BRISTOL-MYERS SQUIBB COMPANY

AND

PFIZER

APIXABAN

EU RISK MANAGEMENT PLAN

Data-lock Point for Current EU RMP: 11-Jan-2018

Version Number: 20.1

Document Date: 19-Sep-2019

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EU RISK MANAGEMENT PLAN (RMP) FOR APIXABAN

RMP version to be assessed as part of this application:

Version Number: 20.1

Data-lock Point for this RMP: 11-Jan-2018

Date of Final Sign-off: 19-Sep-2019

Rationale for submitting an updated RMP:

Reflect the availability of an agent to reverse the anti-factor Xa activity of apixaban in case of the occurrence of a life-threatening Bleeding (important identified risk) during apixaban exposure. In addition, the RMP is updated to reflect the status and results of the long-term open-label extension (LTOLE) phase of the AVERROES study (CV185048; DBL 11-Jan-2018), as per PRAC request during PSUR procedure EMEA/H/C/PSUSA/00000226/201805. The Marketing Authorization Holder (MAH) has also integrated the content of the RMP into the format provided by the European Medicines Agency (EMA) guidance.[1] As a result, several changes are also proposed to the list of safety concerns, as detailed in Section 2.7.2.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	N/A	12.2 / 11-Jun-2014
SII Non-clinical part of the safety specification	N/A	12.2 / 11-Jun-2014
SIII Clinical trial exposure	N/A	13.0 / 07-Jul-2014
SIV Populations not studied in clinical trials	N/A	12.2 / 11-Jun-2014
SV Post-authorization experience	N/A	18.0 / 21-Aug-2017
SVI Additional EU requirements for the safety specification	N/A	14.0 / 19-May-2016
SVII Identified and potential risks	Reflect the availability of an agent to reverse the anti-factor Xa activity of apixaban in case of the occurrence of a life threatening Bleeding (important identified risk) during apixaban exposure. Medication Errors (important potential risk) - reworded to the more specific term "Potential risk of bleeding or thrombosis due to overdose or underdose" Removal of the following from the list of safety concerns:	20.1 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
	• Transient elevation of liver enzymes (important identified risk) • Paediatric patients < 18 years of age (missing information) • AF with valvular disease (missing information) • Patients with prosthetic heart valve (missing information) • Hip fracture surgery (missing information) • Long-term therapy > 3 years (missing information) • Pregnant and/or lactating women (missing information) • Severe hepatic impairment (missing information) • Haemodynamically unstable PE patients (missing information) • Off-label use (missing information) • Black/African American population in AF studies (missing information) • Non-Caucasian and non-Asian ethnicity in VTE prevention studies (missing information)	

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
SVIII Summary of the safety concerns	Medication Errors (important potential risk) - reworded to the more specific term "Potential risk of bleeding or thrombosis due to overdose or underdose" Removal of the following from the list of safety concerns: • Transient elevation of liver enzymes (important identified risk) • Paediatric patients < 18 years of age (missing information) • AF with valvular disease (missing information) • Patients with prosthetic heart valve (missing information) • Hip fracture surgery (missing information) • Long-term therapy > 3 years (missing information) • Pregnant and/or lactating women (missing information) • Severe hepatic impairment (missing information) • Haemodynamically unstable PE patients (missing information) • Off-label use (missing information) • Black/African American population in AF studies (missing information) • Non-Caucasian and non-Asian ethnicity in VTE prevention studies (missing information)	20.1 / pending
Part III Pharmacovigilance Plan	N/A	18.0 / 21-Aug-2017
Part IV Plan for post-authorization efficacy studies	Updated to reflect no post-authorization efficacy studies	20.1 / pending
Part V Risk Minimization Measures	N/A	18.0 / 21-Aug-2017
Part VI Summary of the Risk Management Plan	Aligned with proposed changes in current RMP	20.1 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated to reflect one completed study in the PV programme	20.1 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	Updated to reflect no protocols for proposed, ongoing and completed studies in the PV plan	20.1 / pending
ANNEX 4 Specific adverse drug reaction follow-up forms	Added targeted bleeding questionnaire	20.1 / pending
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	Updated to reflect no studies are conditions or requirements for the MA	20.1 / pending
ANNEX 6 Details of proposed additional risk minimisation activities	N/A	13.0 / 07-Jul-2014
ANNEX 7 Other supporting data	N/A	20.1 / pending
ANNEX 8 Summary of changes to the risk management plan over time	Aligned with proposed changes in current RMP	20.1 / pending

Abbreviations: N/A = not applicable

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 19.0

Approved with procedure: EMEA/H/C/002148/II/050

Date of approval (opinion date): 26-Apr-2018

EU RMP Contact Person: Fanny Pruvot, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Apixaban
Pharmacotherapeutic group(s) (ATC Code)	Anticoagulant, direct Factor Xa inhibitor (B01AF02)
Marketing Authorisation Holder	Bristol-Myers Squibb (BMS)/Pfizer European Economic Interest Grouping (EEIG)
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ELIQUIS
Marketing authorization procedure	Centralised
Brief description of the product	Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of Factor Xa (FXa). It does not require antithrombin III.
Hyperlink to the Product Information	Refer to the proposed Product Information
Indication(s) in the EEA	Current approved indications in the European Union (EU) Summary of Product Characteristics (SmPC) are as follows: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism (SE) 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 (New York Heart Association [NYHA] Class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Table 1-1: Product Details

Dosage in the EEA	**Current:** Prevention of VTE: elective hip or knee replacement surgery The recommended dose of Eliquis is 2.5 mg taken orally (PO) twice daily (BID). 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 SE in patients with NVAF The recommended dose of Eliquis is 5 mg taken PO BID. Dose reduction The recommended dose of Eliquis is 2.5 mg taken PO BID 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 µmole/l). Therapy should be continued long term. Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (eg, recent surgery, trauma, immobilisation). The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in Table 1 below. Table 1: Dose of Apixaban

	Dosing Schedule	Maximum Daily Dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months	2.5 mg twice daily	5 mg

Table 1-1:	Product Details
	of treatment for DVT or PE
	The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.
Pharmaceutical form (s) and strength(s)	**Current:** Film-coated tablets (2.5 and 5 mg)
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Total Knee Replacement and Total Hip Replacement Patients

Table 2.1.1-1: Epidemiologic Characteristics of Total Knee Replacement and Total Hip Replacement Patients

Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery	
Incidence	Total hip replacement (THR) and Total knee replacement (TKR) are common surgical procedures. A 2011 systematic review of the literature including 24 epidemiologic population-based studies of TKR and THR found that the utilization rates for these procedures have increased over the last 2-3 decades. With aging of the population the rates are projected to increase further. Across the United States of America (US) and EU studies included in that review that reported more recent data (year 2000 and beyond), the rates of primary THR ranged from 69 to 131 per 100,000, and the rates of primary TKR ranged from 136 per 100,000 in all age groups to 870 per 100,000 in those 65 years of age or older.[2] THR Based on the data from hip registries in 5 Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) crude country-specific annual incidence of THR (all ages) for 1996–2000 varied between 73 and 90 per 100,000. WHO age-standardized annual incidence (all ages) varied between 61 and 84 per 100,000.[3] TKR In a US study that included patient population with age and sex distributions similar to those of the general US population, the incidence rate of primary TKR was estimated at 11.0 per 10,000 in 2004. The incidence rate of revision TKR was estimated at 0.74 per 10,000 in 2004.[4]

Table 2.1.1-1: Epidemiologic Characteristics of Total Knee Replacement and Total Hip Replacement Patients

Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery

According to US National Hospital Discharge survey between 1990 and 2004, there were approximately 3.8 million primary total knee arthroplasty (revision or partial knee arthroplasty not included) during the study period with the incidence steadily increasing over time:[5]

Prevalence

According to the Nationwide Inpatient Sample database, there were approximately 290,000 THRs in the US between Oct- 2005 and Dec-2006.[6]

Prevalence of THR, incidences of primary THR, and percent revision burden:[7]

Country	Total number	Primary operations	% revision burden	Year
Australia	34,211	30,440	11.02	2005-06
Canada	42,626	39,162	8.13	2003-06
Denmark	8,292	7,244	12.64	2005
England & Wales	65,234	58,962	9.61	2006
Finland	78,175	65,062	16.77	1997-05
France	138,713	120,494	13.13	2005
Germany	218,173	196,391	9.98	2007
Italy	64,180	57,055	11.10	2005
Norway	7,486	6,443	13.93	2007
Scotland	6,891	6,009	12.80	2007
Spain	22,036	19,015	13.71	2005
Sweden	15,679	13,942	11.08	2006
USA	301,181	253,367	15.88	2010*

*projected based on data from 1990-2003

Prevalence of TKR, incidences of primary TKR and percent revision burden:[8]

Table 2.1.1-1: Epidemiologic Characteristics of Total Knee Replacement and Total Hip Replacement Patients

Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery

Country	Total number	Primary operations	% revision burden	Year
Australia	36,466	33,737	7.48	2005-06
Canada	18,055	17,082	5.39	2005-06
Denmark	5,138	4,659	9.32	2006
England & Wales	65,425	62,105	5.07	2006
Finland	68,512	63,266	7.66	1997-05
Germany	145,837	136,262	6.57	2007
Italy	47,574	45,049	5.31	2005
Norway	3,855	3,556	7.76	2007
Scotland	6,678	6,291	5.80	2007
Spain	34,504	32,076	7.04	2005
Sweden	11,149	10,544	5.43	2006
USA	718,257	663,007	7.69	2010*

*projected based on data from 1990-2003

Demographics of the population: age, gender, racial and/or ethnic origin	Over a period from 1990 to 2004, the average age of patients undergoing TKR in the US decreased: • from 69 years in 1990-94 to 67.5 years in 2000-04 • accompanied by a shift from the 65-84 to the 45-64 year old age groups • 63.6% females; 68.9% white[5] Among >110,000 patients in the Nationwide Inpatient Sample database who had a THR between Oct-2005 and Dec-2006, the proportion of females was 53.5%, and 50% were younger than 65 years.[6]
Risk factors for the disease	In the US Nurses' Health Study, higher body mass index and older age were found to significantly increase the risk of THR due to osteoarthritis.[9] The role of obesity is suggested by other studies as well, for example in a study of younger adults (18-59 years of age) obesity was significantly associated with the need for either TKR or THR, confirming the findings from studies in elderly populations.[10]

Table 2.1.1-1: Epidemiologic Characteristics of Total Knee Replacement and Total Hip Replacement Patients

Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery	
Main treatment options	VTE prophylaxis with mechanical and pharmacological methods should be routinely implemented in elective hip or knee replacement surgery. Pharmacological options include low molecular weight heparin (LMWH), warfarin, and novel oral anticoagulants. Mechanical approaches include graduated compression stockings, intermittent pneumatic compression and venous foot. Combination therapy consisting of an antithrombotic agent and mechanical device could be more effective than either alone.[11]
Mortality and morbidity (natural history)	Survival rates for patients undergoing joint replacement has improved over recent decades. A study of ~6,000 patients undergoing THR, TKR, or bilateral TKR in a single Australian institution received physical and chemical prophylaxis against VTE showed fatal in-hospital PE following THR, TKR, or bilateral TKR was 0.05%.[12] The pre-discharge prevalence of DVT within 7 days after THR, TKR, and bilateral TKR was 8.9%, 25.6%, and 36.9%, respectively. The prevalence of symptomatic non-fatal in-hospital PE was 1.2%, 2.8% and 1.9% after THR, TKR, and bilateral TKR respectively.[12] In an Irish hospital, among 4,253 patients undergoing primary joint replacement between Nov-2002 and Nov-2007, the overall death rate, regardless of therapy, was 0.31% (13 of 4253) and the rate of fatal PE was 0.07% (3 of 4253).[13] Both THR and TKR are associated with an immediate, and in the case of THR, prolonged hypercoagulable state with resultant increase in the risk of DVT and VTE.
Important co-morbidities	Data on incidence of comorbidities in elective hip or knee replacement surgery patients are limited. Co-morbidities in patients who have undergone THP or TKP may include hypertension, diabetes mellitus, cancer, fractures, heart failure, peripheral vascular disease, atherosclerosis, peptic ulcer disease and arterial embolism (BMS Study CV185053). In a UK population study including 14,133 patients undergoing THR, fracture risk at 2.5-5 years post-surgery in THR patients was 25% higher compared to that in matched controls without THR. [14] In a global orthopaedic registry with data from 15,020 patients (6,695 THR and 8,325 TKR) in 13 countries, 2.0% and 2.9% had a history of venous thromboembolism.[15] A number of studies describe the prevalence of osteoarthritis and rheumatoid arthritis in THR/TKR patients.

2.1.2 *Atrial Fibrillation Patients*

Table 2.1.2-1: Epidemiologic Characteristics of Atrial Fibrillation Patients

Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).	
Incidence	a) Atrial Fibrillation (AF) is the most common chronic arrhythmia, accounting for one-third of hospitalizations for cardiac rhythm disturbances.[16] b) Incidence increases with age: • < 0.1% per year in those under 40 years old, • > 1.5% per year in women and 2% in men older than 80.[17] c) The incidence of AF is higher in men overall:[18] • In men, approximately 21 per 100,000 person years for age 15-44 years and 1,077 per 100,000 person years for age ≥ 85, • In women, approximately 7 per 100,000 person years for age 15-44 years and 1,204 per 100,000 person years for age ≥ 85. Women appeared to have higher risks for stroke and mortality.[19]
Prevalence	d) Prevalence increases with age, approximately 1-2% for age 55-64 and 14-18% for age 80+ years.[20] e) Approximately 3.2 million Americans had AF in 2005.[21] It was projected that in 2050, approximately 12 million individuals in US would have AF, corresponding to a 2.4-fold increase from year 2000.[22]
Demographics of the population: age, gender, racial and/or ethnic origin	In the Euro Heart Survey in 182 centers from 35 European Society of Cardiology, characteristics of 5,333 patients with AF were:[23] • mean age: 66.7 • gender: women 42% The majority of individuals with non-valvular AF were ≥ 50 years of age and male in a pharmacoepidemiology study of claims database (preliminary data, BMS CV185098).
Risk factors for the disease	Standard AF risk factors have been summarized in the literature as older age, male sex, smoking, obesity, hypertension, diabetes mellitus, myocardial infarction (MI), heart failure; miscellaneous risk factors have been reported to include hyperthyroidism, alcohol use, and exercise[24]
Main treatment options	Warfarin, dabigatran, apixaban, and rivaroxaban are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics.[25]

Table 2.1.2-1: Epidemiologic Characteristics of Atrial Fibrillation Patients

Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).	
Mortality and morbidity (natural history)	In the Framingham Heart Study, individuals with AF had a 1.5- to 1.9-fold increased risk for death, after adjustment for the preexisting cardiovascular conditions with which AF was related.[26] In a retrospective cohort study using the General Practice Research Database (GPRD) in the United Kingdom (UK) 1,035 patients with chronic AF and 5,000 age and sex matched non-AF subjects were followed for a mean follow up period of 2 years. The relative risk of mortality among the AF cohort was 2.5 (95% CI: 2.1-3.0) compared to the general population after adjusting for co-morbidity and major clinical risk factors. When considering only cerebro- and cardio-vascular deaths, the adjusted risk ratio (RR) was 3.7 (95% CI: 3.0-4.7).[27] In the Women's Health Study, among 1011 women who developed incident AF during follow up, the all-cause mortality rate per 1,000 person-year was 10.8 (95% CI: 8.1-13.5) compared to 3.1 (95% CI: 2.9-3.2) among 33711 women who did not develop AF. The rates in the two groups for cardiovascular mortality were 4.3 (95% CI: 2.6-6) and 0.57 (95% CI: 0.5-0.6) respectively. In multivariable analysis the hazard ratios (HR) of new onset AF for all cause-mortality and cardiovascular mortality were 2.14 (95% CI: 1.64-2.77) and 4.18 (95% CI: 2.69-6.51).[28] Among 131,728 subjects with AF or flutter in the Danish National Registry of Patients (328,589 person years of observation), the all-cause mortality rate was 148.5 /1,000 person-years. The rates among male and females were 144.3/1,000 person-years and 153.2/1,000 person-years respectively.[29] In the Copenhagen City Heart Study there were 276 subjects (110 women and 166 men) with AF at baseline among the total study population of 29,310. Among these patients with AF, during a mean follow up of 4.7 years, the crude cardiovascular mortality rates were 61.6/1,000 person-years in women and 52.1/1,000 person years in men. After adjustment of age and relevant comorbidities, AF was a significant risk factor for cardiovascular death in both women (HR 4.4, 95% CI: 2.9-6.6) and men (HR: 2.2, 95% CI: 1.6-3.1) compared to subjects without AF. In multivariate analysis AF was also a significant risk factor for all-cause mortality in both women (HR 2.8, 95% CI: 2-4) and men (HR 1.7, 95% CI: 1.3-2.2).[30] Individuals with AF, including paroxysmal, persistent or permanent, were found to have a 5-fold increased risk of ischaemic stroke incidence and recurrences.[31,32] Other than a higher risk of stroke, AF patients have lower quality of life, and are at higher risks for heart failure, hospitalization and death.[17]

Table 2.1.2-1: Epidemiologic Characteristics of Atrial Fibrillation Patients

Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).	
Important co-morbidities	In claims database studies, AF patients were found to have the following comorbidities:[33,34] (preliminary data, BMS CV185098) • Atrial flutter • Congestive heart failure (CHF) • Arrhythmias/ conduction disorders • Depressive disorder • Stroke • Hypertension • Hyperlipidemia • Diabetes • Coronary artery disease • Peripheral vascular disease • Atherosclerosis • Coronary atherosclerosis • Cancer • Peptic ulcer disease • Peripheral vascular disease • One or more risk factors for stroke Overall, the Euro Heart Survey patient population had less comorbid conditions/diseases as compared to the populations in the claims database studies cited above, presumably as a result from a healthy volunteer effect in the survey participation. On the other hand, the claims studies were designed to include patients with AF and at least one risk factor for stroke, and hence this patient population may have more comorbid conditions. In addition, rule-out diagnoses might also have resulted in over-estimation of the % comorbidities in the claims studies. Data on mortality among AF patients with specific comorbidities are limited. Analysis of Framingham study participants suggests that both pre-existing CHF and subsequently developing (incident) CHF adversely affect survival in AF patients.[35] In that study, death rates in AF patients of both genders who developed subsequent CHF were about 3 times higher versus those without subsequent CHF. Pre-existing CHF was associated with about 2 times higher death rate in AF patients.

2.1.3 Deep Vein Thrombosis and Pulmonary Embolism Patients

Table 2.1.3-1: Epidemiologic Characteristics of Deep Vein Thrombosis and Pulmonary Embolism Patients

Treatment of DVT and/or PE

Incidence

In a one year study of 342,000 inhabitants in western France the overall incidence of VTE was estimated at 183 per 100,000 per year (95% CI 169, 198); the incidence of DVT was 124 per 100,000 per year (95% CI 112, 136) and the incidence of PE was 60 per 100,000 per year (95% CI 52, 69).[36]

In a population-based study in Norway, the incidence rate for first VTE was 143 per 100,000 person-years with incidence of DVT being 93 per 100,000 person-years and incidence of PE estimated at 50 per 100,000 person-years.[37]

In an Italian nation-wide study in the setting of outpatient family medicine, age-adjusted incidence of DVT/PE in 2004 was 96 per 100,000 person-years for males and 117 per 100,000 person-years in females.[38] The incidence peaked in the 60-79 years age group, with substantial decreases among patients aged 80 years and older.

Prevalence

The numbers of prevalent DVT and PE cases in the US and 5 EU countries were estimated and reported[39] as shown in the table below:

	Number of Cases in 2011		Number of Cases in 2012	
	DVT	**PE**	**DVT**	**PE**
US	673,029	338,223	696,969	350,353
UK	144,739	72,773	146,165	73,490
Spain	31,833	16,002	32,345	16,259
Italy	98,175	49,336	99,456	49,980
Germany	195,404	98,197	198,943	99,975
France	153,595	77,223	155,454	78,157

Demographics of the population: age, gender, racial and/or ethnic origin

In the international RIETE registry of 22,133 patients with acute VTE enrolled up to Apr-2008, 10,461 (47%) presented with PE and 11,672 (53%) with DVT.[40] Of all VTE patients, 29% developed this condition in hospital. The demographic characteristics of VTE inpatients and outpatients in the registry population are summarized in the table below.

	Inpatients with VTE (N=6,445)	Outpatients with VTE (N=15,688)
Male gender, %	48%	50%
Mean age (years ± SD)	65±17	65±17
Weight (kg± SD)	73±15	74±14

Table 2.1.3-1: Epidemiologic Characteristics of Deep Vein Thrombosis and Pulmonary Embolism Patients

Treatment of DVT and/or PE

Risk factors for the disease

Understanding of VTE risk factors increased over the past 20 years. As summarized in a literature review by Goldhaber,[41] until recently, risk factors have focused on hospitalized patients and the following were highlighted: general surgery, immobilization, CHF, chronic obstructive pulmonary disease (COPD), and a history of prior VTE. It is now being recognized that additional risk factors should be considered, which overlap with the risk factors for coronary artery disease and are often modifiable. These include cigarette smoking, overweight, metabolic syndrome, hypertension, high red meat consumption, and hyperlipidemia. Goldhaber also summarized clinical risk factors associated with recurrent VTE:

Risk factors for recurrent VTE	
While taking anticoagulants	**After discontinuing anticoagulants**
Immobilization	Male sex
Cancer	Overweight, obesity
COPD	Low high-density lipoprotein cholesterol
	Presenting with symptoms of PE vs. DVT
	Lack of recanalization of DVT on venous ultrasound examination

In RIETE registry including 22,133 patients with acute VTE the prevalence of select risk factors were:[40]

	Inpatients with VTE (N=6,445)	**Outpatients with VTE (N=15,688)**
Surgery, %	18%	10%
Immobility ≥ 4 days, %	28%	23%
Cancer, %	23%	20%
Prior VTE, %	15%	16%

Table 2.1.3-1: Epidemiologic Characteristics of Deep Vein Thrombosis and Pulmonary Embolism Patients

Treatment of DVT and/or PE

Main treatment options

Treatment for VTE has been widely studied, and treatment guidelines have been published and frequently updated by the European Society of Cardiology (ESC), American College of Chest Physicians (ACCP), American College of Emergency Physicians, Eastern Association for the Surgery of Trauma, and Institute for Clinical Systems Improvement.[42, 43,44] Generally, acute treatment consists of LMWH or unfractionated heparin (UFH) for 4 to 5 days, with overlapping therapy with warfarin until an international normalized ratio (INR) of ≥ 2 for two consecutive days is achieved. Anticoagulation should be continued for at least 3 to 12 months, depending on the site of thrombosis and risk factors.[42,44,45,46]

In RIETE registry,[40] the treatment options used among inpatients and outpatients with acute VTE were summarized as follows:

	Inpatients with VTE (N=6,445)	Outpatients with VTE (N=15,688)
Initial therapy, LMWH, %	88%	92%
Initial therapy, UFH, %	10%	6.6%
Initial therapy, thrombolytics, %	0.8%	1.2%
Long-term, VKA drugs, %	69%	70%
Inferior vena cava filter	3.1%	1.8%

Mortality and morbidity (natural history)

VTE patients are at risk for recurrent events, bleeding, and mortality. The cumulative risk of recurrent DVT and PE, major bleeding, fatal PE, fatal bleeding and death from any cause at 3 months following the development of acute VTE event was estimated in the RIETE registry population as follows:[40]

	Inpatients with VTE (N=6,445)	Outpatients with VTE (N=15,688)
Recurrent DVT, %	1.3%	1.0%
Recurrent PE, %	1.3%	1.1%
Major bleeding, %	2.9%	2.1%
Fatal PE, %	2.1%	1.5%
Fatal bleeding, %	0.7%	0.5%
Death, other causes, %	7.0%	5.4%

Important co-morbidities

Inpatients and outpatients with VTE in RIETE registry were found to have the following co-morbidities: chronic lung disease, chronic heart failure, abnormal creatinine levels, recent major bleeding and cancer.

In addition, outpatients with VTE in an Italian study of VTE were found to have the following co-morbidities:[47]

- Transient or definitive paralysis
- Congestive heart failure

Table 2.1.3-1: Epidemiologic Characteristics of Deep Vein Thrombosis and Pulmonary Embolism Patients

Treatment of DVT and/or PE	
	• COPD • Cancer • Stroke • Acute Infection Disease • Intestinal Inflammatory Diseases • Superficial venous thrombosis • Rheumatic diseases • Neurological diseases
	Literature suggests a high prevalence of overweight and obesity in VTE patients. For example, of the 10,114 acute VTE patients enrolled in RIETE registry as of March 2007, 43% were overweight and 27% of patients were obese.[48]
	No epidemiological data on mortality rates in VTE patients by specific comorbidity were identified.
	However, literature suggests that VTE patients with select comorbidities are at increased risk of mortality. For example, in Worcester Venous Thromboembolism Study outpatients with PE who had a history of congestive heart failure, active cancer or severe infection were at increased risk of death at 90 days after the index PE event (HRs 4.16, 5.03 and 3.27 respectively).[49]

2.2 Nonclinical Part of the Safety Specification

The scope and results of the nonclinical toxicity and exposure studies support the clinical use of apixaban at the proposed dose and dosing regimen.

A comprehensive battery of nonclinical toxicity studies, including single- and repeat-dose oral studies in rodents (mouse, rat) and non-rodents (dog, monkey), in vitro and in vivo genetic toxicity studies, reproductive (rat) and developmental (mouse, rat, rabbit) toxicity studies; juvenile toxicity studies (rat) and carcinogenicity studies (mouse, rat) were completed to evaluate the potential toxicity of apixaban.

All pivotal nonclinical toxicology apixaban studies were conducted in compliance with Good Laboratory Practice regulations and according to International Conference on Harmonisation guidelines.

Apixaban was not genotoxic, had no effects on safety pharmacology endpoints that evaluated cardiovascular, neurological, or respiratory functions, and was not phototoxic. Apixaban did not directly impair fertility and is not a teratogen. Nonclinical toxicity studies demonstrated that apixaban was well-tolerated across species at systemic exposures ≤ 30× or ≤ 11× the AUC at the RHDs of 5 mg (2.5 mg BID) or 10 mg (5 mg BID), respectively.

Apixaban is excreted into rat milk.[50] In nursing rats receiving [^{14}C] apixaban (5 mg/kg), the concentration vs. time curve of radioactivity in milk paralleled that in plasma with concentrations in milk being 30-fold higher (based on 24-hour AUC) than those in plasma, possibly due to active transport into the milk. Apixaban constituted 96.0 to 99.4% of the radioactivity in milk. It is unknown whether apixaban or its metabolites are excreted in human milk.

Safety specifications for nonclinical findings are summarized in Table 2.2-1.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Bleeding	
In animal models of thrombosis, apixaban demonstrated antithrombotic efficacy at intravenous doses (≤ 0.3 mg/kg/hr) that resulted in modest (≤ 2-fold) changes in standard coagulation assays. Substantial prevention of both venous and arterial thrombosis was achieved at apixaban doses that produced minor (< 2-fold) changes in bleeding times, while higher doses resulted in more pronounced increases in clotting times and bleeding times. In a dog model of thrombosis and haemostasis, antithrombotic effects were observed at plasma apixaban concentrations 16-fold lower than those associated with > 2-fold increase in bleeding times. By contrast, the maximum thrombus reductions in rats were observed at apixaban concentrations that overlapped with those that caused 2- to 3-fold increases in bleeding times.	Based on the observed overlap between apixaban exposures associated with antithrombotic effects and those that resulted in increased coagulation and bleeding times in animal models of thrombosis, apixaban treatment may result in dose-dependent bleeding events in humans at clinically-relevant doses.
In rats (≤ 6 months dosing) or dogs (≤ 1 year dosing) given apixaban, AUC multiples were ≤ 11× or ≤ 44×, respectively, the AUC at the RHD of 10 mg (5 mg BID) for AF/chronic VTE treatment and ≤ 30× or ≤ 114×, respectively, the AUC at the RHD of 5 mg (2.5 mg BID) for VTE prevention. The principal findings were non-adverse, mildly prolonged PT and aPTT related to expected pharmacology of apixaban without overt bleeding or haemorrhage.	
In cynomolgus monkeys, 2 females at 300 mg/kg died and 1 male at 100 mg/kg was sacrificed in moribund condition due to excessive haemorrhage at the bleeding site likely due to inadvertent puncture of the femoral artery complicated by the presence of apixaban.	
Liver-related findings	
No microscopic evidence of hepatotoxicity has been reported in any of the animal toxicity studies, including chronic toxicity studies in rats dosed for ≤ 6 months at AUC multiples ≤ 11× or ≤ 30× or in dogs dosed ≤ 1 year at AUC multiples of ≤ 44× or ≤ 114× relative to the AUC at the RHD of 10 mg (5 mg BID) for AF/chronic VTE treatment or 5 mg (2.5 mg BID) for VTE prevention, respectively.	None. No clinically relevant nonclinical liver-related findings have been observed.
In a 2-week exploratory study in dogs, minimal increases (~2× relative to pretest) in serum ALT, GGT, and AP activities were observed in 2 of 8 treated dogs without a gross or histopathologic correlate.	

2.3 Clinical Trial Exposure

Apixaban has been studied in a comprehensive clinical development programme in multiple Phase 1, 2, and 3 studies. The evaluation of safety of apixaban is based on analyses of clinical data from

orthopaedic VTE prevention studies, AF studies, and other non-AF studies (eg, acute coronary syndrome [ACS]) as well as VTE treatment and prevention studies. An overview of the pivotal clinical trials in the apixaban programme summarized in this RMP supporting the safe and effective use of apixaban is in Table 2.3-1.

Table 2.3-1: Apixaban Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
Apixaban monotherapy 2.5 mg or 5 mg BID		
CV185035 (THR Orthopaedic VTE Prevention)	A Phase 3, Randomized, Double-blind, Active-controlled, Parallel-group, Multi-center Study to Evaluate the Safety and Efficacy of Apixaban in Subjects Undergoing Elective Total Hip Replacement Surgery (The Advance-3 Study Apixaban Dosed Orally Versus AntiCoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism)	Apix: 2673 Enox: 2659
CV185047 (TKR Orthopaedic VTE Prevention)	A Phase 3, Randomized, Double-blind, Active-controlled (Enoxaparin 40 mg QD), Parallel group, Multi-center Study to Evaluate the Safety and Efficacy of Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery	Apix: 1501 Enox: 1508
CV185034 (TKR Orthopaedic VTE Prevention)	A Phase 3 Randomized, Double-Blind, Active-Controlled (Enoxaparin), Parallel-Group, Multi-Center Study to Evaluate the Safety and Efficacy of Oral Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery	Apix: 1596 Enox: 1588
CV185010 (TKR Orthopaedic VTE Prevention)	A Phase 2 Randomized Double-Blind (BMS-562247 and Enoxaparin), Active-Controlled (Enoxaparin and Warfarin), Parallel-Arm, Dose-Response Study of The Oral Factor Xa Inhibitor BMS-562247 in Subjects Undergoing Elective Total Knee Replacement Surgery	Apix: 917 Enox: 149 Warf: 151
CV185030 (AF)	A Phase 3, Active (Warfarin) Controlled, Randomized, Double-blind, Parallel Arm Study to Evaluate the Efficacy and Safety of Apixaban in Preventing Stroke and Systemic Embolism in Subjects with Non-valvular Atrial Fibrillation	Apix: 9088 Warf: 9052
CV185048 (AF)	Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double-Blind Study	Apix: 2798 ASA: 2780
CV185067 (AF)	A Phase 2b, Randomized, Partially Blind (Open Label Warfarin), Active-Controlled (Warfarin), Multicenter Study to Evaluate the Safety and Efficacy in 2 Doses of Apixaban in Comparison to Warfarin, Administered for 12 Weeks in Subjects with NVAF	Apix: 143 Warf: 75
CV185068 (Secondary Prevention of ACS)	A Phase 3, Randomized, Double-Blind Evaluation of the Safety and Efficacy of Apixaban in Subjects with a Recent Acute Coronary Syndrome	Apix: 3672 Placebo: 3643

Table 2.3-1: Apixaban Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
CV185023 (Secondary Prevention of ACS)	A Phase 2, Placebo-Controlled, Randomized, Double-Blind, Parallel-Arm, Dose Ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients with a Recent Acute Coronary Syndrome	Apix: 1092 Placebo: 599
CV185070 (Secondary Prevention of ACS)	A Phase 2, Placebo-Controlled, Randomized, Double-Blinded, Multicenter, Study to Evaluate the Bleeding Profile of 2.5 mg and 5.0 mg BID Apixaban in Combination with Standard Therapy in Patients with Recent (<=7 Days) Acute Coronary Syndrome (ACS)	Apix: 98 Placebo: 51
CV185017 (VTE)	A Phase 2 Randomized, Parallel-Arm Study of Oral Direct Factor Xa-Inhibitor Apixaban and Low Molecular Weight Heparin, or Fondaparinux with a Vitamin K Antagonist in Subjects with Acute Symptomatic Deep Vein Thrombosis	Apix: 385 LMWH/Fond and VKA: 126
CV185056 (VTE)	A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism	Apix: 2676 Enox/Warf: 2689
CV185057 (VTE)	A Safety and Efficacy Trial Evaluating the Use of Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism	Apix: 1651 Placebo: 826
CV185027 (VTE prevention in subjects with metastatic cancer)	A Randomized, Double-Blind, Placebo-Controlled Study of Apixaban for the Prevention of Thromboembolic Events in Patients Undergoing Treatment for Advanced Cancer: A Phase 2 Pilot Study	Apix: 93 Placebo: 29
CV185036 (VTE prevention in acute mental illness	A Phase 3 Randomized, Double-blind, Parallel-group, Multi-center Study of the Safety and Efficacy of Apixaban for Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Subjects During and Following Hospitalization	Apix: 3184 Enox: 3217

Abbreviations: apix = apixaban; enox = enoxaparin; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; warf = warfarin

2.3.1 All Orthopaedic VTE Prevention Studies (Pooled CV185035/ CV185047/ CV185034/ CV185010)

Pooled exposure analysis for the 4 orthopaedic VTE prevention studies (CV185010, CV185034, CV185035, and CV185047) are summarized in Table 2.3.1-1, Table 2.3.1-2, and Table 2.3.1-3

An exposure table presented by race and gender for the pooled VTE prevention orthopaedic studies is included in Appendix 2.

Table 2.3.1-1: Duration of Exposure, Not Taking Into Account Interruptions for Treated Subjects (Pooled CV185010, CV185034, CV185035, and CV185047)

Length of Exposure (Days)	APIX 2.5MG BID N = 5924		ENOX N = 5904	
	Persons*	Person-time**	Persons*	Person-time**
0-3	5924	48.0	5904	47.9
4-6	5759	47.0	5752	47.0
7-9	5667	46.3	5658	46.2
10-14	5490	61.5	5450	61.2
15-21	2743	48.9	2719	48.4
22-28	2502	47.8	2478	47.3
29-31	2481	20.3	2453	20.1
32-38	2456	33.1	2411	32.8
>38	213	2.0	188	1.0

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the patients entering interval i = number of patients with exposure >= lower bound of interval i
** is the patient-years within interval i = for patients entering interval i, sum of individual exposures within interval i (in days) divided by (365.25)

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposurevtep-v02.sas 25JUN2013:16:58:53

Table 2.3.1-2: Clinical Exposure, Not Taking Into Account Interruptions, by Age Group and Gender Treated Subjects (Pooled CV185010, CV185034, CV185035, and CV185047)

Age Category (Years)	APIX 2.5MG BID N = 5924				ENOX N = 5904			
	Persons*		Person-time**		Persons*		Person-time**	
	M	F	M	F	M	F	M	F
<65	1287	1684	91.9	103.4	1249	1714	90.4	103.4
65–<75	734	1274	43.3	68.2	720	1265	42.5	66.1
>=75	316	629	16.8	31.6	329	627	18.2	31.2

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of the each category

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposurevtepag-v02.sas 25JUN2013:16:59:15

Table 2.3.1-3: Clinical Exposure, Not Taking Into Account Interruptions, by Special Population Treated Subjects (Pooled CV185010, CV185034, CV185035, and CV185047)

Renal Impairment

	APIX 2.5MG BID N = 5924		ENOX N = 5904	
	Persons*	Person-time**	Persons*	Person-time**
SEVERE OR MODERATE	314	16.3	322	17.3
MILD	1818	104.6	1856	106.9
NORMAL	3726	230.5	3671	225.0

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of the each category

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposurevteps-v02.sas 25JUN2013:16:59:25

2.3.2 AF Studies (CV185030/ CV185048/ CV185067)

Data are not pooled for the AF studies due to the significant differences in study design. Exposure tables presented by duration of exposure, age group and gender, and special populations for Study CV185030 and Study CV185048 are presented in Table 2.3.2-1 through Table 2.3.2-6. Exposure tables presented by race and gender are included in Appendix 2.

In the LTOLE period of Study CV185048, the mean extent of exposure to apixaban for all subjects was 147.4 weeks, and the total length of exposure to apixaban was 1321.4 patient-years. Subjects who were randomized to apixaban in the double-blind treatment period of this study and continued on in the LTOLE period had a mean total extent of exposure to apixaban in both periods of 231.0 weeks, whereas subjects randomized to ASA in the double blind treatment period had a mean extent of exposure to apixaban of 147.5 weeks (Table 2.3.2-7).

In the Phase 2, CV185067, the mean extent of exposure to double-blind apixaban was 79 days in the 2.5 mg dose group and 80 days in the 5 mg dose group. The mean exposure to open-label warfarin was 77 days.[51]

Table 2.3.2-1: Duration of Exposure, Not Taking Into Account Interruptions - Treated Subjects (CV185030)

Length of Exposure (Weeks)	Apixaban N = 9088		Warfarin N = 9052	
	Persons*	Person-time**	Persons*	Person-time**
<1	9088	148.5	9052	147.8
1-<4	8971	510.3	8938	507.8
4-<26	8797	3563.0	8746	3517.0
26-<52	8191	3945.5	8006	3852.4
52-<78	7687	3304.3	7469	3226.8
78-<104	5474	2193.0	5328	2120.8
104-<130	3153	1173.3	3055	1136.5
130-<156	1570	531.6	1540	512.4
>=156	562	164.6	525	162.5

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the patients entering interval i = number of patients with exposure >= lower bound of interval i
** is the patient-years within interval i = for patients entering interval i, sum of individual exposures within interval i (in days) divided by (365.25)

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposureaf030-v02.sas 25JUN2013:16:56:29

Table 2.3.2-2: Duration of Exposure, Not Taking Into Account Interruptions - Treated Subjects (CV185048 - double-blind treatment period)

Length of Exposure (Weeks)	APIXABAN N = 2798		ASA N = 2780	
	Persons*	Person-time**	Persons*	Person-time**
<1	2798	45.7	2780	45.5
1-<4	2765	157.7	2750	156.7
4-<26	2724	1092.6	2698	1074.6
26-<52	2494	1059.1	2442	1043.5
52-<78	1688	583.3	1692	586.4
78-<104	730	216.6	736	208.3
104-<130	216	37.4	186	34.7
130-<156	9	0.5	8	0.8
>=156	0	0.0	0	0.0

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the patients entering interval i = number of patients with exposure >= lower bound of interval i
** is the patient-years within interval i = for patients entering interval i, sum of individual exposures within interval i (in days) divided by (365.25)

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposureaf048-v02.sas 25JUN2013:16:57:44

Table 2.3.2-3: Clinical Exposure, Not Taking Into Account Interruptions, by Age Group and Gender Treated Subjects (CV185030)

Age Category (Years)	Apixaban N = 9088				Warfarin N = 9052			
	Persons*		Person-time**		Persons*		Person-time**	
	M	F	M	F	M	F	M	F
<65	1994	729	3544.1	1274.7	1971	761	3500.3	1306.9
65–<75	2236	1293	3904.0	2191.8	2274	1227	3900.6	2057.9
>=75	1638	1198	2676.3	1943.0	1634	1185	2600.6	1817.8

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of the each category

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposureaf030ag-v02.sas 25JUN2013:16:56:49

Table 2.3.2-4: Clinical Exposure, Not Taking Into Account Interruptions, by Age Group and Gender Treated Subjects (CV185048 - double-blind treatment period)

Age Category (Years)	Apixaban N = 2798				ASA N = 2780			
	Persons*		Person-time**		Persons*		Person-time**	
	M	F	M	F	M	F	M	F
<65	592	263	689.4	305.0	594	268	707.1	313.0
65-<75	595	449	694.3	521.9	518	417	594.9	475.3
>=75	469	430	504.6	477.5	501	482	540.1	520.1

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of the each category

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposureaf048ag-v02.sas 25JUN2013:16:57:51

Table 2.3.2-5: Clinical Exposure, Not Taking Into Account Interruptions, by Special Population Treated Subjects (CV185030)

Renal Impairment	Apixaban N = 9088		Warfarin N = 9052	
	Persons*	Person-time**	Persons*	Person-time**
SEVERE OR MODERATE	1493	2312.2	1512	2271.9
MILD	3807	6493.9	3758	6302.3
NORMAL	3750	6660.5	3746	6547.8

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of the each category

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposureaf030s-v02.sas 25JUN2013:16:57:21

Table 2.3.2-6: Clinical Exposure, Not Taking Into Account Interruptions, by Special Population Treated Subjects (CV185048 - double-blind treatment period)

Renal Impairment	Apixaban N = 2798		ASA N = 2780	
	Persons*	Person-time**	Persons*	Person-time**
SEVERE OR MODERATE	544	567.3	536	561.2
MILD	1068	1221.2	1072	1190.1
NORMAL	953	1134.4	919	1108.4

Exposure (in days) calculated as last dose of blinded study drug-first dose of blinded study drug + 1
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of the each category

Program Source: /gbs/prod/clin/programs/cv/185/rmp/may2013/rpt/rt-ex-exposureaf048s-v02.sas 25JUN2013:16:58:37

Table 2.3.2-7: Clinical Exposure, Not Taking Into Account Interruptions (CV185048 - subjects who entered long-term open label extension period)

	Randomized to Apixaban (DB and LTOLE) N = 1669	Randomized to ASA (LTOLE period only) N = 1606	Randomized to Apixaban (LTOLE period only) N = 1669	All Subjects (LTOLE period only) N = 3275
Length of Exposure Weeks (%)				
< 1	0	2 (0.1)	3 (0.2)	5 (0.2)
1 to < 4	0	8 (0.5)	10 (0.6)	18 (0.5)
4 to < 26	0	64 (4.0)	83 (5.0)	147 (4.5)
26 to < 52	5 (0.3)	78 (4.9)	84 (5.0)	162 (4.9)
52 to < 78	34 (2.0)	88 (5.5)	68 (4.1)	156 (4.8)
78 to < 104	65 (3.9)	84 (5.2)	93 (5.6)	177 (5.4)
104 to < 130	72 (4.3)	115 (7.2)	114 (6.8)	229 (7.0)
130 to < 156	67 (4.0)	331 (20.6)	349 (20.9)	680 (20.8)
156 to < 208	278 (16.7)	667 (41.5)	672 (40.3)	1339 (40.9)
208 to < 260	536 (32.1)	127 (7.9)	135 (8.1)	262 (8.0)
260 to < 312	484 (29.0)	10 (0.6)	18 (1.1)	28 (0.9)
312 to < 364	76 (4.6)	32 (2.0)	40 (2.4)	72 (2.2)
364 to < 416	51 (3.1)	0	0	0
416 to < 468	1 (<0.1)	0	0	0
≥ 468	0	0	0	0
Mean (SD)	231.0 (68.82)	147.5 (61.42)	147.2 (64.08)	147.4 (62.78)
Median	240.1	156.9	156.6	156.7
Min, max	(35.6, 419.7)	(0.1, 343.3)	(0.3, 346.4)	(0.1, 346.4)

Table 2.3.2-7: Clinical Exposure, Not Taking Into Account Interruptions (CV185048 - subjects who entered long-term open label extension period)

	Randomized to Apixaban (DB and LTOLE) N = 1669	Randomized to ASA (LTOLE period only) N = 1606	Randomized to Apixaban (LTOLE period only) N = 1669	All Subjects (LTOLE period only) N = 3275
Total patient-years	1055.8	648.5	672.8	1321.4

The denominator to calculate each percentage is the total number of treated subjects who entered LTOLE Period.

Duration of exposure (in days) is calculated as last open-label dose date - first double-blind dose date + 1 for subjects randomized to the apixaban group counting both DB and LTOLE period; and as the last open-label dose date of apixaban - first open-label dose date of apixaban + 1 for subjects randomized to the ASA group and for subjects randomized to the apixaban group counting LTOLE period only; to obtain exposure in weeks divide by 7.

Source: Table 6.1-1 of the CV185048 LTOLE Final Study Report

2.3.3 VTE Treatment Studies (CV185017/ CV185056/CV185057)

Table 2.3.3-1: Duration of Exposure, Not Taking Into Account Interruptions (Combined 2.5 mg and 5 mg Apixaban Doses) - Treated Subjects (Pooled CV185017, CV185056, and CV185057)

	Apixaban[1] N = 4455		Comparator N = 3641	
Length of exposure (days)	Persons[2]	Person-time (yrs)[3]	Persons[2]	Person-time (yrs)[3]
0-30	4455	354.8	3641	287.6
31-91	4241	693.5	3407	554.5
92-182	3979	885.6	3152	680.1
183-365	1537	714.0	723	329.2
>365	190	2.9	88	2.3

Source: SCE Table 1.1.1
Exposure (in days) calculated as last dose of blinded study drug – first dose of blinded study drug + 1.
1. 5 mg group includes 7 days of dosing at 10 mg in CV185056.
2. Persons is the number of patients entering interval with exposure >= lower bound of interval.
3. Patient-years = sum of individual exposures within interval (in days) divided by (365.25).

Table 2.3.3-2: Duration of Exposure, Not Taking Into Account Interruptions (2.5 mg Apixaban Dose) - Treated Subjects (CV185057)

	Apixaban N = 840		Comparator N = 826	
Length of exposure (days)	Persons[1]	Person-time (yrs)[2]	Persons[1]	Person-time (yrs)[2]
0-30	840	68.1	826	66.9
31-91	821	134.9	800	129.7
92-182	791	193.9	759	180.4
183-365	767	365.3	697	326.4
>365	104	1.7	86	1.6

Source: SCE Table 1.1.2
1. Persons is the number of patients entering interval with exposure >= lower bound of interval.
2. Patient-years = sum of individual exposures within interval (in days) divided by (365.25).

Table 2.3.3-3: Extent of Exposure, Not Taking Into Account Interruptions (5 mg Apixaban Dose) - Treated Subjects (Pooled CV185017, CV185056, and CV185057)

	Apixaban[1] N = 3615		Comparator N = 3641	
Length of exposure (days)	Persons[2]	Person-time (yrs)[3]	Persons[2]	Person-time (yrs)[3]

Table 2.3.3-3: Extent of Exposure, Not Taking Into Account Interruptions (5 mg Apixaban Dose) - Treated Subjects (Pooled CV185017, CV185056, and CV185057)

	Apixaban[1] N = 3615		Comparator N = 3641	
0-30	3615	286.7	3641	287.6
31-91	3420	558.7	3407	554.5
92-182	3188	691.6	3152	680.1
183-365	770	348.7	723	329.2
>365	86	1.2	88	2.3

Source: SCE Table 1.1.3
1. 5 mg group includes 7 days of dosing at 10 mg in CV185056.
2. Persons is the number of patients entering interval with exposure >= lower bound of interval.
3. Patient-years = sum of individual exposures within interval (in days) divided by (365.25).

Table 2.3.3-4 and Table 2.3.3-5 provide exposure for the subgroups of age and gender, and renal impairment, respectively. The exposure in the age and gender subgroup was consistent across treatment groups, with more male than female subjects receiving study treatment, the majority of subjects being less than 65 years of age, and more female than male subjects aged 75 years or older receiving study treatment. The exposure in the renal impairment subgroup was also consistent across treatment groups with the majority of subjects having normal renal function and limited exposure in subjects with moderate or severe renal impairment.

Table 2.3.3-4: Extent of Exposure, Not Taking Into Account Interruptions by Age Group and Gender - Treated Subjects (Pooled CV185017, CV185056, and CV185057)

	Apixaban N = 4712				Comparator N = 3641			
	Persons[1]		Person-time (yrs)[2]		Persons[1]		Person-time (yrs)[2]	
Age category (years)	M	F	M	F	M	F	M	F
<65	1888	1195	1109.6	699.1	1459	915	743.3	480.7
65 to <75	534	412	295.7	238.5	434	330	219.3	163.3
>=75	333	350	175.0	188.9	245	258	121.7	125.3

Source: SCE Table 1.2
Exposure (in days) calculated as last dose of blinded study drug – first dose of blinded study drug + 1.
1. Persons is the number of patients entering interval with exposure >= lower bound of interval.
2. Patient-years = sum of individual exposures within interval (in days) divided by (365.25).

Table 2.3.3-5: Extent of Exposure, Not Taking Into Account Interruptions by Renal Impairment - Treated Subjects (Pooled CV185017, CV185056, and CV185057)

	Apixaban N = 4712		Comparator N = 3641	
Renal impairment	Persons[1]	Person-time (yrs)[2]	Persons[1]	Person-time (yrs)[2]
Severe or moderate	286	151.4	219	100.8
Mild	981	550.0	759	394.2
Normal	3125	1858.9	2402	1241.9

Source: SCE Table 1.3
Exposure (in days) calculated as last dose of blinded study drug – first dose of blinded study drug + 1.
1. Persons is the number of patients.
2. Patient-years = sum of individual exposures within interval (in days) divided by (365.25).

2.3.4 Extent of Exposure in Completed, Concluded and Ongoing Studies in Other Indications

Exposure tables for subjects who were treated with apixaban for ACS and venous thromboembolism prevention in completed non-orthopaedic studies are presented in Appendix 2.

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Key exclusion criteria for the majority of completed clinical studies are presented in Table 2.4.1-1.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Bleeding, high risk for bleeding or coagulation disorder[a,b,c]	As an anticoagulant, apixaban is expected to produce a dose-dependent increase in the risk of bleeding	No	Bleeding is included as an important identified risk
MI, uncontrolled hypertension[a,b,c]	Comorbid conditions with potential for increased risk of bleeding	No	Bleeding is included as an important identified risk
Pregnant, breastfeeding or positive pregnancy test[a,b,c]	Effect on fetus and breastfeeding is unknown	Yes	N/A

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Active and clinically significant hepatobiliary disease[a,c]	Hepatic disease may be associated with coagulopathy and clinically relevant bleeding risk	No	Bleeding is included as an important identified risk. Liver Injury is included as an important potential risk
History of thrombocytopaenia[a]	Comorbid condition with potential for increased risk of bleeding	No	Bleeding is included as an important identified risk
Age <18 years[a]	Initial clinical development limited to adult patients	No	Initial clinical development limited to adult patients
ALT or AST > 2X ULN or a Total Bilirubin ≥ 1.5x ULN (no alternative causative factor eg, Gilbert's syndrome)[b]	Elevation of liver enzymes may be associated with an increased bleeding risk	No	Liver injury is included as an important potential risk
Severe renal insufficiency (calculated CrCL < 25 mL/min)[b]	Apixaban plasma concentrations may be increased in patients with severe renal impairment which may lead to an increased bleeding risk	Yes	N/A
Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine)[b]	Concomitant medications with potential for increased risk of bleeding	No	Bleeding is included as an important identified risk
Use of acetylsalicylic acid (ASA) > 165 mg/day[c]	Puts patient at a higher bleeding risk	No	Bleeding is included as an important identified risk
Subjects with indications for long-term treatment with a VKA, other than VTE[c]	Anticoagulants known to increase risk of bleeding	No	Bleeding is included as an important identified risk
Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT (in VTE treatment studies)[c]	These VTE treatments may influence primary endpoints of VTE studies	No	May influence study results

Abbreviations: ALT = alanine aminotransaminase, ASA = acetylsalicylic acid, AST = aspartate aminotransferase, CrCL = creatinine clearance, DVT = deep vein thrombosis, N/A = not applicable, VKA = vitamin k antagonist, VTE = venous thromboembolism, ULN = upper limit of normal

[a] Orthopaedic VTE Prevention Studies

[b] Atrial Fibrillation Studies

[c] VTE Treatment Studies

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical trial development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Post-marketing safety monitoring and epidemiology studies will support the identification of these reactions.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
Patients with hepatic impairment	Mild: 8 subjects
	Moderate: 8 subjects
	Severe: Not included in the clinical development programme
Patients with renal impairment	Mild: 10 subjects
	Moderate: 7 subjects
	Severe:143 subjects
	End stage renal disease: 8 subjects
Patients with cardiovascular impairment	Apixaban adequately studied in patients with cardiovascular impairment including heart failure, coronary arterial disease, peripheral arterial disease, and hypertension
Immunodeficient patients	Not included in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Population with relevant different ethnic origin	6048 subjects
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme
Children[a]	Not included in the clinical development programme
Elderly[b]	39139 subjects

[a] Ongoing paediatric studies are excluded from the list of pivotal clinical studies.

[b] Elderly > 64 years of age

2.5 Post-Authorization Experience

2.5.1 Post-authorization Exposure

2.5.1.1 Method Used to Calculate Exposure

Important Notes:

There is no readily available information on the actual number of patients treated with apixaban during the reporting period. However, an estimate of the number of treated patients is derived from available sales figures.

Approved vendors (eg, Intercontinental Marketing Services [IMS] Health) provide sales figures to BMS for apixaban on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk of the Company' s worldwide sales of apixaban, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. The sales data only capture an estimated 80% - 85% of the true total worldwide sales data. Additionally, the sales data from vendors (eg, IMS Health) may vary from one reporting period to another because of changes in subscription agreements and changes to the number of data channels available within a given country.

2.5.1.2 Exposure

Apixaban has a well-characterized safety profile that is consistent across approved indications. The estimated cumulative patient exposure is derived from sales figures received from IMS Health and is an approximation of total quantity of ELIQUIS sold during the period from IBD (18-May-2011) to 31-Dec-2017, inclusive. However, the calculation of cumulative exposure from sales data is complicated by the presence of 3 separate "phases" of post-marketing exposure since the IBD, predicated by successive indication approvals:

- Periodic Safety Update Report (PSUR) 1-3 exposure estimated using 100% VTE prevention (the only indication approved at that time)
- PSUR (Periodic Benefit-Risk Evaluation Report [PBRER] format) 4-7 exposure estimated using a sales breakdown of 90% NVAF, 10% VTE prevention
- PSUR (PBRER format) 8-13 exposure estimated using a sales breakdown of 95% NVAF, 3.5% VTE prevention, and 1.5% VTE treatment

Cumulatively, the total number of patients exposed to commercial ELIQUIS during the period 18-May-2011 to 31-Dec-2017 is estimated to be 18,898,004 patients. This number also equals the estimated patient-years of exposure to apixaban during this period. This is an estimate and should be interpreted with caution, taking into account the above-mentioned limitations.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Apixaban is not a controlled substance and it is to be administered with a prescription under medically controlled conditions. The potential for illegal use is unlikely. Consistent with other

antithrombotic/anticoagulant agents, there is no evidence that suggests a risk for abuse of apixaban. Symptoms of withdrawal/rebound have not been investigated or reported in apixaban clinical trials.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP[52] (V6.0; 2011) are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Bleeding
	Transient elevation of liver enzymes
Important potential risks	None
Missing information	Paediatrics
	Pregnant/lactating women
	Severe hepatic impairment
	Severe renal impairment
	Hip fracture surgery
	Non-Caucasian and non-Asian ethnicity
	Off-label use

Source: Apixaban Risk Management Plan version 6.0

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Apixaban has a well-characterized safety profile that is consistent across approved indications and is reflected in the SmPC under Sections 4.4 and 4.8. New safety findings that are not categorized as either identified or potential risks in the list of safety concerns will be described, as applicable.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Bleeding	The most clinically significant treatment-related ARs associated with apixaban are bleeding ARs. Severe bleeding ARs were low in frequency. The majority of bleeding-related events observed were non-serious and were mild to moderate in severity. As with any anticoagulant, the use of apixaban 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.
Transient Elevation of Liver Enzymes	Liver safety was designated as an event of special interest due to observations of unfavourable effects with other novel oral anticoagulants, specifically the thrombin inhibitor, ximelagatran. Liver-related ARs, SARs, and laboratory abnormalities are low in frequency. Serious outcomes of elevations in liver tests include hepatitis, hepatotoxicity, liver failure requiring liver transplantation and/or with potential fatal outcome. The majority of transient elevations of liver enzymes either resolved while study drug continued or during follow-up period.
Important potential risks	
None	N/A
Missing Information	
Paediatrics	Paediatric subjects were excluded in the studies. The safety and efficacy of apixaban in paediatric subjects below the age of 18 years were not established.
Pregnancy and/or lactating women	There are limited amounts of data from the use of apixaban in pregnant or lactating women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Apixaban is not recommended during pregnancy. The warning on the use of apixaban in pregnancy and lactating women is presented in the SmPC.
Severe hepatic impairment	Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Apixaban is not recommended in patients with severe hepatic impairment. Patients with active hepatobiliary disease and/or significantly abnormal hepatic function (ALT or AST > 2x ULN or a total bilirubin ≥ 1.5x ULN) were excluded in apixaban clinical trials. Therefore, apixaban should be used with caution in this population.
Severe renal impairment	Patients with severe renal impairment (CrCL<30mL/min) were excluded from major Phase 2 and 3 studies. There is no clinical experience in patients with CrCL <15 mL/min or in patients undergoing dialysis, thus apixaban is not recommended in these patients. There is limited clinical experience in patients with severe renal impairment (creatinine clearance 15-29 ml/min), therefore, apixaban is to be used with caution in these patients
Hip fracture surgery	No data are available on the effects of apixaban in patients undergoing hip fracture surgery or other non-elective orthopedic procedures where the patient populations, risk factors, concomitant medications or procedures and potential outcomes may be different from the postoperative THR and TKR populations. Therefore, safety conclusions cannot be established within this population and apixaban is not recommended.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Non-Caucasian and non-Asian ethnicity	There is limited clinical experience in patients of non-Caucasian and non-Asian ethnic groups in the orthopaedic VTE prevention (VTEp) studies with apixaban
Off-label use	Apixaban studies in indications other than orthopedic VTE prevention were not completed. Therefore, apixaban was not recommended in indications other than orthopedic VTE prevention.

2.7.2 *New Safety Concerns and Reclassification with a Submission of an Updated RMP*

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Important identified risk transient elevation of liver enzymes is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed transient elevation of liver enzymes from the list of safety concerns. As per the guidance, "not all adverse reactions are necessarily considered a risk for the medicinal product in a given therapeutic context and not all risks qualify as important to be included in the list of safety concerns." Transient elevation of liver enzymes is an adverse reaction listed in Section 4.8 of the SmPC, but there is no evidence that this adverse reaction is linked to a clinically significant outcome, namely drug-induced liver injury, which remains an important potential risk. There are no additional PV and/or risk minimization measures in relation to transient elevation of liver enzymes. In addition, transient elevation of liver enzymes does not impact the overall risk-benefit profile of apixaban for the approved indications, and has, therefore, been removed as an important identified risk.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information paediatric patients < 18 years of age is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed paediatric patients < 18 years of age from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Paediatric patients are not part of the on-label indications. Section 4.2 of the SmPC ('Posology and Method of Administration') states: *The safety and efficacy of Eliquis in children and adolescents below age 18 have not been established. No data are available.* Therefore, paediatric patients < 18 years of age are a non-approved population and are not relevant to list among missing information.
Missing information AF with valvular disease is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed AF with valvular disease from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Apixaban is indicated for prevention of stroke and systemic embolism in adult patients with non-vavular atrial fibrillation. Atrial fibrillation with valvular disease is not part of the on-label indications and is, therefore, not relevant to list among missing information.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information patients with prosthetic heart valve is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed patients with prosthetic heart valve from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Patients with prosthetic heart valve are not part of the on-label indications. Section 4.4 of the SmPC ('Special Warnings and Precautions for Use') states: *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.* Therefore, patients with prosthetic heart valves are a non-approved population and are not relevant to list among missing information.
Missing information hip fracture surgery is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed hip fracture surgery from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Patients with hip fracture surgery are not part of the on-label indications. Section 4.4 of the SmPC ('Special Warnings and Precautions for Use') states: *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.* Patients with hip-fracture surgery are a non-approved population and therefore, "hip fracture surgery" is not relevant to list among missing information.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information long-term therapy > 3 years is to be removed from the list of safety concerns.	Background to issue: There was previously limited experience with long-term therapy > 3 years in the AF population with apixaban. Evidence source: CV185048 LTOLE Final Study Report Action Taken: Available post-marketing experience and the completion of the LTOLE period of Study CV185048 fill the gap in knowledge about the safety of apixaban in long-term use in AF patients. The primary safety information in support of the indication of stroke prevention in NVAF comes from two pivotal Phase 3 AF studies, CV185030 and CV185048. Study CV185048 included an optional long-term open-label extension period in which all eligible subjects received open-label apixaban. A total of 3275 subjects entered the LTOLE period. The mean extent of exposure for subjects randomized to apixaban who entered the LTOLE period, from first through last day of dosing, for the combination of double-blind treatment and LTOLE period was 231.0 weeks (approximately 4.4 years). No new important potential or identified risk, not already covered by the safety specification and associated risk minimization measures, have been detected in the context of LTOLE period of Study CV185048.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information pregnant and/or lactating women is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed pregnant and/or lactating women from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Pregnant and/or lactating women are not a relevant population for the on-label indications of apixaban. Section 4.6 of the SmPC ('Fertility, pregnancy and lactation') states that apixaban is not recommended during pregnancy. Additionally, available data from the Company safety database (from 01-Jan-1900 through 21-Jun-2018) does not provide sufficient clinical evidence to suggest a safety signal of birth defects or any other significant safety events in pregnancy, lactation, and fertility in patients receiving apixaban therapy. Results of the comprehensive cumulative safety review of the human data associated with apixaban therapy do not show a potential causal relationship between the AEs, the outcomes of the AEs (including birth defects and other abnormal pregnancy outcomes/events), and the use of ELIQUIS therapy. The cases with birth defects (e.g., congenital anomaly) and/or miscarriages appeared to be confounded with alternative risk factors based the reported data available and/or in line with background incidence level in this patient population with a high thromboembolic/ischemic risk. No clusters or patterns of the cases were observed.[53] Therefore, pregnant and/or lactating women are not a relevant population for the approved indications of apixaban and are not relevant to list among missing information.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information severe hepatic impairment is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed severe hepatic impairment from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Use in patients with severe hepatic impairment is not recommended (Sections 4.2, 4.4 and 5.2 of the SmPC) and contra-indicated in patients with hepatic disease associated with coagulopathy (Section 4.3). Further information on mild to moderate hepatic impairment, including prior liver function testing, is also provided. No new or unique concerns have been identified through routine PV activities related to (mis)use in this population. No further action is required beyond routine PV activities. Therefore, it is proposed that patients with a pre-existing condition of severe hepatic impairment can be removed from the list of safety concern.
Missing information haemodynamically unstable PE patients is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed haemodynamically unstable PE patients from the list of safety concerns. As per the guidance, "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. 'on-label', and if the use in such populations might be associated with risks of clinical significance." Haemodynamically unstable PE patients are not a relevant population for the on-label indications of apixaban. Section 4.4 ('Special warnings and precautions for use') of the SmPC states that Eliquis is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of apixaban have not been established in these clinical situations. Therefore, haemodynamically unstable PE patients are not a relevant population for the approved indications of apixaban and are not relevant to list among missing information.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information off-label use is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed off-label use from the list of safety concerns. As per the guidance, "the safety concern derived from the specific situations/data sources described in GVP Module V Section V.B.5.8. should be specified rather than using the unspecific term ("off-label use"; "medication error") if possible". Evaluation via routine PV activities, including PBRERs/PSURs, has not identified any specific risk for a specific outcome associated with off-label use that is not already covered by the existing safety specification. No further action is required beyond ongoing evaluation in routine PV activities.
Missing information Black/African American population in AF studies is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed Black/African American population in AF studies from the list of safety concerns. As per the guidance, "Missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations within the approved indication, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far." Section 5.2 ('Pharmacokinetic properties') of the SmPC states that the results across phase I 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 I results. Therefore, Black/African American population in AF studies is not relevant to list among missing information.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Missing information Non-Caucasian and non-Asian ethnicity in VTE prevention studies is to be removed from the list of safety concerns.	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. The major revisions in GVP Module V included clarifications of focus in relation to important identified or potential risks and missing information. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has removed Non-Caucasian and non-Asian ethnicity in VTE prevention studies from the list of safety concerns. As per the guidance, "Missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations within the approved indication, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far." Section 5.2 ('Pharmacokinetic properties') of the SmPC states that the results across phase I 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 I results. Therefore, Non-Caucasian and non-Asian ethnicity in VTE prevention studies is not relevant to list among missing information.
Important potential risk medication errors has been reworded to "potential risk of bleeding or thrombosis due to overdose or underdose."	Background to issue: The EMA RMP template (Guidance on the format of the risk management plan in the EU – in integrated format) was updated. As per GVP Module V (rev 2), it is no longer sufficient to just state medication error as being a safety concern, but rather a description of the potential risk of a specific event in the context of a particular action is needed. Evidence source: EMA/PRAC/613102/2015 Rev 2 - 30-Mar-2017 Action Taken: In response to the revisions in GVP Module V, the MAH has reworded medication errors to the more specific term"Potential risk of bleeding or thrombosis due to overdose or underdose."

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

This section reviews important identified risks, potential risks and missing information for apixaban for the approved indications. Key safety events include:

Important Identified Risks

- Bleeding

Important Potential Risks

- Liver injury
- Potential risk of bleeding or thrombosis due to overdose or underdose

Missing Information

- Use in patients with severe renal impairment

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding	
Potential mechanisms	Apixaban is an anticoagulant acting via inhibition of FXa and is expected to produce a dose-dependent increase in the risk of bleeding as well as a dose-dependent increase in the antithrombotic effects, both of which are related to the on-target activity of apixaban, i.e., direct FXa inhibition.
Evidence source and strength of evidence	The risk of bleeding associated with apixaban has been comprehensively evaluated in the nonclinical and clinical apixaban programmes. The most clinically significant treatment-related adverse reactions (ARs) associated with apixaban are bleeding ARs. The majority of bleeding-related events were non-serious and mild to moderate in severity. A bleeding event can be serious if it occurs in a critical anatomical site such as in the brain. Intracranial bleeding can be fatal. Low rates of intracranial bleeding and fatal bleeding were reported. The overall bleeding risk of apixaban was found to be superior to warfarin in the non-valvular AF programme, similar to enoxaparin in the orthopaedic VTE prevention programme, and superior to enoxaparin/warfarin in VTE treatment patients.
Characterization of risk	**I. Orthopaedic VTE Prevention Indication** **Pooled Hip and Knee (pivotal Phase 3 studies CV185035 and CV185047)**

	Apixaban (N = 4,174)	**Enoxaparin (N = 4,167)**
Major bleeding	31 (0.74%) (0.52, 1.06)	32 (0.77%) (0.54, 1.09)
Major or CRNM bleeding	182 (4.36%) (3.78, 5.03)	206 (4.94%) (4.33, 5.65)
Any bleeding	417 (9.99%) (9.12, 10.94)	460 (11.04%) (10.12, 12.03)

Source: Apixaban for the Prevention of Venous Thromboembolic Events Summary of Clinical Safety Table 2.1.5.3

Investigator reported sites of bleeding: surgical site: apixaban 5.7%, enoxaparin 6.1%; gastrointestinal tract: apixaban 0.6%, enoxaparin 0.3%, intraocular: apixaban 1 (< 0.1%),

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

enoxaparin 0, and haemarthrosis resulting in intervention: apixaban 5 (0.1%), enoxaparin 6 (0.1%) (Source: SCS[54] Appendix 7.G1P2)

II. Atrial Fibrillation Indication

In the LTOLE period of Study CV185048, a total of 420 subjects (12.8%) had a bleeding-related adverse event (AE). The most common (> 1%) of these were epistaxis (2.5%), hematuria (1.4%), and contusion (1.1%). Detailed narratives for bleeding-related SAEs are provided in Table S.6 of the final CSR for Study CV185048.

Pivotal study CV185030

CV185030	Apixaban (N = 9,088)	Warfarin (N = 9,052)
Major bleeding	327 (2.13%year) HR 0.69 (0.52, 1.06)	462 (3.09%yr)
Intraarticular bleed	6 (0.04%yr)	10 (0.07%yr)
Intraocular bleed	28 (0.18%yr)	19 (0.13%yr)
Pericardial bleed	0	0
Intraspinal	2 (0.01%yr)	2 (0.01%yr)
Intramuscular with compartment syndrome	1 (<0.01%yr)	1 (<0.01%yr)
Retroperitoneal bleed	2 (0.01%yr)	5 (0.03%yr)
Transfusion of>= 2 units of packed RBC	70 (0.45%yr)	101 (0.67%yr)
Major or CRNM bleeding	613 (4.07%yr) HR 0.68 (0.61, 0.75)	877 (6.01%yr)
Any bleeding	2,356 (18.08%yr) HR 0.71 (0.68, 0.75)	3,060 (25.82%yr)

Source: Study CV185030 CSR Table 8.2A

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

Pivotal study CV185048 - double-blind treatment period

	Apixaban (N = 2798)	ASA (N = 2780)
Major bleeding	45 (1.41%yr) HR 1.54 (0.96, 2.45)	29 (0.92%yr)
Intraarticular bleed	2 (0.07%)	1 (0.04%)
Intraocular bleed	6 (0.21%)	0
Pericardial bleed	1 (0.04)	0
Intramuscular with compartment syndrome	1 (0.04)	0
Retroperitoneal bleed	1 (0.04)	0
Transfusion of> = 2 units of packed RBC	16 (0.57)	13 (0.47)
Major or CRNM bleeding	140 (4.46%yr) HR 1.38 (1.07, 1.78)	101 (3.24%yr)
All bleeding	325 (10.85%yr) HR 1.30 (1.10, 1.53)	250 (8.32%)

Source: Study CV185048 CSR Table 8.2A

Pivotal study CV185067

CV185067 (Phase 2)	Apix 2.5 mg BID (N = 75)	Apix 5 mg BID (N= 72)	Warfarin (N = 71)
Major bleeding	0	0	1 (1.3%)
95% CI	[0.0, 4.9]	[0.0, 5.0]	[0.1, 6.6]
Major/CRNM bleeding, 95% CI	1 (1.4%) [0.1, 6.9]	1 (1.4%) [0.1, 7.0]	4 (5.3%) [1.8, 12.7]
All bleeding	9 (12.5%)	17 (23.9%)	13 (17.3%)
95% CI	[6.5, 21.6]	[15.1, 34.7]	[10.0, 27.6]

Source: Study CV185067 CSR Tables 4 and 16

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

III. VTE Treatment and Prevention of Recurrent VTE Indication

Study CV185056

	Apixaban (N = 2676)	Enoxaparin/Warfarin (N = 2689)
Major bleeding, n (%)	15 (0.6)	49 (1.8)
Risk difference (95% CI)	-0.0113 (-0.0170, -0.0056)	
Fatal bleed, n (%)	1 (<0.1)	2 (<0.1)
Bleeding into a critical site, n (%)	4 (0.1)	13 (0.5)
Intracranial	3 (0.1)	6 (0.2)
Intraspinal	0	0
Intraocular	0	2 (<0.1)
Intra-articular	0	2 (<0.1)
Pericardial	0	0
Intramuscular with compartment syndrome	0	0
Retroperitoneal bleed	1 (<0.1)	3 (0.1)
Decrease in haemoglobin >=2g/dL	9 (0.3)	39 (1.5)
Transfusion of >= 2 units of packed RBC	8 (0.3)	21 (0.8)
Major or CRNM bleeding, n (%)	115 (4.3)	261 (9.7)
Risk difference (95% CI)	-0.0499 (-0.0632, -0.0366)	
CRNM bleeding, n (%)	103 (3.8)	215 (8.0)
Risk difference (95% CI)	-0.0382 (-0.0506, -0.0259)	
Minor bleeding, n (%)	313 (11.7)	505 (18.8)
Risk difference (95% CI)	-0.0651 (-0.0835, -0.0468)	
Total bleeding, n (%)	402 (15.0)	676 (25.1)
Risk difference (95% CI)	-0.0950 (-0.1157, -0.0744)	

Source: Table 4.11.1.1.1 and Table 4.11.7.1.1, Treatment and Prevention of Recurrence of Venous Thromboembolism Summary of Clinical Safety (SCS) Tables

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

Study CV185057

	Apixaban 2.5 mg BID (N = 840)	Apixaban 5 mg BID (N = 811)	Placebo (N = 826)
Major bleeding, n (%)	2 (0.2)	1 (0.1)	4 (0.5)
Risk difference (95% CI)	-0.0022 (-0.0077, 0.0033)	-0.0037 (-0.0090, 0.0016)	
Fatal bleed, n (%)	0	0	0
Bleeding into a critical site, n (%)	0	0	1 (0.1)
Intracranial	2 (0.2)	0	1 (0.1)
Intraocular	0	1 (0.1)	1 (0.1)
Gastrointestinal	0	0	1 (0.1)
Urogenital			
Decrease in haemoglobin ≥ 2g/dL	0	1 (0.1)	2 (0.2)
Transfusion of ≥ 2 units of packed RBC	0	0	1 (0.1)
Major or CRNM bleeding, n (%)	27 (3.2)	35 (4.3)	22 (2.7)
Risk difference (95% CI)	0.0048 (-0.0113, 0.0210)	0.0158 (-0.0018, 0.0335)	
CRNM bleeding, n (%)	25 (3.0)	34 (4.2)	19 (2.3)
Risk difference (95% CI)	0.0065 (-0.0089, 0.0218)	0.0187 (0.0016, 0.0359)	
Minor bleeding, n (%)	75 (8.9)	98 (12.1)	58 (7.0)
Risk difference (95% CI)	0.0190 (-0.0063, 0.0443)	0.0445 (0.0173, 0.0717)	
Total bleeding, n (%)	94 (11.2)	121 (14.9)	74 (9.0)
Risk difference (95% CI)	0.0209 (-0.0074, 0.0492)	0.0538 (0.0234, 0.0842)	

Source: Table 4.11.1.1.2, Table 4.11.1.1.6 and Table 4.11.7.1.2, Treatment and Prevention of Recurrence of Venous Thromboembolism SCS Tables

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding	
	Study CV185017 (Phase 2) The event rates during the treatment period for the primary safety endpoint of major bleeding/CRNM bleeding were comparable across all treatment groups with the apixaban 10 mg BID group having the lowest observed rate. Major bleeding events were only reported in the apixaban 5 mg BID (1 subject) and apixaban 20 mg QD (1 subject) groups during the treatment period. The critical locations of the 2 major bleeding events were intracranial (apixaban 20 mg once daily [QD] group) and 'other – thorax' (apixaban 5 mg BID group). There were no fatal bleeding events in any treatment group.
Risk factors and risk groups	Concurrent use of other anticoagulants or antiplatelet therapies Patient characteristics: comorbid conditions (eg, 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). Past medical history (eg, previous stroke, prior GI bleeding) Coadministration of strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp) (eg, azole antifungals, protease inhibitors) may increase apixaban blood concentration and risk of bleeding. Therefore, coadministration of apixaban with strong inhibitors of both CYP3A4 and P-gp is not recommended. **I. Orthopaedic VTE Prevention Indication** Patient characteristics: age > 75 years old. 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. The risk may also be increased by traumatic or repeated epidural or spinal puncture. **II. VTE Treatment and Prevention of Recurrent VTE Indication** Coadministration of strong inducers of both CYP3A4 and P-gp may lead to a reduction in apixaban exposure and is not recommended for the treatment of DVT and PE. In a clinical study in AF 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.

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding	
Preventability	Avoid administration in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, severe hepatic impairment or active hepatobiliary disease. Avoid administration of apixaban with drugs that strongly inhibit both CYP3A4 and P-gp. Closely monitor for bleeding. Discontinue administration if severe haemorrhage occurs. For subjects with clinically significant bleeding, apixaban should generally be withheld. Apixaban has a T-half of approximately 12 hours. 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, the transfusion of fresh frozen plasma or the administration of a reversal agent for factor Xa inhibitors should be considered. Doses of apixaban (up to 25 mg BID for 7 days and 50 mg QD for 3 days) have been administered to healthy subjects without apparent clinically relevant adverse effects. Activated charcoal may be useful in the management of apixaban overdose. For situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available. 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 **<u>Orthopaedic VTE Prevention Indication</u>** Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first oral dose of apixaban.
Impact on the risk-benefit balance of the product	Major bleeding can be a life threatening complication for all anticoagulants including apixaban and less serious minor bleeding often prompts patients to discontinue the anticoagulant exposing them to the risks of stroke or VTE which anticoagulants are prescribed to prevent. Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. The Patient Alert Card and Prescriber Guide alert healthcare professionals and patients to these risks and their appropriate management.
Public health impact	None
MedDRA terms	MedDRA Standard MedDRA Query (SMQ): Haemorrhages

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

Potential mechanisms

Orthopaedic VTE Prevention

Surgery related: intraoperative hypotension and anesthetic application, transfusions, liver congestion and ischaemia, infections

Other: hepatitis, cholestasis, necrosis

Other indications

None identified

Evidence source and strength of evidence

Across the apixaban clinical programme, there have been infrequent reports of liver-related AEs, SAEs, and laboratory abnormalities. In the VTE prevention orthopaedic population, the majority of events were post-operative transient elevations of ALT, AST, total bilirubin, and/or ALP that either resolved while study drug continued or during follow-up period.

In the AF indication, the low frequency of LFT elevations and liver-related safety events is clinically important, and supports the favourable safety profile of apixaban for this indication.

In VTE Treatment and Prevention of Recurrent VTE indication, most patients who experienced hepatic enzyme elevation were asymptomatic, however, some patients experienced symptoms depending on the severity of the condition.

Characterization of risk

No trend of dose-dependent increase in frequencies of liver-related abnormalities across the apixaban dose groups was observed.

I. Orthopaedic VTE Prevention Indication

In the 4-study pooled VTE prevention dataset, the frequencies of ALT or AST > 3x, 5x, 10x ULN and also ALT > 3x ULN or AST > 3x ULN with concurrent total bilirubin > 2x ULN are comparable between the apixaban and comparator arms.

Laboratory Parameter	Apixaban	Enoxaparin
ALT > 3x ULN	110 [1.9%]	151 [2.6%]
ALT > 5x ULN	40 [0.7%]	48 [0.8%]
ALT > 10x ULN	9 [0.2%]	7 [0.1%]
AST > 3x ULN	134 [2.3%]	135 [2.3%]
AST > 5x ULN	43 [0.7%]	52 [0.9%]
AST > 10x ULN	13 [0.2%]	11 [0.2%]
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	8* [0.1%]	5 [0.09%]
Concurrent elevations of ALT or AST > 3x ULN and total bilirubin > 2x ULN	11* [0.2%]	6 [0.1%]

Source: VTEp SCS Table 2.1.6.2C

*Two subjects in the apixaban group (1 in CV185035 and 1 in CV185047) had these elevations prior to the first apixaban dose. For detailed description of individual cases please see Section 2.1.6.2 of the VTEp SCS and Hepatic Safety Document (VTEp SCS Appendix 13.6).[54]

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

AEs related to LFT elevation were reported for 205 (3.5%) subjects in the apixaban group and 300 (5.1%) subjects in the enoxaparin group. AST increased, ALT increased, and GGT increased were reported for > 1% but < 2% of subjects in either treatment group (VTEp SCS Appendix 8.B1-P4).[54] AEs related to LFT elevations with onset during the Treatment Period and leading to discontinuation were reported for 7 (0.1%) subjects in both treatment groups (VTEp SCS Appendix 8.D1-P4).

SAEs related to LFT elevations with onset during the Treatment Period were reported for 4 (< 0.1%) subjects in the apixaban group and 1 (< 0.1%) subject in the enoxaparin group (SCS Appendix 8.C1-P4).

Long-term Phase 2 ACS CV185023 (apixaban 2.5 mg BID and 10 mg QD):

Laboratory Parameter	Apixaban	Placebo
ALT > 3x ULN	0.5%	2.7%
ALT > 5x ULN	0.2%	0.5%
ALT > 10x ULN	0.2%	0.0%
AST > 3x ULN	0.5%	1.2%
AST > 5x ULN	0.0%	0.5%
AST > 10x ULN	0.0%	0.0%
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	0.0%	0.0%
Concurrent elevations of ALT or AST > 3x ULN and total bilirubin > 2x ULN	0.0%	0.0%

Source: Study CV185023 CSR Table S.7.2A1

II. Atrial Fibrillation Indication

In the pooled AF dataset, the frequencies of ALT or AST > 3x, 5x, 10x ULN and also ALT > 3x ULN or AST > 3x ULN with concurrent total bilirubin > 2x ULN are comparable between the apixaban and comparator arms in studies CV185030 and CV185048, respectively.

During the LTOLE period of Study CV185048, a total of 11 subjects (0.3%) who entered the period reported an AE related to elevation in LFTs that led to treatment discontinuation (CV185048 Final LTOLE CSR, Table S.6.7.1C). A total of 17 subjects (0.5%) reported a SAE related to elevation in LFTs during the LTOLE period (CV185048 Final LTOLE CSR, Table S.6.7.1B).

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

CV185030:

Laboratory Parameter	Apixaban	Warfarin
ALT > 3x ULN	100 [1.1%]	89 [1.0%]
ALT > 5x ULN	45 [0.5%]	47 [0.5%]
ALT > 10x ULN	16 [0.2%]	20 [0.2%]
AST > 3x ULN	106 [1.2%]	99 [1.1%]
AST > 5x ULN	42 [0.5%]	45 [0.5%]
AST > 10x ULN	20 [0.2%]	17 [0.2%]
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	23 [0.3%]	22 [0.3%]
Concurrent elevations of ALT or AST > 3x ULN and total bilirubin > 2x ULN	30 [0.3%]	31 [0.4%]

Source: Study CV185030 CSR, Table 8.7.1B

CV185048 - double-blind treatment period:

Laboratory Parameter	Apixaban	Aspirin
ALT > 3x ULN	23 [0.8%]	31 [1.1%]
ALT > 5x ULN	9 [0.3%]	13 [0.5%]
ALT > 10x ULN	2 [<0.1%]	4 [0.1%]
AST > 3x ULN	28 [1.0%]	33 [1.2%]
AST > 5x ULN	10 [0.4%]	10 [0.4%]
AST > 10x ULN	3 [0.1%]	3 [0.1%]
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	3 [0.1%]	9 [0.3%]
Concurrent elevations of ALT or AST > 3x ULN and total bilirubin > 2x ULN	5 [0.2%]	9 [0.3%];

Source: Study CV185048 CSR, Table 8.7.1B

III. VTE Treatment and Prevention of Recurrent VTE Indication

In the pooled VTE treatment dataset, with the exception of ALT elevation > 3x ULN (apixaban: 1.6%, comparator: 4.8%) and AST or ALT elevation (not not necessarily on same date) > 3x ULN (apixaban: 2.0%, comparator: 5.2%), the event rates for elevations of LFTs were similar in the apixaban and comparator groups. LFTs for the individual VTE treatment studies are provided below.

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

Study CV185056

Laboratory Parameter	Apixaban	Enoxaparin/ Warfarin
ALT > 3x ULN	50 [1.9%]	145 [5.6%]
ALT > 5x ULN	23 [0.9%]	40 [1.5%]
ALT > 10x ULN	5 [0.2%]	4 [0.2%]
ALT > 20x ULN	2 [<0.1%]	0
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	3 [0.1%]	1 [<0.1%]
Concurrent elevations of ALT > 3x ULN, total bilirubin > 2x ULN, and ALP < 2x ULN	1 [<0.1%]	0

Source: Study CV185056 CSR, Table 55

Study CV185057

Laboratory Parameter	Apixaban 2.5 mg BID	Apixaban 5 mg BID	Placebo
ALT > 3x ULN	9 [1.1%]	5 [0.6%]	9 [1.1%]
ALT > 5x ULN	4 [0.5%]	4 [0.5]	4 [0.5%]
ALT > 10x ULN	0	3 [0.4%]	3 [0.4%]
ALT > 20x ULN	0	1 [0.1%]	0
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	1 [0.1%],	0	3 [0.4%]
Concurrent elevations of ALT > 3x ULN, total bilirubin > 2x ULN, and ALP < 2x ULN	0	0	2 [0.2%]

Source: Study CV185057 CSR, Table 47

Study CV185017

Laboratory Parameter	Apixaban 5 mg BID	Apixaban 10 mg BID	Apixaban 20 mg BID	LMWH/ VKA
ALT > 3x ULN	1 [0.8%]	9	4 [3.3%]	2 [1.6%]
ALT > 5x ULN	0	0	1 [0.8]	0
ALT > 10x ULN	0	0	0	0
Concurrent elevations of ALT > 3x ULN and total bilirubin > 2x ULN	0	0	0	0

Source: Study CV185017, Table s.7.1D

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury	
Risk factors and risk groups	Prior hepatitis, cirrhosis, fatty liver, alcohol consumption, poor nutrition, co-existing chronic disease, co-administration of hepatically metabolized drugs (eg, statins), medication overdose, hypoperfusion, transfusion, halogen-anesthetics, analgesics, hepatotoxic antibiotics, autoimmune disease (autoimmune hepatitis), viruses (primarily HAV, HBV, HCV), hereditary conditions (eg, Wilson's disease)
Preventability	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. May be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) Across the apixaban programme all hepatitis SAE cases are reported to Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) in an expedited manner regardless of meeting SUSAR criteria, per prior AFSSAPS request.
Impact on the risk-benefit balance of the product	Liver injury can result in hepatitis, hepatotoxicity, liver failure requiring liver transplantation, and/or fatal outcomes. Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. The Prescriber Guide alerts healthcare professionals to these risks and their appropriate management.
Public health impact	None
MedDRA terms	Hepatic disorder-related preferred terms MedDRA hepatic disorders SMQs: Cholestasis and jaundice of hepatic origin Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions Hepatitis, non-infectious Liver neoplasms, benign (including cysts and polyps) Liver neoplasms, malignant and unspecified (SMQ) Liver related investigations, signs and symptoms Liver-related coagulation and bleeding disturbances Liver infections

Table 2.7.3.1-3: Important Potential Risk: Potential Risk of Bleeding or Thrombosis Due to Overdose or Underdose

Important Potential Risk: Potential risk of bleeding or thrombosis due to overdose or underdose	
Potential mechanisms	Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. As with other oral anticoagulants, overdose of apixaban may result in a higher risk of bleeding. A missed dose or underdose of apixaban may result in a higher risk of thrombosis.

Table 2.7.3.1-3: Important Potential Risk: Potential Risk of Bleeding or Thrombosis Due to Overdose or Underdose

Important Potential Risk: Potential risk of bleeding or thrombosis due to overdose or underdose

Evidence source and strength of evidence

Although post-marketing data has shown that medication errors occur infrequently, overdose as the most prevalent medication error has potentially serious consequences because of the increased risk of bleeding.

The majority of events reported under the Medication errors HGLT for apixaban in pivotal studies were SAEs. The vast majority of cases reporting overdose, accidental overdose, intentional overdose or accidental exposure were asymptomatic. There was a single fatal outcome as a consequence of intentional suicidal overdose with phenazepam and alcohol.

Characterization of risk

The frequencies of medication errors reported in the orthopaedic VTE prevention studies were low and a similar proportion of medication errors were reported in the apixaban and enoxaparin treatment groups in studies

I. Orthopaedic VTE Prevention Indication

AEs reported in the Medication errors HLGT for the three Phase 3 orthopaedic VTE prevention studies are provided in the tables below. The frequencies of medication errors reported in the orthopaedic VTE prevention studies were low and a similar proportion of medication errors were reported in the apixaban and enoxaparin treatment groups in studies CV185034, CV185035, and CV185047.

Study CV185034

High Level Group Term Preferred Term (%)	Apixaban 2.5 mg BID (N = 1596)	Enoxaparin (N = 1588)
Medication errors		
Overdose	2 (0.1)	3 (0.2)
Accidental overdose	0	1 (0.1)

Source: Study CV185034 CSR, Table S.6.5.B1

Study CV185035

High Level Group Term Preferred Term (%)	Apixaban 2.5 mg BID (N = 2673)	Enoxaparin (N = 2659)
Medication errors		
Overdose	5 (0.2)	6 (0.2)
Incorrect dose administered	0	1 (<0.1)

Source: Study CV185035 CSR, Table S.6.5.B1

Study CV185047

High Level Group Term Preferred Term (%)	Apixaban 2.5 mg BID (N = 1501)	Enoxaparin (N = 1508)
Medication errors		
Overdose	1 (0.1)	2 (0.1)

Source: Study CV185047 CSR, Table S.6.5.B1

Table 2.7.3.1-3: Important Potential Risk: Potential Risk of Bleeding or Thrombosis Due to Overdose or Underdose

Important Potential Risk: Potential risk of bleeding or thrombosis due to overdose or underdose

II. Atrial Fibrillation Indication

AEs reported in the Medication errors HLGT for the two Phase 3 AF studies along with the LTOLE period of Study CV185048 are provided in the tables below. The frequencies of medication errors reported in the AF studies were low and a similar proportion of medication errors were reported in the apixaban treatment groups and the warfarin and ASA treatment groups in studies CV185030, CV185048, and CV185048 LTOLE period, respectively.

Study CV185030

High Level Group Term Preferred Term (%)	Apixaban (N = 9088)	Warfarin (N = 9052)
Medication errors		
Overdose	32 (0.4)	43 (0.5)
Accidental overdose	2 (<0.1)	6 (0.1)
Medication error	2 (<0.1)	1 (<0.1)
Accidental exposure	1 (<0.1)	0
Drug administration error	1 (<0.1)	0
Intentional overdose	1 (<0.1)	1 (<0.1)
Drug dispensing error	0	1 (<0.1)
Incorrect dose administered	0	3 (<0.1)

Source: Study CV185030 CSR, Table S.6.8.A1

Study CV185048 - double-blind treatment period

High Level Group Term Preferred Term (%)	Apixaban (N = 2798)	ASA (N = 2780)
Medication errors		
Overdose	3 (0.1)	5 (0.2)
Documented hypersensitivity to administered drug	2 (0.1)	1 (<0.1)

Source: Study CV185048 LTOLE Final Study Report, Table S.6.8.A

Study CV185048 - LTOLE Period

High Level Group Term Preferred Term (%)	OL- Apixaban (N = 3275)
Medication errors	
Overdose	3 (<0.1)
Accidental overdose	1 (<0.1)
Hypersensitivity	4 (0.1)
Drug hypersensitivity	3 (<0.1)

Source: Study CV185048 LTOLE Final Study Report, Table S.6.8.A1

Table 2.7.3.1-3: Important Potential Risk: Potential Risk of Bleeding or Thrombosis Due to Overdose or Underdose

Important Potential Risk: Potential risk of bleeding or thrombosis due to overdose or underdose

III. VTE Treatment and Prevention of Recurrent VTE Indication

AEs reported in the Medication errors HLGT for the two Phase 3 VTE treatment studies are provided in the tables below. A similar proportion of medication errors were reported in the apixaban and enoxaparin/warfarin treatment groups in Study CV185056 and the frequencies of events reported in apixaban 2.5 mg BID and apixaban 5 mg BID treatment groups in Study CV185057 were low.

Study CV185056

High Level Group Term Preferred Term (%)	Apixaban (N = 2676)	Enoxaparin/Warfarin (N = 2689)
Medication errors		
Overdose	20 (0.7)	23 (0.9)
Accidental overdose	2 (<0.1)	1 (<0.1)
Incorrect dose administered	2 (<0.1)	0
Drug administration error	1 (<0.1)	0

Source: Study CV185056 CSR, Table 14.3.1.2.6.2.1

Study CV185057

High Level Group Term Preferred Term (%)	Apixaban 2.5 mg BID (N = 840)	Apixaban 5 mg BID (N = 811)	Placebo (N = 826)
Medication errors			
Overdose	1 (0.1)	1 (0.1)	0
Accidental overdose	0	1 (0.1)	0

Source: Study CV185057 CSR, Table 14.3.1.2.6.3.1

Risk factors and risk groups	Risk factors include complex/unclear patient information, packaging, and product label, and use of the product in emergency situations
Preventability	The risk of medication errors can be reduced with improved packaging, prescribing information in the product label and prescriber education.
Impact on the risk-benefit balance of the product	Overdose of apixaban has potentially serious consequences because of the increased risk of bleeding. An underdose or dose omission has potentially serious consequences because of the increased risk of thrombosis. The Prescriber Guide alerts healthcare professionals to these risks and their appropriate management..
Public health impact	None
MedDRA terms	MedDRA HLGT: Medication errors

2.7.3.2 *Presentation of the Missing Information*

Table 2.7.3.2-1: Missing Information

Missing Information	Is the safety profile expected to be different from the general target population?
Population in need of further characterization	
Use in patients with severe renal impairment	Limited clinical data in patients with severe renal impairment (CrCL 15-29 mL/min) indicate that apixaban plasma concentrations are increased in this patient population. Therefore, apixaban alone or in combination with ASA is to be used with caution in these patients because of a potentially higher bleeding risk. For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and 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. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended

2.8 Summary of the Safety Concerns

The overall safety concerns, including important identified and potential risks and missing information for apixaban, are listed in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Risk Category	Safety Concern
Important identified risks	Bleeding
Important potential risks	Liver Injury Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	Use in patients with severe renal impairment

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are summarized in Table 3.1-1. See Annex 4 for forms, as applicable.

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Specific adverse reaction follow-up questionnaires	
Targeted Post-marketing Questionnaire for: • Bleeding • Spontaneous reports of liver events	Questionnaire records events including signs and symptoms, diagnostic test results, actions taken, event resolution, and relevant medical history

3.2 Additional Pharmacovigilance Activities

No post-authorization safety studies (PASS) are imposed or required by the Competent Authority. A summary of ongoing and completed pharmacovigilance study protocols is provided in Annex 2.

3.3 Summary Table of Additional Pharmacovigilance Activities

No ongoing and planned additional pharmacovigilance activities are imposed by the Competent Authority.

4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No post-authorization efficacy studies (PAES) are imposed by the Competent Authority.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Bleeding	**Routine risk communication:** Text is included in the following sections of the SmPC to communicate the risk of bleeding with explicit description of measures to be taken to avoid haemorrhage and measures to be taken in the event of haemorrhagic complications Section 4.2, Posology and method of administration Section 4.3, Contraindications Section 4.4, Special warnings and precautions for use Section 4.5, Interaction with other medicinal products and other forms of interaction Section 4.8, Undesirable effects Section 4.9, Overdose **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The SmPC provides explicit description of measures to take to avoid haemorrhage and measures to be taken in the event of haemorrhagic complications **Other routine risk minimisation measures beyond the Product Information:** None

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Liver Injury	**Routine risk communication:** SmPC Section 4.2, Posology and method of administration SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Potential risk of bleeding or thrombosis due to overdose or underdose	**Routine risk communication:** SmPC Section 4.2, Posology and method of administration **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The SmPC provides the dosing recommendation for each indication along with the trade name, packaging, labeling, and distinguishing features (colour and size) of the marketed tablet. Spontaneous reports of medication errors will be closely monitored to clarify the factors involved in medication errors, and will provide useful information on the context of medication errors. This will guide future risk mitigation actions. **Other routine risk minimisation measures beyond the Product Information:** None
Use in patients with severe renal impairment	**Routine risk communication:** SmPC Section 4.2, Posology and method of administration SmPC Section 4.4, Special warnings and precautions for use SmPC Section 5.2, Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The SmPC provides the dosing recommendation for patients with severe renal impairment for each indication. **Other routine risk minimisation measures beyond the Product Information:** None

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1. Details of proposed additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimization	Objectives/Rationale
Prescriber Guide	**Objectives:** To further raise awareness of healthcare professionals on important risks of bleeding, and medication errors during treatment with apixaban, and their appropriate management.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimization	Objectives/Rationale
	Rationale for the additional risk minimisation activity: Opportunity to reinforce key messages to early recognition and appropriate management of important risks to maintain favourable benefit/risk of apixaban in market use. **Target audience and planned distribution path:** Prescriber. The MAH must agree to 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. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Routine pharmacovigilance activities and post-marketing epidemiology studies will provide information on any changes in the occurrence, severity, and outcome of the important identified risk of bleeding as it relates to the established safety profile, and will be reported in future regulatory safety reports (eg, PSUR). Spontaneous reports of medication errors will be closely monitored to clarify the factors involved in medication errors, and will provide useful information on the context of medication errors. This will guide future risk mitigation actions. The MAH has included a posology section in the prescriber guide for the NVAF, VTE treatment and VTE prevention indications in order to reduce the risk of potential medication error as an additional risk minimisation measure. Study CV185-365, which evaluated the effectiveness of the Eliquis additional risk minimization (RM) tools (Prescriber Guide and Patient Alert Card) in European Economic Area (EEA) countries, was completed in 2017. Based on the results of this study, the MAH did not propose to make any modifications to the content of the RM tools. The results were consistent with the objectives of the study and supported the effectiveness of the risk minimisation (RM) tools for their intended purpose. Hence, this RMP measure was considered to be completed.
Patient Alert Card	**Objectives:** To further raise awareness of patients and healthcare professionals on the important identified risk of bleeding during treatment with apixaban and its appropriate management. **Rationale for the additional risk minimisation activity:** Opportunity to reinforce key messages to early recognition and appropriate management of important identified risk of bleeding to maintain favourable benefit/risk of apixaban in market use. **Target audience and planned distribution path:** Patients/Caregivers. As of Apr 2015, the Patient Alert Card has been included inside the Eliquis product pack together with the Package Leaflet, which is now the primary mode of distribution.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimization	Objectives/Rationale
	Plans to evaluate the effectiveness of the interventions and criteria for success: Routine pharmacovigilance activities and post-marketing epidemiology studies will provide information on any changes in the occurrence, severity, and outcome of the important identified risk of bleeding as it relates to the established safety profile, and will be reported in future regulatory safety reports (eg, PSUR). Study CV185-365, which evaluated the effectiveness of the Eliquis additional RM tools (Prescriber Guide and Patient Alert Card) in EEA countries, was completed in 2017. Based on the results of this study, the MAH did not propose to make any modifications to the content of the RM tools. The results were consistent with the objectives of the study and supported the effectiveness of the RM tools for their intended purpose. Hence, this RMP measure was considered to be completed.

5.3 Summary Table of Risk Minimization Measures

A summary of risk minimization measures is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Bleeding	**Routine risk minimisation measures:** SmPC Section 4.2, Posology and method of administration SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction SmPC Section 4.8, Undesirable effects SmPC Section 4.9, Overdose	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Post-marketing targeted bleeding questionnaire
	Additional risk minimisation measures: • Prescriber Guide • Patient Alert Card	**Additional pharmacovigilance activities:** None
Liver Injury	**Routine risk minimisation measures:** SmPC Section 4.2, Posology and method of administration SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8 Undesirable effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Post-marketing questionnaire for spontaneous reports of liver events
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Potential risk of bleeding or thrombosis due to overdose or underdose	**Routine risk minimisation measures:** SmPC Section 4.2, Posology and method of administration SmPC Section 4.9, Overdose	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None
	Additional risk minimisation measures: Prescriber Guide	**Additional pharmacovigilance activities:** None
Use in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC provides the dosing recommendation for patients with severe renal impairment for each indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ELIQUIS (apixaban)

This is a summary of the risk management plan (RMP) for ELIQUIS. The RMP details important risks of ELIQUIS, how these risks can be minimised, and how more information will be obtained about ELIQUIS's risks and uncertainties (missing information).

ELIQUIS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ELIQUIS should be used.

This summary of the RMP for ELIQUIS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ELIQUIS's RMP.

I. The medicine and what it is used for

ELIQUIS is authorised for the following indications (see SmPC for the full indication):

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism (SE) 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 (New York Heart Association [NYHA] Class ≥ II).and 3)
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults

It contains apixaban as the active substance and it is given by oral route.

Further information about the evaluation of ELIQUIS's benefits can be found in ELIQUIS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/eliquis

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ELIQUIS, together with measures to minimise such risks and the proposed studies for learning more about ELIQUIS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of ELIQUIS, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of ELIQUIS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ELIQUIS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ELIQUIS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Bleeding
Important potential risks	Liver Injury
	Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	Use in patients with severe renal impairment

II.B Summary of important risks

Important identified risks

Bleeding	
Evidence for linking the risk to the medicine	The risk of bleeding associated with apixaban has been comprehensively evaluated in the nonclinical and clinical apixaban programmes. The most clinically significant treatment-related ARs associated with apixaban are bleeding ARs. The majority of bleeding-related events were non-serious and mild to moderate in severity. A bleeding event can be serious if it occurs in a critical anatomical site such as in the brain. Intracranial bleeding can be fatal. Low rates of intracranial bleeding and fatal bleeding were reported. The overall bleeding risk of apixaban was found to be similar to ASA and superior to warfarin in the non-valvular AF programme, similar to enoxaparin in the orthopaedic VTE prevention programme, and superior to enoxaparin/warfarin in VTE treatment patients.
Risk factors and risk groups	Concurrent use of other anticoagulants or antiplatelet therapies Patient characteristics: comorbid conditions (eg, 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). Past medical history (eg, previous stroke, prior GI bleeding) Coadministration of strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp) (eg, azole antifungals, protease inhibitors) may increase apixaban blood concentration and risk of bleeding. Therefore, coadministration of apixaban with strong inhibitors of both CYP3A4 and P-gp is not recommended. **Orthopaedic VTE Prevention indication** Patient characteristics: age > 75 years old. 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. The risk may also be increased by traumatic or repeated epidural or spinal puncture. **VTE Treatment indication** Coadministration of strong inducers of both CYP3A4 and P-gp may lead to a reduction in apixban exposure and is not recommended for the treatment of DVT and PE. 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.

Important identified risks

Bleeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction SmPC Section 4.8, Undesirable effects SmPC Section 4.9, Overdose Additional risk minimisation measures: Prescriber Guide Patient Alert Card

Important Potential Risks

Liver Injury	
Evidence for linking the risk to the medicine	Across the apixaban clinical program, there have been infrequent reports of liver-related AEs, SAEs, and laboratory abnormalities. In the VTE prevention orthopaedic population, the majority of events were post-operative transient elevations of ALT, AST, total bilirubin, and/or ALP that either resolved while study drug continued or during follow-up period. In the AF indication, the low frequency of LFT elevations and liver-related safety events is clinically important, and supports the favourable safety profile of apixaban for this indication. In VTE Treatment and Prevention of Recurrent VTE indication, most patients who experienced hepatic enzyme elevation were asymptomatic, however, some patients experienced symptoms depending on the severity of the condition.
Risk factors and risk groups	Prior hepatitis, cirrhosis, fatty liver, alcohol consumption, poor nutrition, co-existing chronic disease, co-administration of hepatically metabolized drugs (eg, statins), medication overdose, hypoperfusion, transfusion, halogen-anesthetics, analgesics, hepatotoxic antibiotics, autoimmune disease (autoimmune hepatitis), viruses (primarily HAV, HBV, HCV), hereditary conditions (eg, Wilson's disease)
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Potential risk of bleeding or thrombosis due to overdose or underdose	
Evidence for linking the risk to the medicine	Although post-marketing data has shown that medication errors occur infrequently, overdose as the most prevalent medication error has potentially serious consequences because of the increased risk of bleeding.

	The majority of events reported under the Medication errors HGLT for apixaban in pivotal studies were SAEs. The vast majority of cases reporting overdose, accidental overdose, intentional overdose or accidental exposure were asymptomatic. There was a single fatal outcome as a consequence of intentional suicidal overdose with phenazepam and alcohol.
Risk factors and risk groups	Risk factors include complex/unclear patient information, packaging, and product label, and use of the product in emergency situations
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 4.9, Overdose
	Additional risk minimisation measures: Prescriber Guide

Missing information

Use in patients with severe Renal Impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 4.4, Special warnings and precautions for use SmPC Section 5.2, Pharmacokinetic properties SmPC provides the dosing recommendation for patients with severe renal impairment for each indication
	Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ELIQUIS.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for apixaban.

7 LIST OF ABBREVIATIONS

Term	Definition
ACCP	American College of Chest Physicians
ACS	acute coronary syndrome
AE(s)	adverse event(s)
AF	atrial fibrillation
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
ALP	alkaline phosphatase
ALT	alanine transaminase
AR	adverse reaction
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BMS	Bristol-Myers Squibb
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRNM	clinically relevant non-major
CSR	clinical study report
CV	cardiovascular
DVT	deep vein thrombosis
EEA	European Economic Area
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ESC	European Society of Cardiology
EU	European Union
FXa	Factor Xa
GPRD	General Practice Research Database
HGLT	high level group term
HR	hazard ratio
INR	international normalized ratio
IBD	international birth date
LFT	liver function test
LMWH	low molecular weight heparin

Term	Definition
LTOLE	long-term open-label extension
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
N/A	not applicable
NVAF	non-valvular atrial fibrillation
NYHA	New York Heart Association
PAES	post-authorization efficacy studies
PASS	post-authorization safety studies
PBRER	Periodic Benefit-Risk Evaluation Report
PE	pulmonary embolism
PO	orally
PSUR	Periodic Safety Update Report
QD	once daily
RBC	red blood cell
RM	risk minimization
RMP	Risk Management Plan
SAE	serious adverse event
SCS	summary of clinical safety
SE	systemic embolism
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
THR	total hip replacement
TIA	transient ischaemic attack
TKR	total knee replacement
UFH	unfractionated heparin
ULN	upper limit of normal
US	United States
VKA	vitamin K antagonist
VTE	venous thromboembolic events
VTEp	orthopaedic VTE prevention
VTEt	treatment of DVT, treatment of PE and prevention of recurrent DVT and PE
WHO	World Health Organization

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

7 page(s) excluding cover page

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

Bristol-Myers Squibb

[Case_ID]

Adverse Event Report Questionnaire
Eliquis Bleeding Management

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM

Patient Demographics:

Patient's date of birth (DD/MMM/YYYY) or age: _____
Ethnicity: _____
Patient's weight: _____
Patient's baseline serum creatinine (prior to bleed): _____
Country Report Origin: _____

Gender: ☐ Male
☐ Female

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect product# 1	Suspect product# 2	Suspect product# 3
Product name	Eliquis		
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD/MMM/YYYY)			
Stop date (DD/MMM/YYYY)			
Lot/Batch number(s)			
Expiration date(s)			

Adverse Event (AE) Description: Please provide list diagnosis vs symptoms/signs if diagnosis is available.

	Bleeding
Site of bleeding	
Date of onset (DD/MMM/YYYY)	
Hemodynamically unstable and required treatment for hypotension (Y/N)	
Outcome (Resolved completely/Resolved with sequelae/Did not resolve/ Death/Unknown)	
Date of resolution (DD/MM/YYYY)	

☐Check if Eliquis was discontinued (even temporarily) as a result of this bleeding event.
☐Check if no other actions other than Eliquis discontinuation were used to stop bleeding.

Please check all of the following that were used to potentially reverse the patient's bleeding and provide any other details regarding the administration of any of these agents below:

☐Whole blood or Packed Red Blood Cells (PRBC)
☐Fresh frozen plasma (FFP)
☐Platelets
☐Factor VIIa
☐DDAVP (desmopressin)
☐Prothrombin Complex Concentrate (PCC) provide details such as type e.g. three-factor, four-factor or activated PCC (aPCC)
☐Protamine
☐Vitamin K
☐Trasylol (aprotinin)
☐Tranexamic acid
☐Activated charcoal
☐Surgery/other procedure (e.g. endoscopy)
☐Cautery
☐Hemodialysis
☐Manual Compression
☐Other, specify: _____

Please send the completed questionnaire via e-mail to worldwide.safety@bms.com or fax to 1-609-818-3804.

Bristol-Myers Squibb

[Case_ID]

Additional information (e.g., how much was given, how often, type of procedure, effectiveness, etc.)

Please list signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
Anti-Factor Xa assay					
PT and INR					
PTT					
Thrombin time					
Fibrin split products (FSPs)					
Hemoglobin					
Hematocrit					
Platelets					
D-dimers					

Did the adverse event(s) abate after suspect product(s) was stopped or dose reduced (if applicable)? ☐ Yes ☐ No
Did the adverse event(s) re-appear after re-introduction of the suspect product(s) (if applicable)? ☐ Yes ☐ No

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Was the patient receiving any other medications, concomitantly with Eliquis that may have contributed to this bleeding event (check all that apply and provide details in the table)?:

☐Other anti-thrombotics
☐Aspirin or other salicylates
☐Other antiplatelet drugs
☐HIV protease inhibitors
☐Fibrinolytics
☐Non-steroidal anti-inflammatory drugs
☐Azole-antimycotics (ketoconazole, voriconazole etc)

Please send the completed questionnaire via e-mail to worldwide.safety@bms.com or fax to 1-609-818-3804.

Bristol-Myers Squibb

[Case_ID]

Please list ALL other medications and doses the patient was taking at the time of or prior to (48 hours) the event below:

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)

Please provide any other pertinent details about the bleeding event and any attempts made to stop/control the bleeding:

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

Please check any of the following risk factors or conditions that may have contributed to the bleeding event:

☐Previous history of bleeding at this site
☐Trauma
☐Renal Impairment
☐Liver impairment
☐Coagulopathy
☐Family history of bleeding
☐Other vascular pathology
☐Overdose
☐Hypertension
☐Heart Failure
☐Diabetes
☐Prior Stroke
☐Other (please specify): _____

Additional questions:

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Please send the completed questionnaire via e-mail to worldwide.safety@bms.com or fax to 1-609-818-3804.

Adverse Event Report Questionnaire
For Liver Injury

CARES Number

PLEASE PROVIDE THE INFORMATION CHECKED (X) BELOW FOR THE REPORTED ADVERSE EVENT(S):

Patient's date of birth or age: Gender:

Please provide suspect product(s) [those product(s) that are suspected to be associated with one or more adverse events]:

Daily dose of the suspect product(s) and regimen:

Route of administration:

Indication(s) for which the suspect product(s) was (were) prescribed:

Starting and stop dates of treatment/ treatment duration:

Lot/Batch number(s) and Expiration date(s)

Provide any other suspect medications, not listed above, that may have contributed to the occurrence of the adverse event (s), including indication for which they were prescribed and treatment dates:

Please provide details of adverse event(s):

Start date if known:

Time lag if adverse event(s) occurred after cessation of treatment with the suspect product(s):

Signs and symptoms in chronological order:

Diagnostic tests (provide test names, dates, results and normal ranges – provide pre-treatment results if available):

Serum bilirubin (total and direct):

AST:

ALT:

Alk-P:

Albumin:

PT:

INR:

Labs for viral hepatitis (antigen/antibody/DNA):

Bicarbonate:

Eosinophils:

Imaging:

Histopathology:

Immune-histochemistry:

Other, specify:

Final diagnosis:

Did the event require hospitalization? If yes, specify which

event: Treatment of adverse event(s):

Adverse event(s) stop date and outcome (information on recovery and sequelae, if any):

For fatal outcome, please provide cause of death and a comment on its possible relationship to the suspect product(s):

Did the adverse event(s) abate after use stopped or dose reduced (if applicable)?

Did the adverse event(s) reappear after re-introduction of the suspect product(s) (if applicable)?

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Please list any concomitant medications and provide medication name, daily dose/ regimen, indication; start/stop date and time or duration:

NSAIDs, specify:

Amiodarone

Birth control pills, specify:

Chlorpromazine

Antibiotics, specify:

Anti-retroviral therapy, specify:

Halothane

Chemotherapy, specify:

Statins, specify:

Biologics, specify:

Other, specify:

Are there any other etiological factors: relevant medical and/or drug history (please mark with an "X" all that apply):
Hepato-biliary disease (specify):

Ischemic hepatitis (eg: hypotension or CHF) :

Viral hepatitis A, B, C or E (specify):

Hyperlipidemia

Bleeding disorders

Cardiovascular disease (specify):

Neoplasm (specify):

Autoimmune disease/ immune-compromised status (specify):

Obesity

Alcohol and/or tobacco and/or drug abuse (specify):

Recent vaccinations or travels (specify):

Occupational toxic agent (specify):

Relevant family history (specify):

Other (specify):

Additional questions:

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Annex 6: Details of Proposed Additional Risk Minimisation Activities (If Applicable)

1 page(s) excluding cover page

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

The Marketing Authorization Holder shall ensure that all physicians who are expected to prescribe apixaban are provided with the following educational material:

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

Key Elements of the Prescriber Guide

- Details of populations potentially at higher risk of bleeding
- Recommended dosages and guidance on the posology for different indications
- 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.

Key Elements of the Patient Alert Card

- 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