ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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:
Each film-coated tablet contains 51.43 mg lactose (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated 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.

4.2 Posology and method of administration

Posology
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.

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

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

Renal impairment
Because 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). 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).

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

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). ALT should be measured as part of the standard pre-operative evaluation (see section 4.4).

Body weight
No dose adjustment required (see section 5.2).

Gender
No dose adjustment required (see section 5.2).

Elderly
No dose adjustment required (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of ELIQUIS in children 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.
- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2)

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, such as: congenital or acquired bleeding disorders; active ulcerative gastrointestinal disease; bacterial endocarditis; thrombocytopenia; platelet disorders; history of haemorrhagic stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery. ELIQUIS administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9).

Renal impairment

Because 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).

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 is to be used with caution in these patients because of a potentially higher bleeding risk (see sections 4.2 and 5.2).

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

Elderly patients
There is limited clinical experience in elderly patients co-administered ELIQUIS with acetylsalicylic acid. This combination 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). ALT should be measured as part of the standard pre-operative evaluation.

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. Strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.5).

Interaction with other medicinal products affecting haemostasis
Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid. Other platelet aggregation inhibitors or other antithrombotic agents are not recommended concomitantly with ELIQUIS (see section 4.5).

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 PK data, 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.

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 moderately inhibiting the apixaban elimination pathways, CYP3A4 and/or P-gp, are expected to increase apixaban plasma concentrations 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
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.

Due to an increased bleeding risk, care is to be taken if patients are treated concomitantly with any other anticoagulants (see section 4.4).

Platelet aggregation inhibitors and NSAIDs
Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was co-administered with acetylsalicylic acid 325 mg once a day.

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

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, acetylsalicylic acid and clopidogrel in a clinical study in patients with acute coronary syndrome. Agents associated with serious bleeding are not recommended concomitantly with ELIQUIS, such as: unfractionated heparins and heparin derivatives (including low molecular weight heparins (LMWH)), Factor Xa inhibiting oligosacchrides (e.g., fondaparinux), direct thrombin II inhibitors (e.g., desirudin), thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran, sulfinpyrazone, vitamin K antagonists, and other oral anticoagulants.

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.

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 directly with apixaban have shown no effect on fertility. However, in the female offspring of pregnant rats treated with apixaban there were decreases in mating and 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

The safety of apixaban has been evaluated in one phase II and three phase III studies including 5,924 patients exposed to apixaban 2.5 mg twice daily undergoing major orthopaedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. As with other anticoagulants, bleeding may occur during apixaban therapy in the presence of associated risk factors such as organic lesions liable to bleed. Common adverse reactions were anaemia, haemorrhage, contusion, and nausea. The adverse reactions should be interpreted within the surgical setting.

Adverse reactions in the one phase II study and the three phase III studies are listed in Table 1 by system organ classification (MedDRA) and by frequency.

Table 1: Adverse reactions in patients undergoing elective hip or knee replacement surgery

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Blood and lymphatic system disorders		
Anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)	Thrombocytopenia (including platelet count decreases)	
Immune system disorders		
		Hypersensitivity
Eye disorders		
		Ocular haemorrhage (including conjunctival haemorrhage)
Vascular disorders		
Haemorrhage (including haematoma, and vaginal and	Hypotension (including procedural hypotension)	

Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
urethral haemorrhage)		
Respiratory, thoracic and mediastinal disorders		
	Epistaxis	Haemoptysis
Gastrointestinal disorders		
Nausea	Gastrointestinal haemorrhage (including haematemesis and melaena), haematochezia	Rectal haemorrhage, gingival bleeding
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	
Musculoskeletal and connective tissue disorders		
		Muscle haemorrhage
Renal and urinary disorders		
	Haematuria (including respective laboratory parameters)	
Injury, poisoning and procedural complications		
Contusion	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	

As with any anticoagulant, 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).

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) [10 times the daily maximum recommended human dose] had no clinically relevant adverse effects.

A preclinical study in dogs demonstrated that oral administration of activated charcoal up to 3 hours after apixaban administration reduced apixaban exposure; therefore, activated charcoal may be considered in the management of apixaban overdose.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

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.

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.

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

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.

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.

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.

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 following elective hip or knee replacement surgery were 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 who received apixaban following elective hip or knee replacement surgery 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. In the offspring of pregnant rats treated with apixaban there were decreases in mating and fertility. These effects were minimal and observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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 of 10 film-coated tablets. Cartons of 10, 20 and 60.

Alu-PVC/PVdC perforated unit dose blisters of 60 x 1 film-coated tablet or 100 x 1 film-coated tablet.

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)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Bristol-Myers Squibb S.R.L
Contrada Fontana del Ceraso
03012 Anagni, Frosinone
Italy

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 6.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

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 tablet
100 x 1 film-coated tablet

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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/0/00/000/000
EU/0/00/000/000
EU/0/00/000/000
EU/0/00/000/000
EU/0/00/000/000

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 film-coated tablets
apixaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/Pfizer EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ELIQUIS 2.5 mg film-coated tablets
apixaban

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.

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.

ELIQUIS is specifically used in adults to help prevent blood clots from forming after hip or knee replacement operations.

2. BEFORE YOU TAKE ELIQUIS

Do not take ELIQUIS if:
- **you are allergic** (hypersensitive) to apixaban or any of the other ingredients of ELIQUIS
- you are **bleeding excessively**
- you have a **liver disease** which leads to increased risk of bleeding (hepatic coagulopathy)

Take special care with ELIQUIS

Tell your doctor 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
  - **an active or a recent ulcer** of your stomach or bowel
  - **infection of the heart** (bacterial endocarditis)
  - **recent bleeding in your brain** (haemorrhagic stroke)

- **very high blood pressure,** not controlled by medical treatment
- **a recent operation on your brain, spinal column or eye**

- a **severe kidney disease or if you are on dialysis**
- a **liver problem or a history of liver problems**
  Your doctor will perform a test on your liver function before you take ELIQUIS and it 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

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

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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** (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)
- **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)

Taking ELIQUIS with food and drink

ELIQUIS can be taken with or without food.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any 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 or pharmacist 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.

Important information about some of the ingredients of ELIQUIS

The tablet 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 ELIQUIS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dose

The usual 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 help you to remember to take them.

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

Swallow the tablet with a drink of water.

You should take one tablet twice a day, every day, for as long as your doctor tells you to take this prescription.

Duration of treatment

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

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 or pharmacist.

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 or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ELIQUIS can cause side effects, although not everybody gets them.
ELIQUIS may cause bleedings which may potentially be life threatening. The bleedings may not be obvious and could possibly lead to anaemia, (a low blood cell count which may cause tiredness or paleness).

Frequencies are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000

Common side effects

- 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

- 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 on laboratory testing
    - 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

- 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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ELIQUIS

Keep out of the reach and sight of children.

Do not use ELIQUIS 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER 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 and 60 film-coated tablets.

Unit dose blisters in cartons of 60 and 100 film-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
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Italy

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

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