIS™ 5 mg BID was also studied in the AMPLIFY-EXT trial, these data are not shown as this dose is not approved for extended treatment of VTE.[3]

AMPLIFY early time course post-hoc sub-analysis: Efficacy and safety

- In AMPLIFY, the efficacy of ELIQUIS™ was non-inferior to conventional therapy at each time point, with no excess of early recurrences[4]
- The reduced risk in major bleeding began early during the course of ELIQUIS™ treatment[4]



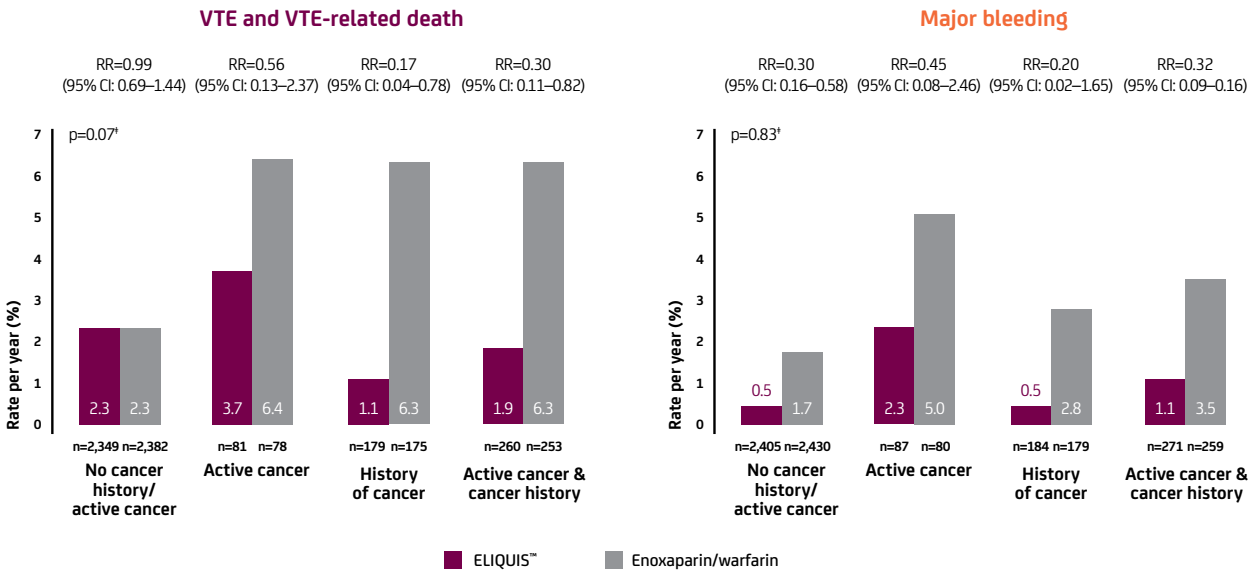
Adapted from Raskob et al. 2016[4]

VTE is a common complication in patients with cancer[5]

~15% Approximately 15% of patients with cancer experience ≥1 VTE[5,6]

>20% Incidence of recurrent VTE in cancer is >20% within 1 year[7]

AMPLIFY sub-analysis: Efficacy and safety results in patients with cancer-associated thrombosis[8†]



Adapted from Agnelli et al. 2015[8]

* ELIQUIS™ 10 mg BID for 7 days followed by 5 mg BID for 6 months[4]

† Sub-analysis by cancer status; p values are for interaction of treatment by 3 cancer subgroups defined as active cancer, cancer history (without active cancer), and no cancer history/no active cancer. Efficacy and safety of apixaban in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in patients with active cancer have not been established.[8] ELIQUIS™ is not licensed for the treatment or prevention of VTE in patients with active cancer.

‡ p values are for interaction of treatment by 3 cancer subgroups defined as active cancer, cancer history (without active cancer), and no cancer history/no active cancer.[8]

ADAM-VTE: ELIQUIS™ is associated with low rates of VTE recurrence and major bleeding in the treatment of cancer-associated VTE[9]*

- ELIQUIS™ was associated with very low rates of **major bleeding** (0% vs 1.4%; p=0.138) and **VTE recurrence** (0.7% vs 6.3%; p=0.028) compared with dalteparin[9]
- The primary safety endpoint (major bleeding) was not met in this study – HR and 95% CI were not estimable due to 0 bleeding events in the ELIQUIS™ arm[9]
- ELIQUIS™ had significantly lower **overall burden** and **negative impact of quality of life** vs dalteparin[9]
- **Overall satisfaction with anticoagulants** was higher with ELIQUIS™; **bruising** also favored ELIQUIS™ at all time intervals (p<0.002)[9]

Cycle (months)	Fear of bleeding limited participation in vigorous activities	Fear of bleeding limited participation in activities of daily life	Concern for excessive bruising	Limited my diet	Added stress to my life	Was diffcult to carry out	Caused me a great deal of worry	Caused me a great deal of irritation	Caused me a great deal of frustration	Was a burden to me	Negatively impacted my quality of life	Confidence that the drug protected me from clots	I am satisified with my blood thinner
0	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
1	Neutral	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors Dalteparin	Favors ELIQUIS™
2	Neutral	Neutral	Neutral	Neutral	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Favors ELIQUIS™	Neutral	Neutral	Favors ELIQUIS™
3	Neutral	Neutral	Neutral	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Neutral	Favors ELIQUIS™
4	Neutral	Neutral	Favors ELIQUIS™	Neutral	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Neutral	Favors ELIQUIS™
5	Neutral	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Neutral	Neutral
6	Neutral	Neutral	Favors ELIQUIS™	Neutral	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Favors ELIQUIS™	Neutral	Neutral	Neutral

Adapted from McBane et al. 2020[9]

Favors ELIQUIS™ | Favors dalteparin

CARAVAGGIO: an independent, investigator-initiated study— the largest multinational NOAC trial for VTE treatment in patients with cancer[9-12†‡]

ELIQUIS™ vs LMWH for the treatment of VTE in patients with cancer

ELIQUIS™ demonstrated BOTH comparable efficacy[§] and rates of major bleeding vs LMWH,[‖] with no increase in major GI or non-GI bleeding[10]

As per the current Summary of Product Characteristics:

- 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
- ELIQUIS™ is contraindicated in patients with malignant neoplasms at high risk of bleeding

* ADAM-VTE was an investigator-initiated, multicenter, randomized, open-label superiority trial for safety comparing ELIQUIS™ to dalteparin in patients with cancer-associated VTE.[9]

† CARAVAGGIO (Apixaban for the treatment of venous thromboembolism associated with cancer) was supported by a research grant from Bristol-Myers Squibb and Pfizer, which did not have any role in study design, conduct, data collection, or analysis.[10]

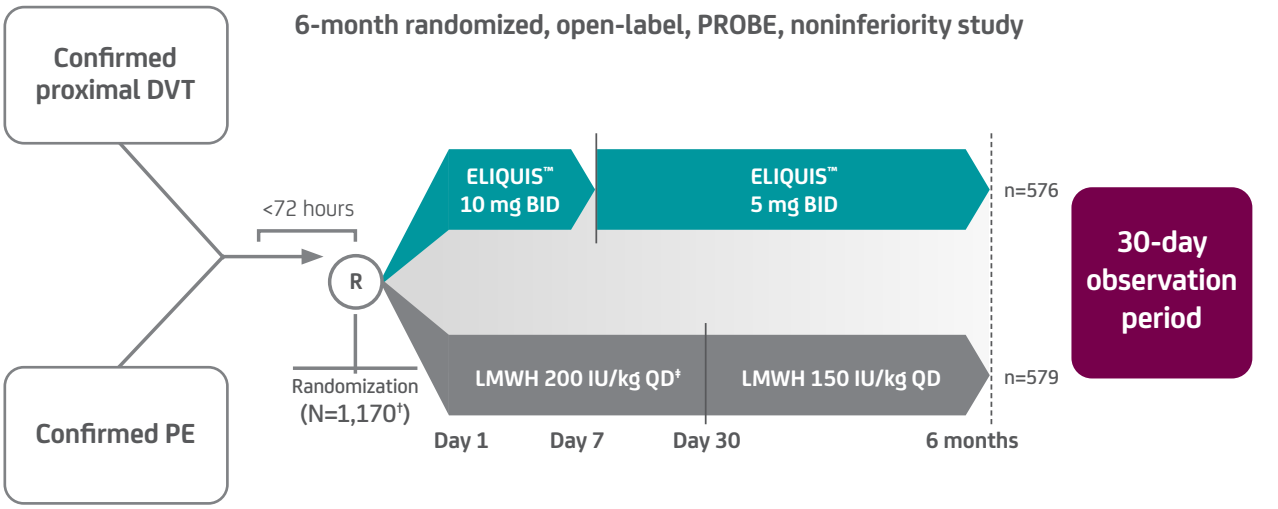
‡ Select patient characteristics for ELIQUIS™: age ~67 years, 20% had incidental DVT or PE, ~97% had active cancer, ~68% had recurrent locally advanced or metastatic cancer, ~60% were on anticancer treatments, ~25% had GI cancer[10]

§ The primary efficacy outcome was recurrent VTE, which included proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, and PE (symptomatic, incidental, or fatal).[10]

‖ Dalteparin was the LMWH used in CARAVAGGIO.[10]

CARAVAGGIO is the largest multinational NOAC trial for VTE treatment in patients with cancer (N=1,170)[9-12]

Study design[6,10*]



~One-third of patients in CARAVAGGIO had cancer at GI sites[10,13§]

Adapted from Agnelli et al. 2020[10]

Inclusion criteria[6,10‖]

- Newly diagnosed symptomatic or incidental DVT, symptomatic or incidental PE, or both
- Active cancer (diagnosed within the past 6 months) or a history of cancer within 2 years
- Any confirmed cancer type other than basal cell or squamous cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, or acute leukemia

Exclusion criteria[6,10]

Exclusion criteria were classified into 4 categories:

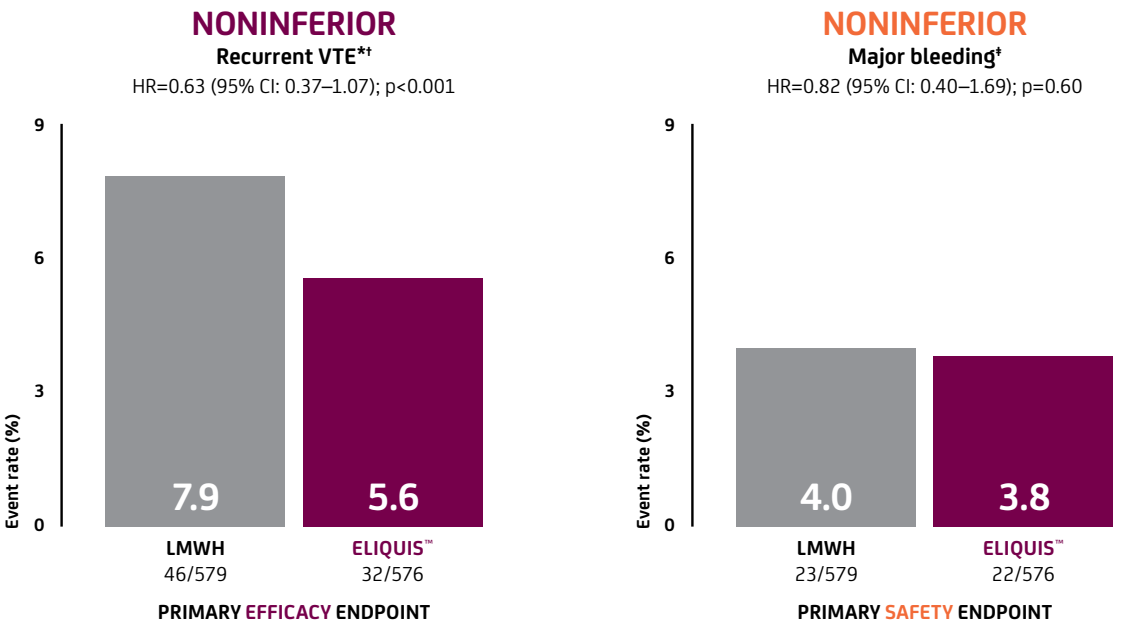
- Patient characteristics (age <18 years, ECOG status III or IV, life expectancy <6 months)
- Anticoagulant-related
- Bleeding risk
- Standard criteria

Adapted from Agnelli et al. 2020[10]

* CARAVAGGIO was a multinational, prospective, randomized, open-label, 6-month noninferiority trial with blinded endpoint evaluation (PROBE), which was chosen over double-blinding to avoid daily subcutaneous injections of placebo in apixaban recipients.[10]
† 15 patients did not receive the assigned treatment.[10]
‡ The maximum daily dose allowed for LMWH was 18,000 IU.[10]
§ GI sites include colorectal, pancreatic or hepatobiliary, and upper GI.
‖ See Table 2 in the study publication supplementary appendix for complete inclusion and exclusion criteria.

In patients with VTE and cancer

ELIQUIS™ demonstrated BOTH comparable efficacy and rates of major bleeding vs LMWH, with no increase in major GI or non-GI bleeding[10]



Adapted from Agnelli et al. 2020[10]

Oral ELIQUIS™ did not increase major bleeding vs subcutaneous LMWH in the treatment of VTE in patients with cancer[10]

- Major GI bleeding was comparable between ELIQUIS™ and LMWH (1.9% vs 1.7%, respectively; HR=1.05 [95% CI: 0.44–2.50])
- CRNM bleeding was also comparable between ELIQUIS™ and LMWH (9.0% vs 6.0%, respectively; HR=1.42 [95% CI: 0.88–2.30])

CARAVAGGIO informs clinical decision making in patients with cancer-associated VTE who are eligible for NOAC treatment, including those with GI cancer.[10]

* p<0.001 for noninferiority; p=0.09 for superiority. The study was designed to test noninferiority with respect to the primary efficacy outcome. Superiority was tested once noninferiority was demonstrated.[10]

† Recurrent DVT or PE, which included proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, and PE (symptomatic, incidental, or fatal), occurring during the study treatment period.[10]

‡ Major bleeding was defined as ISTH major bleeding and bleeding resulting in surgical intervention (CARAVAGGIO included 1 patient who underwent surgical intervention).[10]

ELIQUIS™ Therapeutic Indications[14,15]

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as prior stroke or transient ischemic attack; age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥II).
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
- Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.*

* The recommended dose of ELIQUIS™ is 2.5 mg taken orally BID. The initial dose should be taken 12 to 24 hours after surgery.[14]

BID, twice daily; CI, confidence interval; CRNM, clinically relevant nonmajor; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; ESC, European Society of Cardiology; GI, gastrointestinal; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; IU, international units; IV, intravenous; LMWH, low molecular weight heparin; NOAC, non-VKA oral anticoagulant; NYHA, New York Heart Association; OAC, oral anticoagulant; PE, pulmonary embolism; PROBE, prospective randomized open blinded end-point; QD, once daily; RR, relative risk; RRR, relative risk reduction; VKA, vitamin K antagonist; VTE, venous thromboembolism

Reference:
1. Konstantinides SV, et al. *Eur Heart J* 2020;41:543-603. **2.** Agnelli G, et al. *N Engl J Med* 2013;369:799-808. **3.** Agnelli G, et al. *N Engl J Med* 2013;368:699-708. **4.** Raskob G, et al. *Thromb Haemost* 2016;115:809-816. **5.** Noble S, Pasi J. *Br J Cancer* 2010;102(suppl 1):S2-S9. **6.** Agnelli G, et al. *Thromb Haemost* 2018;118:1668-1678. **7.** Prandoni P, et al. *Blood* 2002;100:3484-3488. **8.** Agnelli G, et al. *J Thromb Haemost* 2015;13:2187-2191. **9.** McBane RD, et al. *J Thromb Haemost* 2020;18:411-421. **10.** Agnelli G, et al. *N Engl J Med* 2020;382:1599-1607. **11.** Mulder FI, et al. *Thromb Res* 2020;185:13-19. **12.** Young AM, et al. *J Clin Oncol* 2018;36:2017-2023. **13.** Agnelli G, et al. *N Engl J Med* 2020;382:1599-1607 (suppl appendix). **14.** ELIQUIS™ (apixaban) 2.5 mg Prescribing Information. Pfizer Corporation Hong Kong Limited. Version: Jun 2021. **15.** ELIQUIS™ (apixaban) 5 mg Prescribing Information. Pfizer Corporation Hong Kong Limited. Version: Sep 2021.

ELIQUIS ABBREVIATED PACKAGE INSERT 1. TRADE NAME: ELIQUIS 2. PRESENTATION: 2.5 mg and 5 mg film-coated tablets **3. INDICATIONS:** 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). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. For 2.5mg only – Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. **4. DOSAGE:** Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF): 5 mg twice daily. 2.5 mg twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L). Treatment of DVT, PE and prevention of recurrent DVT and PE (VTEt): 10 mg twice daily for the first 7 days followed by 5 mg twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with Eliquis 5 mg twice daily or with another anticoagulant. Prevention of VTE in elective hip or knee replacement surgery: 2.5mg twice daily initiated 12 to 24 hours after surgery. **5. METHOD OF ADMINISTRATION:** Eliquis should be swallowed with water, with or without food. For patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water or 5% glucose in water (G5W) and immediately administered orally. Alternatively, Eliquis tablets may be crushed and suspended in 60mL of water or G5W and immediately delivered through a nasogastric tube. Crushed Eliquis tablets are stable in water and G5W for up to 4 hours. **6. CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent. **7. WARNINGS & PRECAUTIONS:** Haemorrhage risk: carefully observed for signs of bleeding. Eliquis should be discontinued if severe haemorrhage occurs. An anti-Factor Xa assay may be useful in exceptional situations (e.g. overdose and emergency surgery) where knowledge of apixaban exposure may help to inform clinical decisions. Use of thrombolytic agents for the treatment of acute ischemic stroke: There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Eliquis. Patients with prosthetic heart valves: Eliquis is not recommended. Surgery and invasive procedures: Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. Patients with active cancer: When Eliquis is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made. Renal impairment: In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. Hepatic impairment: Not recommended in patients with severe hepatic impairment. Laboratory parameters: Clotting tests (e.g., prothrombin time (PT), international normalised ratio (INR), and activated partial thromboplastin time (aPTT)) are affected as expected by the mechanism of action of apixaban. For 2.5mg - Spinal/epidural anaesthesia or puncture: Patients are to be frequently monitored for signs and symptoms of neurological impairment. Patients with antiphospholipid syndrome: Not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, apixaban must be discontinued. The initiation of appropriate treatment should be considered. **8. INTERACTIONS:** Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics and HIV protease inhibitors. Concomitant use of Eliquis with strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced apixaban plasma concentration. No dose adjustment for Eliquis is required but it should be used with caution during concomitant therapy. Eliquis should be used with caution when co-administered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors as they typically increase bleeding risk. Co-administration with other platelet aggregation inhibitors (e.g. GPIIb/IIIa receptor antagonists, dipyridamole) or thrombolytic agents is not recommended. **9. PREGNANCY AND LACTATION:** There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of apixaban during pregnancy. It is unknown whether apixaban or its metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from apixaban therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **10. SIDE EFFECTS:** Common: anaemia, haemorrhage, epistaxis, haematuria, nausea, contusion and haematoma. **(Please refer to the full Prescribing Information for details)**

Reference: Eliquis 2.5mg HK Prescribing Information (June 2021) and Eliquis 5mg HK Prescribing Information (September 2021)
Date of preparation: January 2022 Identifier number: ELIQ0122
FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

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Eliquis™ apixaban

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