ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg apixaban.

Excipients with known effect:
Each 2.5 mg film-coated tablet contains 51.43 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Yellow, round tablets debossed with 893 on one side and 2½ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

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).

4.2 Posology and method of administration

Posology

Prevention of VTE (VTEp): elective hip or knee replacement surgery
The recommended dose of Eliquis is 2.5 mg taken orally twice daily. 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.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
The recommended dose of Eliquis is 5 mg taken orally twice daily.

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 ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 micromole/l).

Therapy should be continued long term.

Missed Dose
If a dose is missed, the patient should take Eliquis immediately and then continue with twice daily intake as before.

Switching
Switching treatment from parenteral anticoagulants to Eliquis (and vice versa) can be done at the next scheduled dose (see section 4.5).

Switching from Vitamin K antagonist (VKA) therapy to Eliquis
When converting patients from Vitamin K antagonist (VKA) therapy to Eliquis, discontinue warfarin or other VKA therapy and start Eliquis when the international normalized ratio (INR) is < 2.0.

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.

Renal impairment
As there is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, apixaban is not recommended in these patients (see sections 4.4 and 5.2).

Prevention of VTE (VTEp): elective hip or knee replacement surgery
No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2). Limited clinical data in patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that apixaban plasma concentrations are increased in this patient population, therefore, apixaban is to be used with caution in these patients (see sections 4.4 and 5.2).

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2). Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/l) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily.
Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily.

Hepatic impairment
Eliquis is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

It is not recommended in patients with severe hepatic impairment (see sections 4.4. and 5.2).

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 (see sections 4.4 and 5.2).

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 with caution in this population (see sections 4.4 and 5.2). Prior to initiating Eliquis, liver function testing should be performed.

Body weight
VTEp - No dose adjustment required (see section 5.2).
NVAF - No dose adjustment required, unless criteria for dose reduction are met (see *Dose reduction* at the beginning of section 4.2).

Gender
No dose adjustment required (see section 5.2).

Elderly
VTEp – No dose adjustment required (see sections 4.4 and 5.2).
NVAF – No dose adjustment required, unless criteria for dose reduction are met (see *Dose reduction* at the beginning of section 4.2).

Paediatric population
The safety and efficacy of Eliquis in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use.
Eliquis should be swallowed with water, with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2).
- Lesion or condition if considered a significant risk factor for major bleeding. This may include 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.
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under the circumstances of switching therapy to or from apixaban (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

4.4 Special warnings and precautions for use

Haemorrhage risk
As with other anticoagulants, patients taking Eliquis are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Eliquis administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9). Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see section 5.1).

Interaction with other medicinal products affecting haemostasis
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding (see section 4.5). 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 (see section 4.5).

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.

In a clinical trial of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.1%) use of concomitant dual antiplatelet therapy.

In a clinical trial of high-risk post acute coronary syndrome patients, characterized by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year) .

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 apixaban.

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.

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.

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 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 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 apixaban with indwelling intrathecal or epidural catheters. In case there is such need and based on the general PK characteristics of apixaban, a time interval of 20-30 hours (i.e., 2 x half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban 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 apixaban in the presence of neuraxial blockade.

Renal impairment
As there is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, apixaban is not recommended in these patients (see sections 4.2 and 5.2).

Prevention of VTE (VTEp): elective hip or knee replacement surgery
No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2).

Limited clinical data in patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that apixaban plasma concentrations are increased in this patient population, therefore, apixaban alone or in combination with acetylsalicylic acid (ASA) is to be used with caution in these patients because of a potentially higher bleeding risk (see sections 4.2 and 5.2).

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 4.2 and 5.2).

Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/l) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily. Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily (see section 4.2).

Elderly patients
The co-administration of Eliquis with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Hepatic impairment
Eliquis is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

It is not recommended in patients with severe hepatic impairment (see section 5.2).

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2 and 5.2).

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 (see section 5.2). Prior to initiating Eliquis, liver function testing should be performed.

Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (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). These medicinal products may increase apixaban exposure by 2-fold (see section 4.5) or greater in the presence of additional factors that increase apixaban exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp
The concomitant use of Eliquis with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone. Strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.5).

Hip fracture surgery
Apixaban 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 (e.g., 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 section 5.1).

Information about excipients
Eliquis contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4 and P-gp
Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max}.

The use of Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) (see section 4.4).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg. diltiazem, naproxen, amiodarone, verapamil, quinidine) are expected to increase apixaban plasma concentration to a lesser extent. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4-fold increase in mean apixaban AUC and a 1.3-fold increase in C_{max}. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. No dose adjustment for apixaban is required when co-administered with less potent inhibitors of CYP3A4 and/or P-gp.

Inducers of CYP3A4 and P-gp
Co-administration of apixaban with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and C_{max}, respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.4).

Anticoagulants, platelet aggregation inhibitors and NSAIDs
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was co-administered with ASA 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and ASA 162 mg once daily in Phase 1 studies did not show a relevant increase in template bleeding time, or further inhibition of platelet aggregation, compared to administration of the antiplatelet agents without apixaban. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of apixaban alone.

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. Corresponding increases in clotting tests were observed for apixaban. No changes were observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are co-administered with apixaban. Eliquis should be used with caution when co-administered with NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with acute coronary syndrome (see section 4.4).

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.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two medicinal products together, mean apixaban AUC and C_{max} were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max}.

Effect of apixaban on other medicinal products
In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 > 45 μM) and weak inhibitory effect on the activity of CYP2C19 (IC50 > 20 μM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

In studies conducted in healthy subjects, as described below, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin: Co-administration of apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, did not affect digoxin AUC or C_{max}. Therefore, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen: Co-administration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max}.

Atenolol: Co-administration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

Activated Charcoal
Administration of activated charcoal reduces apixaban exposure (see section 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy
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. Apixaban is not recommended during pregnancy.

Breast-feeding
It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. In rat milk, a high milk to maternal plasma ratio (C_{max} about 8, AUC about 30) was found, possibly due to active transport into the milk. A risk to newborns and infants cannot be excluded.

A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

Fertility
Studies in animals dosed with apixaban have shown no effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Eliquis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The safety of apixaban has been investigated in 5,924 patients in VTEp studies and in 11,886 patients in NVAF studies, for an average total exposure of 20 days and 1.7 years respectively.

In the VTEp studies, in total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. Common adverse reactions were anaemia, haemorrhage, contusion, and nausea.

Over the two phase III studies in NVAF, 24.4% (apixaban vs warfarin study) and 9.6% (apixaban vs aspirin study) of the patients treated with apixaban (5 mg or 2.5 mg) twice daily experienced adverse reactions.

Common adverse reactions for apixaban were epistaxis, contusion, haematuria, haematoma, eye haemorrhage, and gastrointestinal haemorrhage.

The overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and was 9.6% in the apixaban vs aspirin study (see section 5.1).

In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

Tabulated list of adverse reactions
Table 1 shows the adverse reactions ranked under headings of System Organ Class and frequency using the following convention: very common (≥1/10); 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) for both VTEp and NVAF.

Table 1

System Organ Class	**VTEp**	**NVAF**
Blood and lymphatic system disorders		
Anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)	Common	-
Thrombocytopenia (including platelet count decreases)	Uncommon	-
Immune system disorders		
Hypersensitivity (including skin rash, anaphylactic reaction and allergic edema)	-	Uncommon
Hypersensitivity	Rare	-
Nervous system disorders		
Brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)	-	Uncommon
Eye disorders		
Eye haemorrhage (including conjunctival haemorrhage)	-	Common
Ocular haemorrhage (including conjunctival haemorrhage)	Rare	-
Vascular disorders		
Haemorrhage (including haematoma, and vaginal and urethral haemorrhage)	Common	-
Other haemorrhage, haematoma	-	Common
Hypotension (including procedural hypotension)	Uncommon	-
Intra-abdominal haemorrhage	-	Uncommon
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Uncommon	Common
Haemoptysis	Rare	Uncommon
Respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage and pharyngeal haemorrhage)	-	Rare
Gastrointestinal disorders		
Nausea	Common	-
Gastrointestinal haemorrhage (including haematemesis and melaena). rectal haemorrhage, gingival bleeding	-	Common
Gastrointestinal haemorrhage (including haematemesis and melaena), haematochezia	Uncommon	-
Haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage	-	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	-
Retroperitoneal haemorrhage	-	Rare
Hepatobiliary disorders		
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal), aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	-
Musculoskeletal and connective tissue disorders		
Muscle haemorrhage	Rare	-
Renal and urinary disorders		
Haematuria	-	Common
Haematuria (including respective laboratory parameters)	Uncommon	-

System Organ Class	VTEp	NVAF
Reproductive system and breast disorders		
Abnormal vaginal haemorrhage, urogenital haemorrhage	-	Uncommon
General disorders and administration site conditions		
Application site bleeding	-	Uncommon
Investigations		
Occult blood positive	-	Uncommon
Injury, poisoning and procedural complications		
Contusion	Common	Common
Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage) wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage	Uncommon	-
Traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage	-	Uncommon

The use of Eliquis may be associated with an 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 (see section 4.4 and section 5.1).

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 the national reporting system listed in Appendix V.

4.9 Overdose

There is no antidote to Eliquis. Overdose of apixaban 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 apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily (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 apixaban reduced mean apixaban AUC by 50% and 27%, respectively, and had no impact on C_{max}. Mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct factor Xa inhibitors, ATC code: B01AF02

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as 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 apixaban.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa 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 and results are presented below. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom assay is well within acceptable limits for use in a clinical laboratory. The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

In patients treated with apixaban 2.5 mg twice a day following elective knee or hip replacement surgery the predicted steady-state peak and trough anti-FXa activity with apixaban 2.5 mg BID dosing are 1.3 IU/ml (5th/95th percentile 0.67-2.4 IU/ml) and 0.84 IU/ml (5th/95th percentile 0.37-1.8 IU/ml), respectively, demonstrating less than a 1.6-fold fluctuation in peak-to-trough anti-FXa activity over the dosing interval.

In patients with atrial fibrillation, the predicted steady-state peak and trough anti-FXa activity with apixaban 5 mg BID are 2.55 IU/ml (5th/95th percentile 1.36-4.79 IU/ml) and 1.54 IU/ml (5th/95th percentile 0.61-3.43 IU/ml), respectively. In AF patients who meet the criteria for a dose reduction to 2.5 mg BID, the predicted peak and trough anti-FXa values are 1.84 IU/ml (5th/95th percentile 1.02-3.29 IU/ml) and 1.18 IU/ml (5th/95th percentile 0.51-2.42 IU/ml), respectively.

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.

Clinical efficacy and safety

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

The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of VTE in a broad range of adult patients undergoing elective hip or knee replacement. A

total of 8,464 patients were randomized in two pivotal, double-blind, multi-national studies, comparing apixaban 2.5 mg given orally twice daily (4,236 patients) or enoxaparin 40 mg once daily (4,228 patients). Included in this total were 1,262 patients (618 in the apixaban group) of age 75 or older, 1,004 patients (499 in the apixaban group) with low body weight (≤ 60 kg), 1,495 patients (743 in the apixaban group) with BMI ≥ 33 kg/m^2, and 415 patients (203 in the apixaban group) with moderate renal impairment.

The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement, and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement. Subjects received either apixaban 2.5 mg given orally twice daily (po bid) or enoxaparin 40 mg administered subcutaneously once daily (sc od). The first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Both apixaban and enoxaparin were given for 32-38 days in the ADVANCE-3 study and for 10-14 days in the ADVANCE-2 study.

Based on patient medical history in the studied population of ADVANCE-3 and ADVANCE-2 (8,464 patients), 46% had hypertension, 10% had hyperlipidemia, 9% had diabetes, and 8% had coronary artery disease.

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal DVT, non-fatal PE, and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 2).

Table 2: Efficacy results from pivotal phase III studies

Study	**ADVANCE-3 (hip)**			**ADVANCE-2 (knee)**		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po bid 35 ± 3 d	Enoxaparin 40 mg sc od 35 ± 3 d	p-value	Apixaban 2.5 mg po bid 12 ± 2 d	Enoxaparin 40 mg sc od 12 ± 2 d	p-value
Total VTE/all-cause death						
Number of events/subjects Event Rate	27/1949 1.39%	74/1917 3.86%	<0.0001	147/976 15.06%	243/997 24.37%	<0.0001
Relative Risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Major VTE						
Number of events/subjects Event Rate	10/2199 0.45%	25/2195 1.14%	0.0107	13/1195 1.09%	26/1199 2.17%	0.0373
Relative Risk 95% CI	0.40 (0.15, 0.80)			0.50 (0.26, 0.97)		

The safety endpoints of major bleeding, the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 3). All the bleeding criteria included surgical site bleeding.

Table 3: Bleeding results from pivotal phase III studies*

	ADVANCE-3		**ADVANCE-2**	
	Apixaban 2.5 mg po bid 35 ± 3 d	Enoxaparin 40 mg sc od 35 ± 3 d	Apixaban 2.5 mg po bid 12 ± 2 d	Enoxaparin 40 mg sc od 12 ± 2 d
All treated	n = 2673	n = 2659	n = 1501	n = 1508
Treatment Period [1]				
Major	22 (0.8%)	18 (0.7%)	9 (0.6%)	14 (0.9%)
Fatal	0	0	0	0

Major + CRNM	129 (4.8%)	134 (5.0%)	53 (3.5%)	72 (4.8%)
All	313 (11.7%)	334 (12.6%)	104 (6.9%)	126 (8.4%)
Post-surgery treatment period [2]				
Major	9 (0.3%)	11 (0.4%)	4 (0.3%)	9 (0.6%)
Fatal	0	0	0	0
Major + CRNM	96 (3.6%)	115 (4.3%)	41 (2.7%)	56 (3.7%)
All	261 (9.8%)	293 (11.0%)	89 (5.9%)	103 (6.8%)

* All the bleeding criteria included surgical site bleeding
[1] Includes events occurring after first dose of enoxaparin (pre-surgery)
[2] Includes events occurring after first dose of apixaban (post-surgery)

The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g., alanine aminotransferase levels) were numerically lower in patients on apixaban compared to enoxaparin in the phase II and phase III studies in elective hip and knee replacement surgery.

In the knee replacement surgery study during the intended treatment period, in the apixaban arm 4 cases of PE were diagnosed against no cases in the enoxaparin arm. No explanation can be given to this higher number of PE.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
A total of 23,799 patients were randomised in the clinical program (ARISTOTLE: apixaban versus warfarin, AVERROES: apixaban versus ASA) including 11,927 randomised to apixaban. The program was designed to demonstrate the efficacy and safety of apixaban for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and one or more additional risk factors, such as:

- prior stroke or transient ischaemic attack (TIA)
- age ≥ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥ II)

ARISTOTLE STUDY
In the ARISTOTLE study a total of 18,201 patients were randomized to double-blind treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [4.7%], see section 4.2) or warfarin (target INR range 2.0-3.0), patients were exposed to study drug for a mean of 20 months. The mean age was 69.1 years, the mean $CHADS_2$ score was 2.1 and 18.9 % of patients had prior stroke or TIA.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 4) compared with warfarin.

Table 4: Efficacy Outcomes in Patients with Atrial Fibrillation in the ARISTOTLE Study

	Apixaban N=9120 n (%/yr)	**Warfarin N=9081 n (%/yr)**	**Hazard Ratio (95% CI)**	**p-value**
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
Stroke				
Ischaemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	
Haemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

For patients randomized to warfarin, the median percentage of time in therapeutic range (TTR) (INR 2-3) was 66%.

Apixaban showed a reduction of stroke and systemic embolism compared to warfarin across the different levels of center TTR; within the highest quartile of TTR according to center, the hazard ratio for apixaban vs warfarin was 0.73 (95% CI, 0.38, 1.40).

Key secondary endpoints of major bleeding and all cause death were tested in a pre-specified hierarchical testing strategy to control the overall type 1 error in the trial. Statistically significant superiority was also achieved in the key secondary endpoints of both major bleeding and all-cause death (see Table 5). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

Table 5: Secondary endpoints in Patients with Atrial Fibrillation in the ARISTOTLE Study

	Apixaban N = 9088 n (%/year)	**Warfarin N = 9052 n (%/year)**	**Hazard Ratio (95% CI)**	**p-value**
Bleeding Outcomes				
Major*	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	< 0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	< 0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	< 0.0001
Other Endpoints				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66, 1.17)	

*Major bleeding defined per International Society on Thrombosis and Haemostasis (ISTH) criteria.

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study.

The efficacy results for prespecified subgroups, including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

The incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) was 0.76%/year with apixaban and 0.86%/year with warfarin.

The major bleeding results for prespecified subgroups including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the results for the overall population studied in the trial.

AVERROES STUDY

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomized to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], see section 4.2) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study drug for a mean of 14 months. The mean age was 69.9 years, the mean $CHADS_2$ score was 2.0 and 13.6% of patients had prior stroke or TIA.

Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS2 score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

AVERROES was stopped early based on a recommendation by the independent Data Monitoring Committee due to clear evidence of reduction of stroke and systemic embolism with an acceptable safety profile.

The overall discontinuation rate due to adverse reactions was 1.5% for apixaban and 1.3% for ASA in the AVERROES study.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism (see Table 6) compared to ASA.

Table 6: Key Efficacy Outcomes in Patients with Atrial Fibrillation in the AVERROES Study

	Apixaban N = 2807 n (%/year)	**ASA N = 2791 n (%/year)**	**Hazard Ratio (95% CI)**	**p-value**
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
Ischaemic or unspecified	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	
Haemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	
Stroke, systemic embolism, MI, or vascular death*†	132 (4.21)	197 (6.35)	0.66 (0.53, 0.83)	0.003
Myocardial infarction	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	
Vascular Death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	
All-cause death†	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068

* Assessed by sequential testing strategy designed to control the overall type I error in the trial.
† Secondary endpoint.

There was no statistically significant difference in the incidence of major bleeding between apixaban and ASA (see Table 7).

Table 7: Bleeding Events in Patients with Atrial Fibrillation in the AVERROES Study

	Apixaban N = 2798 n(%/year)	**ASA N = 2780 n (%/year)**	**Hazard Ratio (95%CI)**	**p-value**
Major*	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal, n	5 (0.16)	5 (0.16)		
Intracranial, n	11 (0.34)	11 (0.35)		
Major + CRNM	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

*Major bleeding defined per International Society on Thrombosis ad Haemostasis (ISTH) criteria.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Eliquis in one or more subsets of the paediatric population in venous and arterial embolism and thrombosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

Distribution
Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 litres.

Biotransformation and elimination
Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3.3 l/h and a half-life of approximately 12 hours.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolized mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

Renal impairment
There was no impact of impaired renal function on peak concentration of apixaban. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51-80 ml/min), moderate (creatinine clearance 30-50 ml/min) and severe (creatinine clearance 15-29 ml/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44% respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity.

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36% when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14% in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment
In a study comparing 8 subjects with mild hepatic impairment, Child-Pugh A score 5 (n = 6) and score 6 (n = 2), and 8 subjects with moderate hepatic impairment (Child-Pugh B score 7 (n = 6) and score 8 (n = 2), to 16 healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-Factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Elderly
Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher and no difference in C_{max}.

Gender
Exposure to apixaban was approximately 18% higher in females than in males.

Ethnic origin and race

The results across phase 1 studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects. Findings from a population pharmacokinetic analysis in patients who received apixaban were generally consistent with the phase 1 results.

Body weight
Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30% lower exposure and body weight < 50 kg was associated with approximately 30% higher exposure.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic /pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 – 50 mg). The relationship between apixaban plasma concentration and anti-factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-foetal development and juvenile toxicity.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the toxicity studies little to no increase of bleeding tendency was found. However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Anhydrous lactose
Microcrystalline cellulose (E460)
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate (E470b)

Film coat:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Alu-PVC/PVdC blisters. Cartons of 10, 20, 60 and 168 film-coated tablets.

Alu PVC/PVdC perforated unit dose blisters of 60x1 and 100x1 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House,
Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex
UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/001
EU/1/11/691/002
EU/1/11/691/003
EU/1/11/691/004
EU/1/11/691/005
EU/1/11/691/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 May 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5.0 mg apixaban.

Excipients with known effect:
Each 5 mg film-coated tablet contains 102.86 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Pink, oval tablets debossed with 894 on one side and 5 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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).

4.2 Posology and method of administration

Posology

The recommended dose of Eliquis is 5 mg taken orally twice daily.

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 ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 micromole/l).

Therapy should be continued long term.

Missed Dose
If a dose is missed, the patient should take Eliquis immediately and then continue with twice daily intake as before.

Switching
Switching treatment from parenteral anticoagulants to Eliquis (and vice versa) can be done at the next scheduled dose (see section 4.5).

Switching from Vitamin K antagonist (VKA) therapy to Eliquis
When converting patients from Vitamin K antagonist (VKA) therapy to Eliquis, discontinue warfarin or other VKA therapy and start Eliquis when the international normalized ratio (INR) is < 2.0.

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.

Renal impairment
As there is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, apixaban is not recommended in these patients (see sections 4.4 and 5.2).
No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2).

Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/l) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily.
Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily.

Hepatic impairment
Eliquis is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

It is not recommended in patients with severe hepatic impairment (see sections 4.4. and 5.2).

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 (see sections 4.4 and 5.2).

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 with caution in this population (see sections 4.4 and 5.2). Prior to initiating Eliquis, liver function testing should be performed.

Body weight
No dose adjustment required, unless criteria for dose reduction are met (see *Dose reduction* at the beginning of section 4.2).

Gender
No dose adjustment required (see section 5.2).

Elderly
No dose adjustment required, unless criteria for dose reduction are met (see *Dose reduction* at the beginning of section 4.2).

Paediatric population
The safety and efficacy of Eliquis in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use.
Eliquis should be swallowed with water, with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2).
- Lesion or condition if considered a significant risk factor for major bleeding. This may include 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.
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under the circumstances of switching therapy to or from apixaban (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

4.4 Special warnings and precautions for use

Haemorrhage risk
As with other anticoagulants, patients taking Eliquis are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Eliquis administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9).

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see section 5.1).

Interaction with other medicinal products affecting haemostasis
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding (see section 4.5). 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 (see section 4.5).

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.

In a clinical trial of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.1%) use of concomitant dual antiplatelet therapy.

In a clinical trial of high-risk post acute coronary syndrome patients, characterized by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).

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 apixaban.

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.

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.

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.

Renal impairment
As there is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, apixaban is not recommended in these patients (see sections 4.2 and 5.2).

No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 4.2 and 5.2).

Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/l) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily. Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily (see section 4.2).

Elderly patients
The co-administration of Eliquis with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Hepatic impairment
Eliquis is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

It is not recommended in patients with severe hepatic impairment (see section 5.2).

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2 and 5.2).

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 (see section 5.2). Prior to initiating Eliquis, liver function testing should be performed.

Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (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). These medicinal products may increase apixaban exposure by 2-fold (see section 4.5) or greater in the presence of additional factors that increase apixaban exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp
The concomitant use of Eliquis with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone. Strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.5).

Laboratory parameters
Clotting tests (e.g., 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 section 5.1).

Information about excipients
Eliquis contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4 and P-gp
Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max}.

The use of Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) (see section 4.4).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg. diltiazem, naproxen, amiodarone, verapamil, quinidine) are expected to increase apixaban plasma concentration to a lesser extent. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4-fold increase in mean apixaban AUC and a 1.3-fold increase in C_{max}. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. No dose adjustment for apixaban is required when co-administered with less potent inhibitors of CYP3A4 and/or P-gp.

Inducers of CYP3A4 and P-gp
Co-administration of apixaban with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and C_{max}, respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.4).

Anticoagulants, platelet aggregation inhibitors and NSAIDs
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was co-administered with ASA 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and ASA 162 mg once daily in Phase 1 studies did not show a relevant increase in template bleeding time, or further inhibition of platelet aggregation, compared to administration of the antiplatelet agents without apixaban. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of apixaban alone.

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. Corresponding increases in clotting tests were observed for apixaban. No changes were observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are co-administered with apixaban. Eliquis should be used with caution when co-administered with NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with acute coronary syndrome (see section 4.4).

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.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two medicinal products together, mean apixaban AUC and C_{max} were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max}.

Effect of apixaban on other medicinal products

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 > 45 μM) and weak inhibitory effect on the activity of CYP2C19 (IC50 > 20 μM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

In studies conducted in healthy subjects, as described below, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin: Co-administration of apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, did not affect digoxin AUC or C_{max}. Therefore, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen: Co-administration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max}.

Atenolol: Co-administration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

Activated Charcoal
Administration of activated charcoal reduces apixaban exposure (see section 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy
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. Apixaban is not recommended during pregnancy.

Breast-feeding
It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. In rat milk, a high milk to maternal plasma ratio (C_{max} about 8, AUC about 30) was found, possibly due to active transport into the milk. A risk to newborns and infants cannot be excluded.

A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

Fertility
Studies in animals dosed with apixaban have shown no effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Eliquis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The safety of apixaban has been investigated in 11,886 patients in NVAF studies treated for an average total exposure of 1.7 years.

Over the two phase III studies, 24.4% (apixaban vs warfarin) and 9.6% (apixaban vs aspirin) of the patients treated with apixaban (5 mg or 2.5 mg) twice daily experienced adverse reactions.

Common adverse reactions for apixaban were epistaxis, contusion, haematuria, haematoma, eye haemorrhage, and gastrointestinal haemorrhage.

The overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and was 9.6% in the apixaban vs aspirin study (see section 5.1).

In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

Tabulated list of adverse reactions
Table 1 shows the adverse reactions ranked under headings of System Organ Class and frequency using the following convention: very common (≥1/10) 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).

Table 1

System Organ Class	**NVAF**
Immune system disorders	
Hypersensitivity (including skin rash, anaphylactic reaction and allergic edema)	Uncommon
Nervous system disorders	
Brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)	Uncommon
Eye disorders	
Eye haemorrhage (including conjunctival haemorrhage)	Common
Vascular disorders	
Other haemorrhage, haematoma	Common
Intra-abdominal haemorrhage	Uncommon
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Uncommon
Respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage and pharyngeal haemorrhage)	Rare
Gastrointestinal disorders	
Gastrointestinal haemorrhage (including haematemesis and melaena). rectal haemorrhage, gingival bleeding	Common
Haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage	Uncommon
Retroperitoneal haemorrhage	Rare
Renal and urinary disorders	
Haematuria	Common
Reproductive system and breast disorders	
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon
General disorders and administration site conditions	
Application site bleeding	Uncommon
Investigations	
Occult blood positive	Uncommon
Injury, poisoning and procedural complications	
Contusion	Common
Traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage	Uncommon

The use of Eliquis may be associated with an 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 (see section 4.4 and section 5.1).

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 the national reporting system listed in Appendix V.

4.9 Overdose

There is no antidote to Eliquis. Overdose of apixaban 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 apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily (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 apixaban reduced mean apixaban AUC by 50% and 27%, respectively, and had no impact on C_{max}. Mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct factor Xa inhibitors, ATC code: B01AF02

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as 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 apixaban.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa 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 and results are presented below. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching

maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom assay is well within acceptable limits for use in a clinical laboratory. The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

In patients with atrial fibrillation, the predicted steady-state peak and trough anti-FXa activity with apixaban 5 mg BID are 2.55 IU/ml (5th/95th percentile 1.36-4.79 IU/ml) and 1.54 IU/ml (5th/95th percentile 0.61-3.43 IU/ml), respectively. In AF patients who meet the criteria for a dose reduction to 2.5 mg BID, the predicted peak and trough anti-FXa values are 1.84 IU/ml (5th/95th percentile 1.02-3.29 IU/ml) and 1.18 IU/ml (5th/95th percentile 0.51-2.42 IU/ml), respectively.

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.

Clinical efficacy and safety

A total of 23,799 patients were randomised in the clinical program (ARISTOTLE: apixaban versus warfarin, AVERROES: apixaban versus ASA) including 11,927 randomised to apixaban. The program was designed to demonstrate the efficacy and safety of apixaban for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and one or more additional risk factors, such as:

- prior stroke or transient ischaemic attack (TIA)
- age ≥ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥ II)

ARISTOTLE STUDY

In the ARISTOTLE study a total of 18,201 patients were randomized to double-blind treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [4.7%], see section 4.2) or warfarin (target INR range 2.0-3.0), patients were exposed to study drug for a mean of 20 months. The mean age was 69.1 years, the mean $CHADS_2$ score was 2.1, 18.9 % of patients had prior stroke or TIA.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 2) compared with warfarin.

Table 2: Efficacy Outcomes in Patients with Atrial Fibrillation in the ARISTOTLE Study

	Apixaban N=9120 n (%/yr)	**Warfarin N=9081 n (%/yr)**	**Hazard Ratio (95% CI)**	**p-value**
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.0114
Stroke				
Ischaemic or unspecified	162 (0.97)	175 (1.05)	0.92 (0.74, 1.13)	
Haemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

For patients randomized to warfarin, the median percentage of time in therapeutic range (TTR) (INR 2-3) was 66%.

Apixaban showed a reduction of stroke and systemic embolism compared to warfarin across the different levels of center TTR; within the highest quartile of TTR according to center, the hazard ratio for apixaban vs warfarin was 0.73 (95% CI, 0.38, 1.40).

Key secondary endpoints of major bleeding and all cause death were tested in a pre-specified hierarchical testing strategy to control the overall type 1 error in the trial. Statistically significant superiority was also achieved in the key secondary endpoints of both major bleeding and all-cause death (see Table 3). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

Table 3: Secondary endpoints in Patients with Atrial Fibrillation in the ARISTOTLE Study

	Apixaban N = 9088 n (%/year)	**Warfarin N = 9052 n (%/year)**	**Hazard Ratio (95% CI)**	**p-value**
Bleeding Outcomes				
Major*	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	< 0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM†	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	< 0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	< 0.0001
Other Endpoints				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66, 1.17)	

*Major bleeding defined per International Society on Thrombosis and Haemostasis (ISTH) criteria.
† Clinically Relevant Non-Major

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study.

The efficacy results for prespecified subgroups, including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

The incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) was 0.76%/year with apixaban and 0.86%/year with warfarin.

The major bleeding results for prespecified subgroups including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the results for the overall population studied in the trial.

AVERROES STUDY
In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomized to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], see section 4.2) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study drug for a mean of 14 months. The mean age was 69.9 years, the mean $CHADS_2$ score was 2.0 and 13.6% of patients had prior stroke or TIA.

Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS2 score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

AVERROES was stopped early based on a recommendation by the independent Data Monitoring Committee due to clear evidence of reduction of stroke and systemic embolism with an acceptable safety profile.

The overall discontinuation rate due to adverse reactions was 1.5% for apixaban and 1.3% for ASA in the AVERROES study.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism (see Table 4) compared to ASA.

Table 4: Key Efficacy Outcomes in Patients with Atrial Fibrillation in the AVERROES Study

	Apixaban N = 2807 n (%/year)	**ASA N = 2791 n (%/year)**	**Hazard Ratio (95% CI)**	**p-value**
Stroke or systemic embolism*	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	< 0.0001
Stroke				
Ischaemic or unspecified	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	
Haemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	
Stroke, systemic embolism, MI, or vascular death*†	132 (4.21)	197 (6.35)	0.66 (0.53, 0.83)	0.003
Myocardial infarction	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	
Vascular Death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	
All-cause death†	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068

* Assessed by sequential testing strategy designed to control the overall type I error in the trial
† Secondary endpoint.

There was no statistically significant difference in the incidence of major bleeding between apixaban and ASA (see Table 5).

Table 5: Bleeding Events in Patients with Atrial Fibrillation in the AVERROES Study

	Apixaban N = 2798 n(%/year)	**ASA N = 2780 n (%/year)**	**Hazard Ratio (95%CI)**	**p-value**
Major*	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal, n	5 (0.16)	5 (0.16)		
Intracranial, n	11 (0.34)	11 (0.35)		
Major + CRNM†	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

*Major bleeding defined per International Society on Thrombosis ad Haemostasis (ISTH) criteria.
† Clinically Relevant Non-Major

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Eliquis in one or more subsets of the paediatric population in venous and arterial embolism and thrombosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food.

Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased

bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20% CV and ~30% CV, respectively.

Distribution
Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 litres.

Biotransformation and elimination
Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3.3 l/h and a half-life of approximately 12 hours.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolized mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

Renal impairment
There was no impact of impaired renal function on peak concentration of apixaban. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51-80 ml/min), moderate (creatinine clearance 30-50 ml/min) and severe (creatinine clearance 15-29 ml/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44% respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity.

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36% when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14% in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment
In a study comparing 8 subjects with mild hepatic impairment, Child-Pugh A score 5 (n = 6) and score 6 (n = 2), and 8 subjects with moderate hepatic impairment (Child-Pugh B score 7 (n = 6) and score 8 (n = 2), to 16 healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-Factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Elderly
Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher and no difference in C_{max}.

Gender
Exposure to apixaban was approximately 18% higher in females than in males.

Ethnic origin and race
The results across phase 1 studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects. Findings from a population

pharmacokinetic analysis in patients who received apixaban were generally consistent with the phase 1 results.

Body weight
Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30% lower exposure and body weight < 50 kg was associated with approximately 30% higher exposure.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic /pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 – 50 mg). The relationship between apixaban plasma concentration and anti-factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-foetal development and juvenile toxicity.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the toxicity studies little to no increase of bleeding tendency was found. However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Anhydrous lactose
Microcrystalline cellulose (E460)
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate (E470b)

Film coat:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Alu-PVC/PVdC blisters. Cartons of 14, 20, 56, 60, 168 and 200 film-coated tablets.
Alu-PVC/PVdC perforated unit dose blisters of 100x1 film coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House,
Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex
UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/006
EU/1/11/691/007
EU/1/11/691/008
EU/1/11/691/009
EU/1/11/691/010
EU/1/11/691/011
EU/1/11/691/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:- 18 May 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S)RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.r.l
Loc. Fontana del Ceraso
03012 Anagni (FR)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Eliquis, prior to the launch of the new indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.

The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Eliquis and providing guidance on how to manage that risk.
The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
- Guidance regarding switching from or to Eliquis treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure.

The Patient alert card should contain the following key safety messages:

- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg film-coated tablets
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg apixaban

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
20 film-coated tablets
60 film-coated tablets
60 x 1 film-coated tablets
100 x 1 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House,
Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex
UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/001
EU/1/11/691/002
EU/1/11/691/003
EU/1/11/691/004
EU/1/11/691/005
EU/1/11/691/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 2.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 2.5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

sun as symbol
moon as symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg film-coated tablets
apixaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg apixaban

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
20 film-coated tablets
56 film-coated tablets
60 film-coated tablets
100x 1 film-coated tablets
168 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House,
Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex
UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/691/006
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EU/1/11/691/008
EU/1/11/691/009
EU/1/11/691/010
EU/1/11/691/011
EU/1/11/691/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eliquis 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Eliquis 5 mg tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

sun as symbol
moon as symbol

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Eliquis 2.5 mg film-coated tablets
Apixaban

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eliquis is and what it is used for

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in adults:
- to prevent blood clots (deep vein thrombosis [DVT]) from forming after hip or knee replacement operations. After an operation to the hip or knee you may be at a higher risk of developing blood clots in your leg veins. This can cause the legs to swell, with or without pain. If a blood clot travels from your leg to your lungs, it can block blood flow causing breathlessness, with or without chest pain. This condition (pulmonary embolism) can be life-threatening and requires immediate medical attention.

- to prevent a blood clot from forming in the heart in patients with an irregular heart beat (atrial fibrillation) and at least one additional risk factor. Blood clots may break off and travel to the brain and lead to a stroke or to other organs and prevent normal blood flow to that organ (also known as a systemic embolism). A stroke can be life-threatening and requires immediate medical attention.

2. What you need to know before you take Eliquis

Do not take Eliquis if:
- **you are allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6)
- you are **bleeding excessively**
- you have a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of your stomach or bowel, **recent bleeding in your brain**)
- you have a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy)

- you are **taking medicines to prevent blood clotting** (e.g., warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment or while having a venous or arterial line and you get heparin through this line to keep it open.

Warnings and precautions

Tell your doctor, pharmacist or nurse before you take this medicine if you have any of the following:
- an **increased risk of bleeding**, such as:
    - **bleeding disorders**, including conditions resulting in reduced platelet activity
    - **very high blood pressure,** not controlled by medical treatment
- a **severe kidney disease or if you are on dialysis**
- a **liver problem or a history of liver problems**
  Eliquis will be used with caution in patients with signs of altered liver function.
- **had a tube (catheter) or an injection into your spinal column** (for anaesthesia or pain reduction), your doctor will tell you to take Eliquis 5 hours or more after catheter removal
- if you have a **prosthetic heart valve**

If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask your doctor.

Children and adolescents

Eliquis is not recommended in children and adolescents under 18 years of age.

Other medicines and Eliquis

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the effects of Eliquis and some may decrease its effects. Your doctor will decide, if you should be treated with Eliquis when taking these medicines and how closely you should be monitored.

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:
- some **medicines for fungal infections** (e.g., ketoconazole, etc.)
- some **antiviral medicines for HIV / AIDS** (e.g., ritonavir)
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.)
- **anti-inflammatory** or **pain medicines** (e.g., aspirin or naproxen). Especially, if you are older than 75 years and are taking aspirin, you may have an increased chance of bleeding.
- **medicines for high blood pressure or heart problems** (e.g., diltiazem)

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:
- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.)
- **St John's Wort** (a herbal supplement used for depression)
- **medicines to treat tuberculosis** or **other infections** (e.g., rifampicin)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

The effects of Eliquis on pregnancy and the unborn child are not known. You should not take Eliquis if you are pregnant. **Contact your doctor immediately** if you become pregnant while taking Eliquis.

It is not known if Eliquis passes into human breast milk. Ask your doctor, pharmacist or nurse for advice before taking this medicine while breast-feeding. They will advise you to either stop breast-feeding or to stop/not start taking Eliquis.

Driving and using machines

Eliquis has not been shown to impair your ability to drive or use machines.

Eliquis contains lactose (a type of sugar).

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Eliquis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Dose

The recommended dose is one tablet twice a day, for example, one in the morning and one in the evening. Try to take the tablets at the same times every day to have the best treatment effect.

Swallow the tablet with a drink of water. Eliquis can be taken with or without food.

Take Eliquis as recommended for the following:

To prevent blood clots from forming after hip or knee replacement operations.
The recommended dose is one tablet of Eliquis 2.5 mg twice a day.

You should take the first tablet 12 to 24 hours after your operation.

If you have had a major **hip** operation you will usually take the tablets for 32 to38 days
If you have had a major **knee** operation you will usually take the tablets for 10 to 14 days

To prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.
The recommended dose is one tablet of Eliquis **5 mg** twice a day.

The recommended dose is one tablet of Eliquis **2.5 mg** twice a day if:

- you have **severely reduced kidney function**
- **two or more of the following apply to you**:
  - your blood test results suggest poor kidney function (value of serum creatinine is 1.5 mg/dL (133 micromole/l) or greater)
  - you are 80 years old or older
  - your weight is 60 kg or lower.

Your doctor might change your anticoagulant treatment as follows:

- *Changing from Eliquis to anticoagulant medicines*
Stop taking Eliquis. Start treatment with the anticoagulant medicines (for example heparin) at the time you would have taken the next tablet.

- *Changing from anticoagulant medicines to Eliquis*
Stop taking the anticoagulant medicines. Start treatment with Eliquis at the time you would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing Vitamin K antagonist (e.g. warfarin) to Eliquis*
Stop taking the medicine containing a vitamin-K antagonist. Your doctor needs to do blood-measurements and instruct you when to start taking Eliquis.

- *Changing from Eliquis to anticoagulant treatment containing Vitamin K antagonist (e.g. warfarin).*
If your doctor tells you that you have to start taking the medicine containing a Vitamin K antagonist, continue to take Eliquis for at least 2 days after your first dose of the medicine containing a Vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to stop taking Eliquis.

If you take more Eliquis than you should

Tell your doctor immediately if you have taken more than the prescribed dose of Eliquis. Take the medicine pack with you, even if there are no tablets left.

If you take more Eliquis than recommended, you may have an increased risk of bleeding. If bleeding occurs, surgery or blood transfusions may be required.

If you forget to take Eliquis

-Take the tablet as soon as you remember and:
- take the next tablet of Eliquis at the usual time
- then continue as normal.

If you are not sure what to do or have missed more than one dose, ask your doctor, pharmacist or nurse.

If you stop taking Eliquis

Do not stop taking Eliquis without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Eliquis can be given for two different medical conditions. The known side effects and how frequently they occur for each of these medical conditions may differ and are listed separately below. For both conditions, the most common general side effect of Eliquis is bleeding which may be potentially life threatening and require immediate medical attention.

<u>The following side effects are known if you take Eliquis to prevent blood clots from forming after hip or knee replacement operations.</u>

Common side effects (may affect up to 1 in 10 people)

- Anaemia which may cause tiredness or paleness
- Bleeding including:
    - blood in the urine (that stains the urine pink or red)
    - bruising and swelling
    - vaginal bleeding

- Nausea (feeling sick)

Uncommon side effects (may affect up to 1 in 100 people)

- Reduced number of platelets in your blood (which can affect clotting)
- Bleeding including:
    - bleeding occurring after your operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion)
    - bleeding in your stomach, bowel or blood in the stools
    - blood found in the urine
    - bleeding from your nose
- Low blood pressure which may make you feel faint or have a quickened heartbeat
- Blood tests may show:
    - abnormal liver function
    - an increase in some liver enzymes
    - an increase in bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.

Rare side effects (may affect up to 1 in 1000 people)

- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.
- Bleeding:
    - into a muscle
    - in your eyes
    - from your gums and blood in your spit when coughing
    - from your rectum

<u>The following side effects are known if you take Eliquis to prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor.</u>

Common side effects (may affect up to 1 in 10 people)

Bleeding including:
- in your eyes
- in your stomach, bowel or dark/black blood in the stools
- blood found in the urine on laboratory testing
- from your nose
- from your gums
- bruising and swelling

Uncommon side effects (may affect up to 1 in 100 people)

Bleeding including:
- in your brain or in your spinal column
- in your mouth or blood in your spit when coughing
- into your abdomen, into the rectum or from the vagina
- bright/red blood in the stools
- bleeding occurring after any operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site

- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.

Rare side effects (may affect up to 1 in 1000 people)

- bleeding in your lungs or your throat
- bleeding into the space behind your abdominal cavity

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eliquis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eliquis contains

- The active substance is apixaban. Each tablet contains 2.5 mg of apixaban.
- The other ingredients are:
  - Tablet core: **lactose anhydrous**, microcrystalline cellulose, croscarmellose sodium, sodium laurilsulfate, magnesium stearate (E470b).
  - Film coat: **lactose monohydrate**, hypromellose (E464), titanium dioxide (E171), triacetin, yellow iron oxide (E172)

What Eliquis looks like and contents of the pack

The film-coated tablets are yellow, round and marked with “893” on one side and “2½” on the other side.

- They come in blisters in cartons of 10, 20 ,60 and 168 film-coated tablets.
- Unit dose blisters in cartons of 60 x 1 and 100 x 1film-coated tablets for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House,
Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex
UB8 1DH - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l
Loc. Fontana del Ceraso
03012 Anagni (FR)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Eliquis 5 mg film-coated tablets
Apixaban

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eliquis is and what it is used for

Eliquis contains the active substance apixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

Eliquis is used in adults to prevent a blood clot from forming in the heart in patients with an irregular heart beat (atrial fibrillation) and at least one additional risk factor. Blood clots may break off and travel to the brain and lead to a stroke or to other organs and prevent normal blood flow to that organ (also known as a systemic embolism). A stroke can be life-threatening and requires immediate medical attention.

2. What you need to know before you take Eliquis

Do not take Eliquis if:
- **you are allergic** to apixaban or any of the other ingredients of this medicine (listed in section 6)
- you are **bleeding excessively**
- you have a **disease in an organ** of the body that increases the risk of serious bleeding (such as **an active or a recent ulcer** of your stomach or bowel, **recent bleeding in your brain**)
- you have a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy)
- you are **taking medicines to prevent blood clotting** (e.g. warfarin, rivaroxaban, dabigatran or heparin), except when changing anticoagulant treatment or while having a venous or arterial line and you get heparin through this line to keep it open.

Warnings and precautions

Tell your doctor, pharmacist or nurse before you take this medicine if you have any of the following:
- an **increased risk of bleeding**, such as:
    - **bleeding disorders**, including conditions resulting in reduced platelet activity
    - **very high blood pressure,** not controlled by medical treatment
- a **severe kidney disease or if you are on dialysis**
- a **liver problem or a history of liver problems**
  Eliquis will be used with caution in patients with signs of altered liver function.
- if you have a **prosthetic heart valve**

If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask your doctor.

Children and adolescents

Eliquis is not recommended in children and adolescents under 18 years of age.

Other medicines and Eliquis

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the effects of Eliquis and some may decrease its effects. Your doctor will decide, if you should be treated with Eliquis when taking these medicines and how closely you should be monitored.

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:
- some **medicines for fungal infections** (e.g., ketoconazole, etc.)
- some **antiviral medicines for HIV / AIDS** (e.g., ritonavir)
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.)
- **anti-inflammatory** or **pain medicines** (e.g., aspirin or naproxen). Especially, if you are older than 75 years and are taking aspirin, you may have an increased chance of bleeding.
- **medicines for high blood pressure or heart problems** (e.g., diltiazem)

The following medicines may reduce the ability of Eliquis to help prevent blood clots from forming:
- **medicines to prevent epilepsy or seizures** (e.g., phenytoin, etc.)
- **St John's Wort** (a herbal supplement used for depression)
- **medicines to treat tuberculosis** or **other infections** (e.g., rifampicin)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

The effects of Eliquis on pregnancy and the unborn child are not known. You should not take Eliquis if you are pregnant. **Contact your doctor immediately** if you become pregnant while taking Eliquis.

It is not known if Eliquis passes into human breast milk. Ask your doctor, pharmacist or nurse for advice before taking this medicine while breast-feeding. They will advise you to either stop breast-feeding or to stop/not start taking Eliquis.

Driving and using machines

Eliquis has not been shown to impair your ability to drive or use machines.

Eliquis contains lactose (a type of sugar).

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Eliquis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Dose

The recommended dose is one tablet twice a day, for example, one in the morning and one in the evening. Try to take the tablets at the same times every day to have the best treatment effect.

Swallow the tablet with a drink of water. Eliquis can be taken with or without food.

The recommended dose is one tablet of Eliquis **5 mg** twice a day.

The recommended dose is one tablet of Eliquis **2.5 mg** twice a day if:

- you have **severely reduced kidney function**
- **two or more of the following apply to you:**
  - your blood test results suggest poor kidney function (value of serum creatinine is 1.5 mg/dL (133 micromole/l) or greater)
  - you are 80 years old or older
  - your weight is 60 kg or lower.

<u>Your doctor might change your anticoagulant treatment as follows:</u>

- *Changing from Eliquis to anticoagulant medicines*
Stop taking Eliquis. Start treatment with the anticoagulant medicines (for example heparin) at the time you would have taken the next tablet.

- *Changing from anticoagulant medicines to Eliquis*
Stop taking the anticoagulant medicines. Start treatment with Eliquis at the time you would have had the next dose of anticoagulant medicine, then continue as normal.

- *Changing from treatment with anticoagulant containing Vitamin K antagonist (e.g. warfarin) to Eliquis*
Stop taking the medicine containing a vitamin-K antagonist. Your doctor needs to do blood-measurements and instruct you when to start taking Eliquis.

- *Changing from Eliquis to anticoagulant treatment containing Vitamin K antagonist (e.g. warfarin).*
If your doctor tells you that you have to start taking the medicine containing a Vitamin K antagonist, continue to take Eliquis for at least 2 days after your first dose of the medicine containing a Vitamin K antagonist. Your doctor needs to do blood-measurements and instruct you when to stop taking Eliquis.

If you take more Eliquis than you should

Tell your doctor immediately if you have taken more than the prescribed dose of Eliquis. Take the medicine pack with you, even if there are no tablets left.

If you take more Eliquis than recommended, you may have an increased risk of bleeding. If bleeding occurs, surgery or blood transfusions may be required.

If you forget to take Eliquis

- Take the tablet as soon as you remember and:
  - take the next tablet of Eliquis at the usual time
  - then continue as normal.

If you are not sure what to do or have missed more than one dose, ask your doctor, pharmacist or nurse.

If you stop taking Eliquis

Do not stop taking Eliquis without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common general side effect of Eliquis is bleeding which may be potentially life threatening and require immediate medical attention.

Common side effects (may affect up to 1 in 10 people)

Bleeding including:
- in your eyes
- in your stomach, bowel or dark/black blood in the stools
- blood found in the urine on laboratory testing
- from your nose
- from your gums
- bruising and swelling

Uncommon side effects (may affect up to 1 in 100 people)

Bleeding including:
- in your brain or in your spinal column
- in your mouth or blood in your spit when coughing
- into your abdomen, into the rectum or from the vagina
- bright/red blood in the stools
- bleeding occurring after any operation including bruising and swelling, blood or liquid leaking from the surgical wound/incision (wound secretion) or injection site

- Allergic reactions (hypersensitivity) which may cause: swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Contact your doctor immediately** if you experience any of these symptoms.

Rare side effects (may affect up to 1 in 1000 people)

- bleeding in your lungs or your throat
- bleeding into the space behind your abdominal cavity

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eliquis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eliquis contains

- The active substance is apixaban. Each tablet contains 5 mg of apixaban.
- The other ingredients are:
  - Tablet core: **lactose anhydrous**, microcrystalline cellulose, croscarmellose sodium, sodium laurilsulfate, magnesium stearate (E470b).
  - Film coat: **lactose monohydrate**, hypromellose (E464), titanium dioxide (E171), triacetin, red iron oxide (E172).

What Eliquis looks like and contents of the pack

The film coated tablets are pink, oval and marked with “894” on one side and “5” on the other side.

- They come in blisters in cartons of 14, 20 , 56, 60 , 168 and 200 film-coated tablets.
- Unit dose blisters in cartons of 100 x 1 film-coated tablets for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.