# ELIQUIS®▼ (apixaban) 2.5 mg & 5 mg Film-coated Tablets

## PRESCRIBING INFORMATION

Consult summary of product characteristics (SmPC) prior to prescribing and for full list of adverse events.

**PRESENTATION:** Film-coated tablets; 2.5mg and 5mg apixaban.

**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 or 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 (see Special warnings and precautions for information on haemodynamically unstable PE patients). Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery (2.5mg only).

**DOSAGE AND ADMINISTRATION:** Oral.

Prevention of stroke and systemic embolism in patients with NVAF:

The recommended dose is 5mg taken twice a day with water, with or without food. Patients who meet at least two of the following criteria: serum creatinine ≥ 1.5 mg/dL (133 micromole/l), age ≥ 80 years, or body weight ≤ 60 kg should receive the lower dose of Eliquis, 2.5 mg twice daily. All patients with severe renal impairment (creatinine clearance 15-29 ml/min) should receive the lower dose of Eliquis 2.5 mg twice daily. Therapy should be continued long term.

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

The recommended dose 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. 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 for the prevention of recurrent DVT and PE is 2.5 mg taken orally 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.

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

Prevention of VTE (VTEp): elective hip or knee replacement surgery:

The recommended dose is 2.5mg taken twice a day 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.

*Missed Dose for All Indications:* If a dose is missed, Eliquis should be taken immediately and then continue with twice daily dose as before.

*Switching:* 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 treatment from VKA therapy to Eliquis:* discontinue warfarin or other VKA therapy and start Eliquis when the international normalized ratio (INR) is < 2.0.

*Switching treatment from Eliquis to VKA therapy*: continue administration of Eliquis for at least 2 days after beginning VKA therapy. After 2 days of co-administration of Eliquis with VKA therapy, obtain an INR prior to next scheduled dose of Eliquis. Continue co-administration of Eliquis and VKA therapy until the INR is ≥2.0.

*Renal impairment:* Not recommended in patients with creatinine clearance < 15mL/min or in patients undergoing dialysis. No dose adjustment in mild or moderate renal impairment. In severe renal impairment (creatinine clearance 15- 29 mL/min) there may be an increased risk of bleeding, the following recommendations apply: for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), Eliquis is to be used with caution. For the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of Eliquis 2.5 mg twice daily. Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should also receive the lower dose of Eliquis, 2.5 mg twice daily. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore Eliquis is not recommended.

*Hepatic impairment:* Eliquis is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment. Eliquis should be used with caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN. Prior to initiating Eliquis, liver function testing should be performed.

Eliquis is not recommended in children and adolescents below the age of 18.

**CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients listed in SmPC, 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 (refer to SmPC). Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter (refer to SmPC).

**SPECIAL WARNINGS AND PRECAUTIONS:** *Haemorrhage risk:* Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs.

*Interaction with other medicinal products affecting haemostasis*: Concomitant treatment with any other anticoagulant is contraindicated (see contraindications). The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid. Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with Eliquis. In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with Eliquis.

*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:* 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.

*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. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable. Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. Eliquis should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see SmPC).

*Temporary discontinuation:* 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.

*Spinal/epidural anaesthesia or puncture:* 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. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Eliquis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

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 PK characteristics of Eliquis, a time interval of 20-30 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.

*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 pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Eliquis have not been established.

*Patients with active cancer:* efficacy and safety of Eliquis in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established.

*Renal impairment:* see dosage and administration section.

*Elderly patients:* increasing age may increase haemorrhagic risk. Also, the co-administration of Eliquis with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

*Body weight:* low body weight (< 60 kg) may increase haemorrhagic risk.

*Hepatic impairment:* see dosage and administration section.

*Interaction with Inhibitors of CYP3A4 and P-gp:* the use of Eliquis 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). Thesemedicinal products may increase Eliquis exposure by 2-fold or greater in the presence of additional factors that increase Eliquis exposure (e.g. severe renal impairment).

*Interaction with Inducers of CYP3A4 and P-gp:* No dose adjustment for Eliquis is required during concomitant therapy with such agents, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp Eliquis should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE. Eliquis should not be used for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised.

*Hip fracture surgery (2.5mg only):* Eliquis has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, it is not recommended in these patients.

*Laboratory parameters:* Clotting tests (PT, INR, and 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 SmPC).

*Information about excipients:* Eliquis contains lactose. Patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Eliquis.

**DRUG INTERACTIONS:** Agents 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.

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated.

Administration of activated charcoal reduces Eliquis exposure. Also see contraindications and special warnings and precautions section; Consult SmPC (contraindications, special warnings and precautions and drug interactions) for full details on interactions. **PREGNANCY AND LACTATION:** *Pregnancy:* Not recommended during pregnancy. *Breastfeeding:* Discontinue breastfeeding or discontinue Eliquis therapy.

**UNDESIRABLE EFFECTS:** Increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding.

*Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp):* Common (≥ 1/100 to < 1/10): anaemia, haemorrhage, haematoma, nausea, contusion, Uncommon (≥1/1,000 to < 1/100): gastrointestinal haemorrhage, haematochezia, post procedural haemorrhage Rare (≥1/10,000 to < 1/1,000): hypersensitivity, allergic oedema and anaphylaxis.

*Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF):* Common (≥ 1/100 to < 1/10): eye haemorrhage (including conjunctival haemorrhage), haemorrhage, haematoma, epistaxis, gastrointestinal haemorrhage, rectal haemorrhage, gingival bleeding, haematuria, contusion, Uncommon (≥1/1,000 to < 1/100): hypersensitivity, allergic oedema, anaphylaxis, brain haemorrhage, intra-abdominal haemorrhage, haematochezia, abnormal vaginal haemorrhage, urogenital haemorrhage, traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage, *Rare (≥1/10,000 to < 1/1,000):* respiratory tract haemorrhage.

*Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt):* Common (≥ 1/100 to < 1/10): haemorrhage, haematoma, epistaxis, gastrointestinal haemorrhage, rectal haemorrhage, gingival bleeding, haematuria, contusion, Uncommon (≥1/1,000 to < 1/100): haematochezia, abnormal vaginal haemorrhage, urogenital haemorrhage, traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage *Rare (≥1/10,000 to < 1/1,000):* brain haemorrhage, respiratory tract haemorrhage

Please refer to the SmPC for further details of adverse reactions including other types of haemorrhage.

**LEGAL CATEGORY:** POM. **PACKAGE QUANTITIES AND BASIC NHS PRICE:** Carton of 10 film-coated tablets 2.5mg £10.98, 20 film-coated tablets 2.5mg £21.96, 60 film-coated tablets 2.5mg £65.90, 56 film-coated tablets 5mg £61.50, 28 film-coated tablets 5mg £30.75. **MARKETING AUTHORISATION NUMBERS:** EU/1/11/691/001-3, EU/1/11/691/008, EU/1/11/691/014 **MARKETING AUTHORISATION HOLDER:** Bristol-Myers Squibb/Pfizer EEIG, BMS House, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH. Telephone: 0800-731-1736.

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**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bristol-Myers Squibb Pharmaceuticals Ltd Medical Information on 0800 731 1736 or medical.information@bms.com**