ELIQUIS® (apixaban) PRESCRIBING INFORMATION
Ireland

Consult Summary of Product Characteristics (SmPC) before prescribing.

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

INDICATION: *Adults:* Prevention of stroke and systemic embolism in adults 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 adults who have undergone elective hip or knee replacement surgery (2.5 mg only). *Paediatric population:* Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

DOSAGE AND ADMINISTRATION: Oral. Taken with water, with or without food. *Prevention of stroke and systemic embolism in adult patients with NVAF*: The recommended dose is 5 mg twice a day. In 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 the recommended dose is apixaban 2.5 mg twice daily. Patients with severe renal impairment (creatinine clearance 15-29 ml/min) should receive apixaban 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) in adults:* The recommended dose for the treatment of acute DVT and treatment of PE is 10 mg twice daily for the first 7 days followed by 5 mg 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 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 apixaban 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 in adults*: The recommended dose is 2.5 mg twice a day. The initial dose should be taken 12 to 24 hours after surgery. Hip replacement surgery, the recommended duration of treatment is 32 to 38 days. Knee replacement surgery, the recommended duration of treatment is 10 to 14 days. *Treatment of VTE and prevention of recurrent VTE in paediatric patients:* Apixaban treatment for paediatric patients should be initiated following at least 5 days of initial parenteral anticoagulation therapy. Treatment with apixaban in paediatric patients is based on weight-tiered dosing. The recommended dose of apixaban in paediatric patients weighing ≥ 35 kg is 10 mg twice daily at Days 1-7 (maximum daily dose of 20 mg) and 5 mg twice daily at Day 8 and beyond (maximum daily dose of 10 mg). For paediatric patients weighing < 35 kg, refer to the summary of product characteristics for Eliquis granules in capsules for opening and Eliquis coated granules in sachets. 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.

Missed Dose in adults and paediatric patients: 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.

Switching: 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 treatment from VKA therapy to Eliquis*: Warfarin or other VKA therapy should be discontinued and Eliquis started when the international normalized ratio (INR) is < 2. *Switching treatment from Eliquis to VKA therapy*: Administration of Eliquis should be continued for at least 2 days after beginning VKA therapy. After 2 days of co- administration of Eliquis with VKA therapy, an INR should be obtained prior to next scheduled dose of Eliquis. Co-administration of Eliquis and VKA therapy should be continued until the INR is ≥2. *Renal Impairment - adult patients with mild or moderate renal impairment:* 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), no dose adjustment is necessary. For the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg, a dose reduction is necessary. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary. *Adult patients with severe renal impairment (creatinine clearance 15-29 mL/min):* 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), apixaban 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 apixaban 2.5mg twice daily. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. *Paediatric population:* Based on adult data and limited data in paediatric patients, no dose adjustment is necessary in paediatric patients with mild to moderate renal impairment. Apixaban is not recommended in paediatric patients with severe renal impairment. See SmPC for further details. *Hepatic impairment:* Contraindicated in adult patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Use 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. Use with caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥ 1.5 x ULN. Prior to initiating apixaban, liver function testing should be performed. Apixaban has not been studied in paediatric patients with hepatic impairment. *Catheter ablation (NVAF)*: Patients can continue apixaban use while undergoing catheter ablation. *Cardioversion (NVAF)*: Apixaban can be initiated or continued in NVAF adult patients who may require cardioversion. See SmPC for further details. *Patients with NVAF and acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI)*: There is limited experience of treatment with apixaban at the recommended dose for NVAF patients when used in combination with antiplatelet agents in patients with ACS and/or undergoing PCI after haemostasis is achieved. See SmPC for further details. *Paediatric population*: The safety and efficacy of Eliquis in paediatric patients aged 28 days to less than 18 years have not been established in indications other than treatment of venous thromboembolism (VTE) and prevention of recurrent VTE. No data are available in neonates and for other indications. Therefore, 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.

CONTRAINDICATIONS: Hypersensitivity to active substance or to 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, see SmPC for further details. Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin (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, see SmPC for further details.

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. A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of apixaban is available for adults. However, its safety and efficacy have not been established in paediatric patients (refer to the summary of product characteristics of andexanet alfa). Transfusion of fresh frozen plasma, administration of prothrombin complex concentrates (PCCs), or recombinant factor VIIa may be considered. However, there is no clinical experience with the use of 4 factor PCC products to reverse bleeding in paediatric and adult patients who have received apixaban. For information on reversal and managing bleeding, see SmPC for further details. *serious adverse drug reaction. *Interaction with other medicinal products affecting haemostasis*: Concomitant treatment with any other anticoagulant is contraindicated (see contraindications). Concomitant use of apixaban with antiplatelet agents increases the risk of bleeding. Care with concomitant SSRIs, SNRIs or NSAIDs, including acetylsalicylic acid. Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with apixaban. 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 apixaban. A clinical trial enrolled patients with atrial fibrillation with ACS and/or undergoing PCI and a planned treatment period with a P2Y12 inhibitor, with or without ASA, and oral anticoagulant (either apixaban or VKA) for 6 months. Concomitant use of ASA increased the risk of ISTH (International Society on Thrombosis and Hemostasis) major or CRNM (Clinically Relevant Non-Major) bleeding in apixaban-treated subjects. See SmPC for further details. *Use of thrombolytic agents for the treatment of acute ischemic stroke*: Limited experience. *Adults and paediatric patients with prosthetic heart valves*: safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of apixaban is not recommended in this setting. *Patients with antiphospholipid syndrome*: Direct acting Oral Anticoagulants (DOACs), including apixaban, are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (see SmPC for further details). *Surgery and invasive procedures*: Discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. Discontinue at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. Apixaban 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. For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted. *Temporary discontinuation*: Discontinuing anticoagulants, including apixaban, 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 apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible. *Spinal/epidural anaesthesia or puncture*: 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 post- operative 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 apixaban. 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 apixaban with indwelling intrathecal or epidural catheters. No data are available on the timing of the placement or removal of neuraxial catheter in paediatric patients while on apixaban. In such cases, discontinue apixaban and consider a short acting parenteral anticoagulant. See SmPC for further details. *Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy*: Apixaban is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of apixaban have not been established. *Patients with active cancer*: Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made. *Renal impairment*: see dosage and administration section. *Elderly patients*: Increasing age may increase haemorrhagic risk. Also, the co-administration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk. *Body weight*: In adults low body weight (< 60 kg) may increase haemorrhagic risk. *Hepatic impairment*: see dosage and administration section. *Interaction with Inhibitors of CYP3A4 and P-gp*: Not recommended with strong inhibitors of both CYP3A4 and P-gp. These medicinal products may increase apixaban exposure by 2-fold or greater in the presence of additional factors that increase apixaban exposure (e.g. severe renal impairment). No clinical data are available in paediatric patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp. See SmPC for further details. *Interaction with Inducers of CYP3A4 and P-gp*: Apixaban 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. Concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp, apixaban 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, though no dose adjustment for apixaban is required during concomitant therapy with such medicinal products. No clinical data are available in paediatric patients receiving concomitant systemic treatment with strong inducers of both CYP 3A4 and P-gp. *Hip fracture surgery*: Apixaban has not been studied in clinical trials in patients undergoing hip fracture surgery. Therefore, it is not recommended in these patients. *Laboratory parameters*: Clotting tests (PT, INR, and aPTT) are affected by the mechanism of action of apixaban. Changes observed at the expected therapeutic dose are small and subject to a high degree of variability, see SmPC for further details. *Information about excipients*: Eliquis contains lactose. Patients with galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Eliquis.

DRUG INTERACTIONS: Apixaban should be used with caution when

co-administered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicinal products typically increase the bleeding risk. There is limited experience of co-administration 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, co-administration of these products with apixaban is not recommended. In study CV185325, no clinically important bleeding events were reported in the 12 paediatric patients treated with apixaban and ASA ≤ 165 mg daily concomitantly. See SmPC for further details. Due to an increased bleeding risk, concomitant treatment with any other anticoagulants 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. Administration of activated charcoal reduces apixaban exposure. *Paediatric population:* Interaction studies have not been performed in paediatrics. 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*: As a precautionary measure, it is preferable to avoid the use of apixaban during pregnancy. *Breastfeeding:* 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.

UNDESIRABLE EFFECTS: Increased risk of occult or overt bleeding from any tissue or organ, which may result in post haemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Frequencies: common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). **Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp):** *Common*: anaemia; haemorrhage*; haematoma*; nausea; contusion. *Uncommon*: thrombocytopenia*; epistaxis*; haematochezia*; liver function test abnormal (including blood bilirubin increased)*; haematuria*; specific haemorrhage such as gastrointestinal*, abnormal vaginal*, urogenital*, post procedural*, wound secretion*, incision site*, operative*. *Rare*: hypersensitivity*; anaphylaxis*; haemoptysis*; gingival bleeding*; specific haemorrhage such as eye (including conjunctival)*, rectal*, muscle*. *Not known*: angioedema*; erythema multiforme*; cutaneous vasculitis*; specific haemorrhage such as brain (encompassing intracranial, intraspinal)*, intra-abdominal*, respiratory tract*, haemorrhoidal*, mouth*, retroperitoneal*, application site bleeding*, occult blood positive*, traumatic*. **Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF):** *Common*: anaemia; haemorrhage*; haematoma*; hypotension (including procedural hypotension); epistaxis*; nausea; gingival bleeding*; gamma-glutamyltransferase increased; haematuria*; contusion; specific haemorrhage such as eye (including conjunctival)*, gastrointestinal*, rectal*. *Uncommon*: thrombocytopenia*; hypersensitivity*; anaphylaxis*; haemoptysis*; haematochezia*; liver function test abnormal (including blood bilirubin increased)*; specific haemorrhage such as brain (encompassing intracranial, intraspinal)*, intra-abdominal*, haemorrhoidal*, mouth*, abnormal vaginal*, urogenital*, application site bleeding*, occult blood positive*, post procedural*, wound secretion*, incision site*, operative*, traumatic*. *Rare*: specific haemorrhage such as respiratory tract*, retroperitoneal*, muscle*. *Very Rare*: erythema multiforme*. *Not known:* angioedema*; cutaneous vasculitis*.

Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt) in adult patients: *Common*: anaemia; thrombocytopenia*; haemorrhage*; haematoma*; epistaxis*; nausea; gingival bleeding*; gamma-glutamyltransferase increased; alanine aminotransferase increased; skin rash; haematuria*; contusion; specific haemorrhage such as gastrointestinal*, mouth*, rectal*, abnormal vaginal*, urogenital*. *Uncommon*: hypersensitivity*; anaphylaxis*; haemoptysis*; haematochezia*; liver function test abnormal (including blood bilirubin increased)*; specific haemorrhage such as eye (including conjunctival)*, haemorrhoidal*, muscle*, application site bleeding*, occult blood positive*, post procedural*, wound secretion*, incision site*, operative*, traumatic*. *Rare*: specific haemorrhage such as brain (encompassing intracranial, intraspinal)*, respiratory tract*. *Not Known*: angioedema*; erythema multiforme*; cutaneous vasculitis*; specific haemorrhage such as intra-abdominal* and retroperitoneal*.

Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age: *Very Common*: epistaxis*; specific haemorrhage such as abnormal vaginal (including heavy menstrual bleeding, intermenstrual bleeding, and vaginal haemorrhage)* and urogenital*. *Common*: anaemia; thrombocytopenia*; hypersensitivity‡*; allergic oedema‡; anaphylaxis‡*; pruritus; haemorrhage*; haematoma*; hypotension (including procedural hypotension); nausea; haematochezia*; gingival bleeding*; liver function test abnormal (including blood bilirubin increased)*; aspartate aminotransferase increased; blood alkaline phosphatase increased; alanine aminotransferase increased; skin rash; alopecia; haematuria*; contusion; specific haemorrhage such as rectal*, post procedural*, wound secretion*, incision site*, operative*. *Not Known*: angioedema*; haemoptysis*; erythema multiforme*; cutaneous vasculitis*; specific haemorrhage such as brain (encompassing intracranial, intraspinal)*, eye (including conjunctival)*, intra-abdominal*, respiratory tract*, gastrointestinal*, haemorrhoidal*, mouth*, retroperitoneal*, muscle*, application site bleeding*, occult blood positive* and traumatic*.

*serious adverse drug reaction

‡ Includes anaphylactic reaction, drug hypersensitivity, and hypersensitivity.

Refer to SmPC for all other adverse events

LEGAL CATEGORY: POM.

MARKETING AUTHORISATION NUMBER: EU/1/11/691/002 (carton of 20 film-coated tablets 2.5 mg), EU/1/11/691/003 (carton of 60 film-coated tablets 2.5 mg), EU/1/11/691/008 (carton of 56 film-coated tablets 5 mg), EU/1/11/691/014 (carton of 28 film- coated tablets 5 mg).

MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb/Pfizer EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland.

FOR FURTHER INFORMATION CONTACT:
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ADDITIONAL INFORMATION AVAILABLE ON REQUEST

Approval code: 432-IE-2400014

Adverse events should be reported. Reporting forms and information can be found at:
Ireland - via HPRA Pharmacovigilance at www.hpra.ie
Adverse events should also be reported to Bristol-Myers Squibb via medical.information@bms.com or 1 800 749 749 (Ireland).