

RESEARCH AND DEVELOPMENT

APIXABAN

EU RISK MANAGEMENT PLAN

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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
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine transaminase
APIX	Apixaban
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
CVC	central venous catheters
DVT	deep vein thrombosis
EEA	European Economic Area
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ENOX	enoxaparin
ESC	European Society of Cardiology
EU	European Union
FXa	Factor Xa
GPRD	General Practice Research Database
HGLT	high level group term
HR	hazard ratio

Term	Definition
INR	international normalized ratio
IBD	international birth date
KID	Kid's Inpatient Database
LFT	liver function test
LMWH	low molecular weight heparin
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 minimisation
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
	orthopaedic VTE prevention

Term	Definition
VTEt	treatment of DVT, treatment of PE and prevention of recurrent DVT and PE
WARF	warfarin
WHO	World Health Organization

EU RISK MANAGEMENT PLAN (RMP) FOR APIXABAN

RMP version to be assessed as part of this application:

Version Number: 21.3

Data-lock Point for this RMP: 25-Mar-2022

Date of Final Sign-off: 27-May-2024

Rationale for submitting an updated RMP:

- Updated to include proposed indication of treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.
- Updated to include clinical exposure and safety data from CV185325, CV185155, CV185362, and CV185118
- Updated targeted bleeding and liver injury questionnaires in Annex 4
- Updated Annex 6 to include text referring to paediatric patients
- Updated Post-Authorization Exposure in Part 2.5

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)	Added epidemiology for VTE patients from 28 days to less than 18 years of age.	21.3 / pending
SII Non-clinical part of the safety specification	N/A	12.2 / 11-Jun-2014
SIII Clinical trial exposure	Updated to include clinical trial exposure from CV185325, CV185155, CV185362, and CV185118.	21.3 / pending
SIV Populations not studied in clinical trials	Updated Table 2.4.3-1 for CV185325, CV185155, CV185362, and CV185118.	21.3 / pending
SV Post-authorization experience	Updated post-authorization exposure.	21.3 / pending
SVI Additional EU requirements for the safety specification	N/A	14.0 / 19-May-2016
SVII Identified and potential risks	Updated to include safety data from CV185325, CV185155, CV185362, and CV185118.	21.3 / pending
SVIII Summary of the safety concerns	N/A	20.1 / 03-Oct-2019
Part III Pharmacovigilance Plan	N/A	18.0 / 21-Aug-2017
Part IV Plan for post-authorization efficacy studies	N/A	20.1 / 03-Oct-2019
Part V Risk Minimisation ures	N/A	18.0 / 21-Aug-2017

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part VI Summary of the Risk Management Plan	Aligned with proposed changes in current RMP	21.3 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Administrative update.	21.3 / pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	20.1 / 03-Oct-2019
ANNEX 4 Specific adverse drug reaction follow-up forms	Updated targeted bleeding and liver injury questionnaires	21.3 / pending
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	N/A	20.1 / 03-Oct-2019
ANNEX 6 Details of proposed additional risk minimisation activities	Updated to include text referring to paediatric patients.	21.3 / pending
ANNEX 7 Other supporting data	N/A	20.1 / 03-Oct-2019
ANNEX 8 Summary of changes to the risk management plan over time	Aligned with proposed changes in current RMP	21.3 / pending

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 20.1

Approved with procedure: EMEA/H/C/002148/II/0063

Date of approval (opinion date): 03-Oct-2019

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, 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:** 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. **Proposed:** Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.
Dosage in the EEA	**Current:** <u>Prevention of VTE: elective hip or knee replacement surgery in adults</u> The recommended dose of apixaban 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. <u>In patients undergoing hip replacement surgery</u> The recommended duration of treatment is 32 to 38 days. <u>In patients undergoing knee replacement surgery</u> The recommended duration of treatment is 10 to 14 days. <u>Prevention of stroke and SE in adult patients with NVAF</u> The recommended dose of apixaban is 5 mg taken PO BID.

Table 1-1: Product Details

Dose reduction
The recommended dose of apixaban 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) in adults
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.
The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily.

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

Table 1-1: Product Details

Proposed:

Treatment of VTE and prevention of recurrent VTE in paediatric patients:
Apixaban is available for paediatric use as a tablet or granules for oral suspension.
Treatment with apixaban in paediatric patients is based on weight-tiered dosing.
Apixaban is dosed based on body weight (Table 1) using the most appropriate formulation.
Apixaban treatment for paediatric patients from 28 days to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation therapy.
For weight not listed in the dosing table, no dosing recommendation can be provided.

Table 1: Dose recommendations for treatment of VTE and prevention of recurrent VTE in paediatric patients, by weight in kilograms (kg)

		Days 1-7		Day 8 and beyond	
Pharmaceutical forms	Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
Granules in Capsules for Opening 0.15 mg	4 to < 5	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
Coated Granules in Sachet 0.5 mg, 1.5 mg, 2.0 mg	5 to < 6	1 mg twice daily	2 mg	0.5 mg twice daily	1 mg
	6 to < 9	2 mg twice daily	4 mg	1 mg twice daily	2 mg
	9 to < 12	3 mg twice daily	6 mg	1.5 mg twice daily	3 mg
	12 to < 18	4 mg twice daily	8 mg	2 mg twice daily	4 mg
	18 to < 25	6 mg twice daily	12 mg	3 mg twice daily	6 mg
	25 to < 35	8 mg twice daily	16 mg	4 mg twice daily	8 mg
Film Coated Tablets 2.5 mg and 5.0 mg	≥ 35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

Based on VTE treatment guidelines in the paediatric population, duration of overall therapy should be individualised after careful assessment of the treatment benefit and the risk for bleeding.

Table 1-1:	Product Details
Pharmaceutical form (s) and strength(s)	**Current:** Film-coated tablets (2.5 and 5 mg) **Proposed:** 0.15 mg granules in capsules for opening 0.5 mg coated granules packaged in 0.5, 1.5, and 2 mg sachets
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 in Adult Patients

Table 2.1.1-1: Epidemiologic Characteristics of Total Knee Replacement and Total Hip Replacement in Adult 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.[1] 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.[2] 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.[3] 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:[4]
Prevalence	According to the Nationwide Inpatient Sample database, there were approximately 290,000 THRs in the US between Oct- 2005 and Dec-2006.[5] Prevalence of THR, incidences of primary THR, and percent revision burden:[6]

Table 2.1.1-1: Epidemiologic Characteristics of Total Knee Replacement and Total Hip Replacement in Adult 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	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:[7]

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:	Over a period from 1990 to 2004, the average age of patients undergoing TKR in the US decreased:

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

Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery	
age, gender, racial and/or ethnic origin	• 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[4] 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.[5]
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.[8] 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.[9]
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.[10]
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%.[11] 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.[11] 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).[12] 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. [13] 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.[14] A number of studies describe the prevalence of osteoarthritis and rheumatoid arthritis in THR/TKR patients.

2.1.2 *Atrial Fibrillation in Adult Patients*

Table 2.1.2-1: Epidemiologic Characteristics of Atrial Fibrillation in Adult 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	• Atrial Fibrillation (AF) is the most common chronic arrhythmia, accounting for one-third of hospitalizations for cardiac rhythm disturbances.[15] • 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.[16] • The incidence of AF is higher in men overall:[17] • 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.[18]
Prevalence	• Prevalence increases with age, approximately 1-2% for age 55-64 and 14-18% for age 80+ years.[19] • Approximately 3.2 million Americans had AF in 2005.[20] 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.[21]
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:[22] • 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[23]
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.[24]

Table 2.1.2-1: Epidemiologic Characteristics of Atrial Fibrillation in Adult 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.[25] 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).[26] 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).[27] 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.[28] 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).[29] Individuals with AF, including paroxysmal, persistent or permanent, were found to have a 5-fold increased risk of ischaemic stroke incidence and recurrences.[30,31] 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.[16]

Table 2.1.2-1: Epidemiologic Characteristics of Atrial Fibrillation in Adult 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:[32,33] (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.[34] 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 in Adult Patients

Table 2.1.3-1: Epidemiologic Characteristics of Deep Vein Thrombosis and Pulmonary Embolism in Adult 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).[35]

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.[36]

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.[37] 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[38] 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.[39] 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 in Adult 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,[40] 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:[39]

	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 in Adult 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.[41, 42,43] 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.[41,43,44,45]

In RIETE registry,[39] 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:[39]

	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:[46]

- Transient or definitive paralysis
- Congestive heart failure
- COPD
- Cancer
- Stroke

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

Treatment of DVT and/or PE	
	• 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.[47] 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).[48]

2.1.4 Venous Thromboembolism Paediatric Patients from 28 days to less than 18 years of age

Table 2.1.4-1: Epidemiologic Characteristics of Venous Thromboembolism in Paediatric Patients from 28 days to less than 18 years of age

Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.	
Incidence	• The incidence of VTE in children at a population level is very low; 0.07 to 0.14 per 10,000 children and varies in different age groups and is asymptomatic in 35% of children.[49] In hospitalized children, the reported rate was higher, at ≥ 58 per 10,000 admissions.[50] • Based on data from the National Hospital Discharge Registry,[49] for the years 1979 to 2001 inclusive, the incidence rates of assignment of ICD 9 diagnostic codes for VTE and pulmonary embolism in hospitalized patients from the neonatal period to < 18 years of age, were 0.9/100,000/year and 4.9/100,000/year, respectively. The rates were higher for infants and adolescents 15 - 17 years of age than for children 2 - 14 years of age.[49] • The incidence of VTE in children with ALL or other malignancies has been reported to vary widely, from 1 to 50%.[51] More recently, the incidence among children with newly diagnosed ALL in the Netherlands was reported to be 7.6%.[52]
Prevalence	In a report from the Netherlands registry study, in 1999, a total of 99 children had VTE. The prevalence of VTE was estimated to be 2.7 per 100,000 paediatric patients 29 days to 18 years of age, based on the at-risk population in this country at the same time (3,626,343).[49]

Table 2.1.4-1: Epidemiologic Characteristics of Venous Thromboembolism in Paediatric Patients from 28 days to less than 18 years of age

Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.	
Demographics of the population: age, gender, racial and/or ethnic origin	In The Netherlands, the annual incidence of VTE was calculated based on the age range: [49] The annual incidence of VTE per age category was: • Ages 0 – 28 days: 14.5 per 10,000 children • Ages 29 - 265 days: 0.25 per 10,000 children • Ages 1- 4 years old: 0.08 per 10,000 children. • Ages 5 - 9 years old: 0.1 per 10,000 children. • Ages 10 - 14 years old: 0.18 per 10,000 children • Ages 15 - 18 years old: 0.05 per 10,000 children. • Overall incidence rate from 0-18 years old: 0.14 per 10,000 children. A study report from a children's hospital in Alabama (US) showed: • The incidence of thrombosis was 21.9 per 10,000 admissions (0.22%) with no gender or racial differences.[53] • The incidence of VTE was 58 VTE in 23,548 white children=24.6/ 10,000 and 32 VTE in 15,518 African-American children=20.6/10,000 (P=ns) with no gender or racial differences.[53]
Risk factors for the disease	A systematic literature review identified a total of eight potential risk factors associated with VTE in children. The presence of CVC was found to be the single most prevalent predisposing risk factor associated with VTE in children. CVC was present in 29% (210/727) of the patients diagnosed with VTE. Infections including osteomyelitis, septic arthritis, septicemia, and local infection was the second most common (20%) associated risk factors of the disease. Miscellaneous risk factors included cystic fibrosis, use of oral contraceptives, congenital diaphragmatic hernia, cleft palate with dehydration, renal dialysis, fibrosing mediastinitis, diabetes, sickle cell disease, and lower extremity venous malformation.[54]
Main treatment options	Goals of treating VTE are to prevent local extension and embolization of the thrombus, aid in resolving the existing thrombus, prevent VTE recurrence, and minimize long-term complications .[55] Treatment options for VTE include LMWH (e.g. dalteparin), UFH, DOAC (e.g. dabigatran and rivaroxiban), and VKA (e.g. warfarin). The use of other anticoagulant agents such as fondaparinux, argatroban, and bivalorudin is limited in childern.[55]
Mortality and morbidity (natural history)	Age-specific mortality estimated at 6.4 per 1,000 child-years in a population-based study conducted in Canada.[53,56]
Important co-morbidities	A large population claims database from Kid's Inpatient Database (KID) reported that underlying chronic illnesses were associated with most VTE (76.2%). Cardiovascular (18.4%), malignancy (15.7%), and neuromuscular disease (9.9%)

Table 2.1.4-1: Epidemiologic Characteristics of Venous Thromboembolism in Paediatric Patients from 28 days to less than 18 years of age

Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.	
	were most commonly reported. VTE not associated with chronic illness were most often idiopathic (12.6%), followed by infections (9.5%) and trauma (9.1%).[57]

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 caused no adverse effects, including no effects on mating or fertility, in juvenile rats dosed for 3 months at AUC multiples ≤ 5.4×.[58]

Apixaban is excreted into rat milk.[59] 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	Based on the observed overlap between apixaban exposures associated with antithrombotic

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

Key Safety Findings	Relevance to human usage
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.	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
Adult patients		

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

Study Number (Indication)	Study Title	Number Treated Subjects
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
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

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

Study Number (Indication)	Study Title	Number Treated Subjects
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 medical 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
Paediatric patients		
CV185325 (VTE)[a]	A Randomized, Open-Label, Active Controlled, Safety and Descriptive Efficacy Study in Pediatric Subjects Requiring Anticoagulation for the Treatment of a Venous Thromboembolic Event	Apix: 143 SOC: 71
CV185155 (VTE)	A Phase III Randomized, Open Label, Multi-center Study of the Safety and Efficacy of Apixaban for Venous Thromboembolism Prevention versus No Systemic Anticoagulant Prophylaxis during Induction Chemotherapy in Children with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (T or B cell) Treated with Asparaginase	Safety Population[b] Apix:256 SOC: 256
CV185362 (VTE)	A Prospective, Randomized, Open Label, Multi-center Study of the Safety and Pharmacokinetics of Apixaban versus Vitamin K Antagonist or LMWH in Pediatric Subjects with Congenital or Acquired Heart Disease Requiring Chronic Anticoagulation for Thromboembolism Prevention	Apix: 126 SOC: 62
CV185118 (VTE)	Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Apixaban in Pediatric Subjects at Risk for a Venous or Arterial Thrombotic Disorder	Apix: 49

[a] Ongoing

[b] Safety Population: All randomized subjects, as there is no intervention on top of the standard of care in the SOC arm.

2.3.1 All Orthopaedic Adult 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 Adult 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.[60]

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 Adult 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]
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 VTE Treatment and Prevention Studies in Paediatric Patients (CV185325/CV185155/CV185362/CV185118)

Data are not pooled for the paediatric studies due to substantial differences in study design and the clinical diagnoses of the at-risk paediatric patients included in CV185325, CV185155, CV185362 and CV185118. In CV185325, subjects randomized to the SOC arm received a dosing regimen of anticoagulation treatment based on usual and customary care per local clinical practices and that was aligned with the current, internationally recognized ACCP and ASH guidelines, or equivalent, for at least 12 weeks (> 2 years to < 18 years of age limited to heparins and VKA). Neonates (birth to ≤ 27 days) and children 28 days to < 2 years of age received SOC for 6 to 12 weeks. SOC was limited to heparin in subjects < 2 years old (UFH or LMWH). The SOC in CV185155 was no systemic anticoagulant prophylaxis, and in CV185362 was VKA or LMWH.

Exposure tables presented by duration of exposure, age group and gender for Study CV185325, CV185155, and Study CV185362 are presented in Table 2.3.4-1 through Table 2.3.4-6. Exposure tables presented by race and gender are included in Appendix 2.

CV185118 was a single dose study. The number of subjects dosed by age group is presented in Table 2.3.4-7. Demographic characteristics are included in Appendix 2.

Table 2.3.4-1: Duration of Exposure (Main Phase) - Safety Analysis Set (CV185325)

	Apixaban N = 143		SOC N = 71	
Duration	Persons	Person-time (Years)	Persons	Person-time (Years)
≤ 14 days	4	0.038	4	0.066
15 - 42 days	6	0.485	4	0.350
43 - 84 days	66	14.11	36	7.674
ays	67	16.53	27	6.522

Table 2.3.4-1: Duration of Exposure (Main Phase) - Safety Analysis Set (CV185325)

	Apixaban N = 143		SOC N = 71	
Total	143	31.16	71	14.61

Main Study Treatment Phase was defined as from Day 1 to Day 84 End of Treatment.

SDTM Creation: 22AUG2022 (15:17) Source Data: adex Table Generation: 16MAR2023 (11:34) Output File: ./Unblinded_IA/B0661037_RMP/adex_s001_rmp

Table 2.3.4-2: Clinical Trial Exposure by Age Group and Gender (Main Phase) - Safety Analysis Set (CV185325)

	Apixaban N = 143					
	Male		Female		Total	
Age Group	Persons	Person-Time (Years)	Persons	Person-Time (Years)	Persons	Person-Time (Years)
Neonates up to 27 days	1	0.016	1	0.123	2	0.140
28 days to < 2 Years	10	2.133	11	2.015	21	4.148
2 Years - < 12 Years	10	1.985	19	4.474	29	6.459
12 Years - < 18 Years	40	8.523	51	11.89	91	20.42

	SOC N = 71					
	Male		Female		Total	
Age Group	Persons	Person-Time (Years)	Persons	Person-Time (Years)	Persons	Person-Time (Years)
Neonates up to 27 days	1	0.233	1	0.101	2	0.334
28 days to < 2 Years	7	1.344	3	0.561	10	1.906
2 Years - < 12 Years	8	1.629	6	1.068	14	2.697
12 Years - < 18 Years	14	2.943	31	6.732	45	9.676

Main Study Treatment Phase was defined as from Day 1 to Day 84 End of Treatment.

SDTM Creation: 22AUG2022 (15:17) Source Data: adex Table Generation: 16MAR2023 (11:34) Output File: ./Unblinded_IA/B0661037_RMP/adex_s002_rmp

Table 2.3.4-3: Duration of Exposure, Not Taking Into Account Interruptions During the Treatment Period - Study Safety Population (CV185155)

	Apixaban N = 256		SOC N = 256	
Length of Exposure (Days)	Persons[1]	Person-time (yrs)[2]	Persons[1]	Person-time (yrs)[2]
≤ 30	256	17.14	256	18.66
31 - 61	13	0.14	13	0.15

Exposure (in days) calculated as date of end of treatment period - randomization date + 1.

1. is the patients entering interval i = number of patients with exposure >= lower bound of interval i

2. 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: BMS_GBS\CV185\PZA88817\Biostatistics\Production\Tables\RMP\rt-ex-durcv185155.sas 14MAR2023:23:48

Table 2.3.4-4: Clinical Exposure, Not Taking Into Account Interruptions, by Age Group and Gender During the Treatment Period - Study Safety population (CV185155)

	Apixaban N = 256				SOC N = 256			
	Persons[1]		Person-time (yrs)[2]		Persons[1]		Person-time (yrs)[2]	
Age Category	M	F	M	F	M	F	M	F
28 days to < 24 months	1	0	0.07	0	4	3	0.30	0.23
2 years to < 12 years	103	103	7.10	6.79	110	82	8.01	6.10
12 years ≤ 18 years	37	12	2.43	0.90	35	22	2.53	1.64

Exposure (in days) calculated as date of end of treatment period - randomization date + 1.

1. is the total number of subjects in each category of the subgroup

2. is the cumulative patient-year of each category

Program Source: BMS_GBS\CV185\PZA88817\Biostatistics\Production\Tables\RMP\rt-ex-aggencv185155.sas 14MAR2023:23:48

Table 2.3.4-5: Duration of Exposure, Not Taking Into Account Interruptions -All Treated Subjects (CV185362)

	Apixaban N = 126		VKA/LMWH N = 62	
Length of Exposure (Days)	Persons[1]	Person-time (yrs)[2]	Persons[1]	Person-time (yrs)[2]
≤ 30	126	10.19	62	5.09
31 - 180	122	49.06	62	25.17
181 - 336	118	47.75	59	24.35
337 - 360	101	5.40	47	2.65
> 360	58	1.65	32	1.20

Exposure (in days) calculated as last dose of study drug - first dose of study drug + 1.

1. is the patients entering interval i = number of patients with exposure >= lower bound of interval i

2. 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: BMS_GBS\CV185\PZA88818\Biostatistics\Production\Tables\RMP\rt-ex-durcv185362.sas 15MAR2023:00:59

Table 2.3.4-6: Clinical Exposure, Not Taking Into Account Interruptions, by Age Group and Gender During the Treatment Period - All Treated Subjects (CV185362)

	Apixaban N = 126				VKA/LMWH N = 62			
	Persons[1]		Person-time (yrs)[2]		Persons[1]		Person-time (yrs)[2]	
Age Category	M	F	M	F	M	F	M	F
28 days to < 24 months	3	5	1.90	3.80	1	2	0.45	1.22
2 years to < 12 years	41	46	36.37	42.70	25	19	22.90	19.07
12 years ≤ 18 years	16	15	14.61	14.65	13	2	12.85	1.96

Exposure (in days) calculated as last dose of study drug - first dose of study drug + 1.

1. is the total number of subjects in each category of the subgroup

2. is the cumulative patient-year of each category

Program Source: BMS_GBS\CV185\PZA88818\Biostatistics\Production\Tables\RMP\rt-ex-aggencv185362.sas 15MAR2023:00:59

Table 2.3.4-7: Apixaban Dose in Each Age Group - CV185118

Paediatric Subject Groups	Dose	Number Treated
Group 1 Neonates up to 27 days[a]	0.1 mg	1
Group 2B Infants 28 days to < 9 months	1.08 mg/m^2	11
Group 2A Young Children 9 months to < 2 years	1.08 mg/ m^2	5
Group 2A[b] Young Children 9 months to < 2 years	2.43 mg/ m^2	4
Group 3 Young Children 2 years to < 6 years	1.17 mg/ m^2	8
Group 4 Children 6 years to <12 years	1.80 mg/ m^2	10
Group 5 Adolescents 12 years to <18 years	2.19 mg/ m^2	10

[a] Neonates up to 27 days of age (≥ 34 weeks gestational age or ≥ 37 weeks post conceptual age)

[b](n=4 additional subjects)

Source: SCS Table 2.2.1.1-1

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

Exposure tables for adult 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,d]	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,d]	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,d]	Effect on fetus and breastfeeding is unknown	No	Population excluded from clinical development program. Apixaban is not recommended for pregnant and/or lactating women.
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] ALT > 3X ULN or conjugated bilirubin > 2x ULN[d]	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] Inadequate renal function defined by estimated glomerular filtration rate assessment based on the Schwartz formula[d]	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

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
Use of acetylsalicylic acid (ASA) > 165 mg/day[c,d]	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,d]	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

[d] VTE Treatment and Prevention Studies in Paediatric Patients

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

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

Type of special population	Exposure
Patients with renal impairment	Severe: Not included in the clinical development programme 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]	Paediatric subjects: • 143 subjects treated in CV185325 • 126 treated in CV185362 • 250 subjects treated in CV185155 • 49 subjects treated in CV185118
Elderly[b]	39139 subjects

[a] CV185325 (interim data cutoff date 25-Mar-2022); CV185362 (data cutoff date18-Oct-2021); CV185155 (data cutoff date 07-Jul-2021); CV185118 (data cutoff date 27-May-2020).

[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. However, an estimate of the number of treated patients is derived from available sales figures.

Sales figures for apixaban are available to the MAH 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 available to the MAH 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 (e.g., direct to consumer sales, hospital sales, and home care sales).[61]

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 available to the MAH and is an approximation of total quantity of ELIQUIS sold during the period from IBD (18-May-2011) to 31-Dec-2021, 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) 8-17 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-2021 is estimated to be 87,255,011 patients. The cumulative patient years of exposure for this period is estimated to be 42,007,471 patient-years.This is an estimate and should be interpreted with caution, taking into account the above-mentioned limitations.[61]

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[62] (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

There are no new or reclassification of safety concerns with the submission of the updated RMP.

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. 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. In pediatric subjects requiring anticoagulation for the treatment of a VTE event (CV185325), no subjects in the apixaban or SOC groups had an adjudicated Major bleeding event. There were 2 (1.4%) subjects in the apixaban arm and 1 (1.4%) subject in the SOC group who had at least 1 adjudicated CRNM bleeding event. The events in the apixaban group were mild epistaxis in a subject in the 12 to < 18 years age group and moderate pericardial haemorrhage in a subject in the 28 days to < 2 years age group. Neither event was an SAE or considered by the investigator to be related to treatment, and both had an outcome of recovered/resolved. The frequency of all adjudicated bleeding events (Major, CRNM, or Minor) was 36.4% in the apixaban group and 29.6% in the SOC group.[63] In paediatric subjects with ALL or LL receiving induction chemotherapy (CV185155), the incidence of Major bleeding during treatment with induction chemotherapy in the apixaban and SOC (no prophylaxis) treatment groups was similar, with events having occurred in 2 subjects (0.8%) in each group. The incidence of the composite of adjudicated Major bleeding and adjudicated CRNM bleeding events during treatment with induction chemotherapy was numerically higher in the apixaban treatment group (13 [5.1%]) as compared to that in the SOC group (5 [2.0%]). The most common

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

reported treatment-related CRNM bleeding event was epistaxis, reported in 8 (3.1%) subjects in the apixaban treatment group and reported in no subjects in the SOC treatment group. Epistaxis is consistent with the known safety profile of apixaban in adult patients and therefore is neither a new nor an unexpected event. Overall, the rate of clinically important bleeding events was low.[63]

In paediatric subjects with congenital or acquired heart disease requiring chronic prophylactic anticoagulation (CV185362), 1 (0.79%) subject in the apixaban treatment group and 3 (4.84%) subjects in the VKA/LMWH treatment group met the primary safety endpoint of the composite of adjudicated Major or CRNM bleeding events. Epistaxis was reported more frequently in the apixaban treatment group relative to the VKA/LMWH treatment group (all causality 15.9% vs 9.7%; treatment-related 7.1% vs 3.2%) but all events were Grade 1. This finding is consistent with previous experience with apixaban in adults, in whom epistaxis was identified as a common adverse reaction[63].

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.l%; gastrointestinal tract: apixaban 0.6%, enoxaparin 0.3%, intraocular: apixaban 1 (< 0.1%), enoxaparin 0, and haemarthrosis resulting in intervention: apixaban 5 (0.1%), enoxaparin 6 (0.1%) (Source: SCS[64] Appendix 7.G1P2)

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

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

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)

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

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

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

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding			
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

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.

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

IV VTE Treatment and Prevention of Recurrent VTE in Paediatric Patients Study CV185325

	Apixaban (N = 143)		Standard of Care (N = 71)
Major bleeding	0		0
95% CI[a]			
Relative Risk			
95% CI[b]			
p-value[b]			
CRNM bleeding	2 (1.4)		1 (1.4)
95% CI[a]	(0.1, 5.3)		(0.0, 8.3)
Relative Risk		0.98	
95% CI[b]		(0.1, 10.7)	
p-value[b]		0.9846	
Minor bleeding	51 (35.7)		21 (29.6)
95% CI[a]	(28.3, 43.8)		(20.2, 41.1)
Relative Risk		1.19	
95% CI[b]		(0.8, 1.8)	
p-value[b]		0.3795	
All Bleeding	52 (36.4)		21 (29.6)
95% CI[a]	(28.9, 44.5)		(20.2, 41.1)
Relative Risk		1.22	
95% CI[b]		(0.8, 1.8)	
p-value[b]		0.3309	

[a] 95% CI was calculated using the Agresti-Coull method.

[b] 95% CI and p-value were calculated using the Cochran-Mantel-Haenszel test stratified by age group.

Source: Study CV185325 Interim CSR[65] Table 18

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding

Study CV185155

	Apixaban n = 256	SOC n = 256
Major Bleeding Events	2 (0.8%)	2 (0.8%)
95% CI	(0.03%, 2.99%)	(0.03%, 2.99%)
Relative Risk	1.00	
95% CI	(0.14, 7.01)	
p-value	1.00	
CRNM bleeding	11 (4.3%)	3 (1.2%)
95% CI	(2.33%, 7.62%)	(0.24%, 3.55%)
Relative Risk	3.67	
95% CI	(1.04, 12.97)	
p-value	0.0303	
Minor bleeding	37 (14.5%)	20 (7.8%)
95% CI	(10.64%, 19.32%)	(5.06%, 11.82%)
Relative Risk	1.85	
95% CI	(1.10, 3.10)	
p-value	0.0169	

95% confidence interval for single event rates is constructed based on Agresti-Coull's method.

Two-sided p-value and 95% CI for relative risk are calculated using Cochran-Mantel-Haenszel test stratified by age at baseline. Adjusted relative risk of event rates takes into consideration age at baseline as a stratification factor.

Treatment period refers to the period from the day of randomization through either 2 days after early discontinuation or end of treatment Day 29 ±5 visit.

Percentage is calculated based on number of randomized subjects

Source: SCS[63] Table 3.1.2-1

Study CV185362

	Apixaban n = 126	VKA/LMWH n = 62
Major Bleeding	1 (0.79)	1 (1.61)
95% CI	(0.02, 4.34)	(0.04, 8.66)
Difference from VKA/LMWH	-0.82	
95% CI	(-8.14, 3.29)	
Relative Risk	NE	
CRNM Bleeding	1 (0.79)	2 (3.23)
95% CI	(0.02, 4.34)	(0.39, 11.17)
Difference from VKA/LMWH	-2.43	
95% CI	(-10.54, 1.94)	
Relative Risk	NE	
All Bleeding	47 (37.30)	23 (37.10)
95% CI	(28.86, 45.75)	(25.07, 49.12)
Difference from VKA/LMWH	0.20	
95% CI	(-14.49, 14.90)	

Table 2.7.3.1-1: Important Identified Risk: Bleeding

Important Identified Risk: Bleeding	
	Relative Risk 1.01 95% CI 0.68, 1.51 Relative risk and 95% CI calculated based on Mantel-Haenszel's method stratified by age and clinical diagnosis were to be evaluated if the total number of events is above 5. This was applicable to primary and secondary endpoints only. Included events with onset between first dose and within 2 days of last dose of study medication. 95% CI of event rate was calculated based on normal approximation, if the number of events in that treatment group is ≥ 5, otherwise exact approximation was used. This was applicable to primary and secondary endpoints only. Source: SCS[63] Table 3.2.2-1 **Study CV185118** In CV185118, AEs of clinical interest were defined as those relating to Major bleeding or CRNM bleeding events. One subject had an AE of mild contusion considered by the investigator to be a procedural complication and not related to apixaban treatment and 1 subject had a clinical laboratory AE of prolonged aPTT that was not associated with any bleeding events.[63]
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 **Orthopaedic VTE Prevention Indication** 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

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

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).[64]

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).[64] 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):

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

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.

Study CV185056

Laboratory Parameter	Apixaban	Enoxaparin/ Warfarin

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

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%]	0	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.7.3A

IV VTE Treatment and Prevention of Recurrent VTE in Paediatric Patients

CV185325

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

One treatment-emergent SAE corresponding to hepatobiliary disorders was reported in 1 subject in the apixaban group (0.7%), and none in the SOC group. This SAE of DILI, which was reported in a subject in the 12 to < 18 year age group, was investigator-assessed as severe and not related to apixaban but, instead, to concomitant antitumor chemotherapy for on-going acute lymphocytic leukaemia. Chemotherapy received during the 7 days prior to the onset of DILI on Day 40 included cytarabine, mercaptopurine, methotrexate, pegylated asparaginase, and vincristine. Study drug was temporarily interrupted and the outcome of the event was subsequently reported as recovered/resolved. No subjects in either treatment group met Hy's law criteria for possible DILI.[63,65]

CV185155

While SAEs corresponding to hepatobiliary disorders were not reported in either treatment group, serum AST or ALT elevations to > 3× the ULN, associated with subsequent elevations of serum total bilirubin concentrations to > 2× the ULN, findings consistent with the Hy's Law criteria for possible DILI, were reported for 13 subjects for whom the combined findings were available: 5/247 (2.0%) and 8/248 (3.2%) subjects in the apixaban and SOC treatment (no anticoagulant treatment) groups, respectively.[63]

Summary of Liver Related Elevations During the Treatment Period SI Units Randomized Subjects with Available Measurements - CV185155

	Apixaban N = 256	Standard of Care N = 256
AST ELEVATION		
> 3xULN, n/N (%)	21/247 (8.5)	23/247 (9.3)
> 5xULN, n/N (%)	13/247 (5.3)	9/247 (3.6)
> 10xULN, n/N (%)	5/247 (2.0)	4/247 (1.6)
> 20xULN, n/N (%)	0/247	2/247 (0.8)
ALT ELEVATION		
> 3xULN, n/N (%)	76/247 (30.8)	79/248 (31.9)
> 5xULN, n/N (%)	42/247 (17.0)	35/248 (14.1)
> 10xULN, n/N (%)	15/247 (6.1)	17/248 (6.9)
> 20xULN, n/N (%)	4/247 (1.6)	5/248 (2.0)
ALT OR AST ELEVATION (NOT NECESSARILY ON SAME DATE)		
> 3xULN, n/N (%)	78/247 (31.6)	83/248 (33.5)
> 5xULN, n/N (%)	43/247 (17.4)	38/248 (15.3)
> 10xULN, n/N (%)	15/247 (6.1)	17/248 (6.9)
> 20xULN, n/N (%)	4/247 (1.6)	5/248 (2.0)
BOTH ALT AND AST ELEVATION ON SAME DATE		
> 3xULN, n/N (%)	19/247 (7.7)	18/248 (7.3)
> 5xULN, n/N (%)	12/247 (4.9)	6/248 (2.4)
> 10xULN, n/N (%)	4/247 (1.6)	4/248 (1.6)
> 20xULN, n/N (%)	0/247	2/248 (0.8)
CONJUGATED BILIRUBIN ELEVATION		
> 1.5xULN, n/N (%)	24/179 (13.4)	21/164 (12.8)
> 2xULN, n/N (%)	17/179 (9.5)	12/164 (7.3)
DIRECT BILIRUBIN (BILDIR) > 2XULN	17/179 (9.5)	12/164 (7.3)
TOTAL BILIRUBIN (BILI) > 2XULN	8/101 (7.9)	10/102 (9.8)
AT AND TOTAL BILIRUBIN (BILI) ELEVATION		

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

(ALT>3XULN OR AST>3XULN) AND BILI>2XULN ON SAME DATE, n/N (%)	5/247 (2.0)	8/248 (3.2)
(ALT>3XULN OR AST>3XULN) AND BILI>1.5XULN ON SAME DATE, n/N (%)	6/247 (2.4)	10/248 (4.0)
TREATMENT DISCONTINUATIONS RELATED TO ELEVATION	7 (2.7)	0
IN LIVER FUNCTION TESTS (%) WITHIN 14 DAYS PRIOR TO THE ONSET OF THE AE THAT LED TO DISCONTINUATION:		
(ALT>3xULN or AST>3xULN) AND TBILI >2xULN ON SAME DATE	3 (1.2)	1 (0.4)
ALT>5xULN ON TWO CONSECUTIVE LAB DRAWS	1 (0.4)	0

The denominator to calculate percentages for each event is the total number of treated subjects with available laboratory results associated with that event during Treatment Period.
Marked Abnormality Criteria are based on the result in SI units.
Source: SCS[63] Table 5.3.1-1

CV185362

SAEs corresponding to hepatobiliary disorders were not reported in either treatment group. Serum ALT or AST elevations > 3 × ULN associated with subsequent elevations of serum total bilirubin concentrations > 2 × ULN (findings consistent with the Hy's Law criteria for possible DILI) were reported in none of the subjects with available measurements in either treatment group.[63]

Summary of Liver-Related Elevations During the Treatment Period - SI Units - All Treated Subjects with Available Measurements - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
AST ELEVATION		
> 3xULN, n/N (%)	0/125	2/62 (3.2)
> 5xULN, n/N (%)	0/125	0/62
> 10xULN, n/N (%)	0/125	0/62
> 20xULN, n/N (%)	0/125	0/62
ALT ELEVATION		
> 3xULN, n/N (%)	1/125 (0.8)	0/62
> 5xULN, n/N (%)	0/125	0/62
> 10xULN, n/N (%)	0/125	0/62
> 20xULN, n/N (%)	0/125	0/62
ALT OR AST ELEVATION (NOT NECESSARILY ON SAME DATE)		
> 3xULN, n/N (%)	1/125 (0.8)	2/62 (3.2)
> 5xULN, n/N (%)	0/125	0/62
> 10xULN, n/N (%)	0/125	0/62
> 20xULN, n/N (%)	0/125	0/62
BOTH ALT AND AST ELEVATION ON SAME DATE		
> 3xULN, n/N (%)	0/125	0/62
> 5xULN, n/N (%)	0/125	0/62
> 10xULN, n/N (%)	0/125	0/62
> 20xULN, n/N (%)	0/125	0/62
TOTAL BILIRUBIN ELEVATION		
> 2xULN, n/N (%)	6/125 (4.8)	3/62 (4.8)
CONJUGATED BILIRUBIN ELEVATION		

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury

	> 2xULN, n/N (%) 4/114 (3.5) 1/57 (1.8) AT AND TOTAL BILIRUBIN (TBILI) ELEVATION (ALT>3XULN OR AST>3XULN) AND TBILI>2XULN ON SAME DATE, n/N (%) 0/125 0/62 AT AND CONJUGATED BILIRUBIN (DBILI) ELEVATION (ALT>3XULN OR AST>3XULN) AND DBILI>2XULN ON SAME DATE, n/N (%) 0/125 0/62

The denominator to calculate percentages for each event was the total number of treated subjects with available laboratory results associated with that event.

Included values that meet the criteria during treatment period (first dose up to 2 days after last dose of study medication) and were larger than the baseline value.

Source: SCS[63] Table 5.3.2-1

CV185118

Summary of marked laboratory abnormalities results of protocol-specific MA criteria-SI Units - CV185118

	Total N = 49		
	n	Low	High
ALT (U/L)	46	NE	1 (2.2)
AST (U/L)	47	NE	1 (2.1)
BILIRUBIN, TOTAL (UMOL/L)	47	NE	2 (4.3)

NE=Not Evaluated

Percentages based on subjects with laboratory test results. Includes all records after first dose.

n denotes number of subjects with no-missing test result as per MA Criteria.

Source: CV185118 CSR[66] Table S.7.1.2a

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)
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.

Table 2.7.3.1-2: Important Potential Risk: Liver Injury

Important Potential Risk: Liver Injury	
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.
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

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

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

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)

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

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

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

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	
	IV VTE Treatment and Prevention of Recurrent VTE in Paediatric Patients There were no instances of intentional overdose in CV185325, CV185118, CV185155, or CV185362. In CV185325, 2 incidences of overdose were reported in the apixaban treatment group. One incidence of overdose was associated with an AE of Heavy Menstrual Bleeding (outcome reported as resolved) and one incidence of overdose no AEs occurred due to the overdose. In CV185362, one case of unintentional overdose was reported in the apixaban treatment group. No AEs occurred due to the overdose[63]

Study CV185362

High Level Group Term Preferred Term (%)	**Apixaban n = 126**	**VKA/LMWH n = 62**
Injury, poisoning and procedural complications		
Incorrect dose administered	1 (0.8)	0

Source: SCS[63] Table 4.1.3.3-2

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	

Table 2.7.3.2-1: Missing Information

Missing Information	Is the safety profile expected to be different from the general target population?
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 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 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 Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 **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
Liver Injury	**Routine risk communication:** SmPC Sections 4.2, 4.3, 4.4, and 4.8 **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 **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 of the marketed formulations. 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 Sections 4.2, 4.4, and 5.2 **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.

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

Safety concern	Routine risk minimisation activities
	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 Minimisation	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. **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 minimisation (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 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/ or caregivers and healthcare professionals on the important identified risk of bleeding during treatment with apixaban and its appropriate management.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimisation	Objectives/Rationale
	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 and/ or 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. **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 Minimisation Measures

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

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Bleeding	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9	**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

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Liver Injury	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, and 4.8	**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 Sections 4.2 and 4.9,	**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
- Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age

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/or caregivers 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.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 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 Sections 4.2, 4.3, 4.4, and 4.8 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 Sections 4.2, and 4.9 Additional risk minimisation measures: Prescriber Guide

Missing information

Use in patients with severe Renal Impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 5.2 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.

APPENDIX 2: CLINICAL TRIAL EXPOSURE

21 page(s) excluding cover page

APPENDIX 2: CLINICAL TRIAL EXPOSURE

1 APIXABAN

Clinical trial exposure analyses include cumulative dose and clinical exposure by duration, age, gender, and racial origin. For apixaban, clinical trial exposure analyses are presented in the following tables:

- Tables 1: CV185030
- Table 2: CV185048
- Table 3: Pooled CV185010, CV185034, CV185035, and CV185047
- Table 4: CV185030
- Table 5: CV185048
- Table 6: Pooled CV185010, CV185034, CV185035, and CV185047
- Table 7: CV185030
- Table 8: CV185048
- Table 9: Pooled CV185010, CV185034, CV185035, and CV185047
- Table 10: CV185030
- Table 11: CV185048
- Table 12: Pooled CV185010, CV185034, CV185035, and CV185047
- Table 13: CV185030
- Table 14: CV185048
- Table 15: Pooled CV185010, CV185034, CV185035, and CV185047
- Table 16: CV185155
- Table 17: CV185362
- Table 18: CV185118
- Tables 19 and 20: CV185325

Table 1: Extent of Exposure from First Through Last Day of Dosing, 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: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions Treated Subjects (CV185048)

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 3: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions 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 4: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Dose Treated Subjects (CV185030)

Dose	Apixaban N = 9088		Warfarin N = 9052	
	Persons*	Person-time**	Persons*	Person-time**
APIX/PLACEBO 2.5 MG BID	424	621.7	402	565.8
APIX/PLACEBO 5 MG BID	8664	14912.3	8650	14618.0

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-exposureaf030d-v02.sas 25JUN2013:16:57:06

Table 5: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Dose Treated Subjects (CV185048)

Dose	Apixaban N = 2798		ASA N = 2780	
	Persons*	Person-time**	Persons*	Person-time**
APIX/PLACEBO 2.5 MG BID	178	178.9	182	188.7
APIX/PLACEBO 5 MG BID	2620	3014.0	2598	2961.6

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-exposureaf048d-v02.sas 25JUN2013:16:57:56

Table 6: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Dose Treated Subjects (Pooled CV185010, CV185034, CV185035, and CV185047)

Dose	APIX 2.5MG BID N = 5924		ENOX N = 5904	
	Persons*	Person-time**	Persons*	Person-time**
APIX / PLACEBO 2.5MG BID	5924	354.9	5904	351.9

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-exposurevtepd-v02.sas 25JUN2013:16:59:11

Table 7: Extent of Exposure from First Through Last Day of Dosing, 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 8: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Age Group and Gender Treated Subjects (CV185048)

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 9: Extent of Exposure from First Through Last Day of Dosing, 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 10: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Race and Gender Treated Subjects (CV185030)

Race	Apixaban N = 9088				Warfarin N = 9052			
	Persons*		Person-time**		Persons*		Person-time**	
	M	F	M	F	M	F	M	F
WHITE	4892	2620	8531.7	4456.1	4867	2602	8396.0	4295.9
BLACK/AFRICAN AMERICAN	88	37	131.4	68.8	61	41	95.1	60.7
ASIAN	794	508	1321.0	808.0	845	483	1376.3	766.6
OTHER	94	55	140.2	76.7	106	47	133.9	59.4

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-exposureaf030rg-v02.sas 25JUN2013:16:57:16

Table 11: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Race and Gender Treated Subjects (CV185048)

Race	Apixaban N = 2798				ASA N = 2780			
	Persons*		Person-time**		Persons*		Person-time**	
	M	F	M	F	M	F	M	F
WHITE	1316	900	1539.7	1065.5	1222	949	1442.1	1086.3
BLACK/AFRICAN AMERICAN	7	3	8.2	3.3	15	11	18.9	12.0
ASIAN	312	225	315.5	220.3	355	186	355.4	188.1
OTHER	21	14	25.3	15.4	21	21	25.8	21.7

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-exposureaf048rg-v02.sas 25JUN2013:16:58:21

Table 12: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Race and Gender Treated Subjects (Pooled CV185010, CV185034, CV185035, and CV185047)

Race	APIX 2.5MG BID N = 5924				ENOX N = 5904			
	Persons*		Person-time**		Persons*		Person-time**	
	M	F	M	F	M	F	M	F
WHITE	2116	3157	138.1	181.8	2086	3170	138.1	178.7
BLACK/AFRICAN AMERICAN	48	102	2.7	5.7	57	84	3.7	4.0
ASIAN	154	279	10.3	13.7	140	311	9.0	16.0
OTHER	19	49	0.6	1.8	15	41	0.4	1.4

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-exposurevteprg-v02.sas 25JUN2013:16:59:04

Table 13: Extent of Exposure from First Through Last Day of Dosing, 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 14: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions, by Special Population Treated Subjects (CV185048)

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 15: Extent of Exposure from First Through Last Day of Dosing, 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

Table 16: Extent of Exposure, Not Taking Into Account Interruptions, by Race and Gender During the Treatment Period for CV185155 (Study Safety Population)

	Apixaban N = 256				Standard of Care N = 256			
	Persons*		Person-time**		Persons*		Person-time**	
Race	M	F	M	F	M	F	M	F
WHITE	109	85	7.33	5.77	114	80	8.25	5.95
BLACK OR AFRICAN AMERICAN	7	5	0.48	0.33	4	8	0.30	0.62
ASIAN	11	14	0.68	0.89	17	10	1.13	0.73
AMERICAN INDIAN OR ALASKA NATIVE	1	0	0.08	0	1	0	0.09	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	0	0.07	0	0	0	0	0
OTHER	12	11	0.95	0.69	13	9	1.08	0.66

Exposure (in days) calculated as date of end of treatment period - randomization date + 1.
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of each category
Program Source: BMS_GBS\CV185\PZA88817\Biostatistics\Production\Tables\RMP\rt-ex-racgencv185155.sas 14MAR2023:23:48

Table 17: Extent of Exposure, Not Taking Into Account Interruptions, by Race and Gender for CV185362 Study (All Treated Subjects)

	Apixaban N = 126				VKA/LMWH N = 62			
	Persons*		Person-time**		Persons*		Person-time**	
Race	M	F	M	F	M	F	M	F
WHITE	55	52	47.86	49.44	30	20	27.95	19.01
BLACK OR AFRICAN AMERICAN	1	6	1.00	5.11	0	2	0	2.02
ASIAN	3	3	3.01	1.67	4	0	3.35	0
AMERICAN INDIAN OR ALASKA NATIVE	0	1	0	1.00	0	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0	0	0	0
OTHER	1	4	1.02	3.93	5	1	4.91	1.23

Exposure (in days) calculated as last dose of study drug - first dose of study drug + 1.
* is the total number of subjects in each category of the subgroup
** is the cumulative patient-year of each category
Program Source: BMS_GBS\CV185\PZA88818\Biostatistics\Production\Tables\RMP\rt-ex-racgencv185362.sas 15MAR2023:00:59

Table 18: Demographic and Baseline Characteristics - CV185118

Parameter	Group 5 (N=10)	Group 4 (N=10)	Group 3 (n=8)	Group 2A (N=9)	Group 2B (N=11)	Group 1 (N=1)	All Subjects (N=49)
Age, years, months, or days	**(years)**	**(years)**	**(years)**	**(months)**	**(days)**	**(days)**	**(years)**
Mean (SD)	13.7 (1.4)	7.4 (1.2)	3.6 (1.2)	13.3 (4.2)	126.9 (67.2)	9.0 (-)[a]	5.1 (5.2)
Range	12-15	7-8	2 -5	9-22	30-263		0 -16.0
Gender, n (%)							
Male	4 (40.0)	4 (40.0)	4 (50.0)	4 (44.4)	5 (45.3)	0	21 (42.9)
Female	6 (60.0)	6 (60.0)	4 (50.0)	5 (55.6)	6 (54.5)	1 (100.0)	28 (57.1)
Race, %							
White	7 (70.0)	8 (80.0)	8 (100.0)	9 (100.0)	9 (82.0)	1 (100.0)	42 (85.7)
Black or African American	3 (30.0)	2 (20.0)	0	0	0	0	5 (10.2)
Other	0	0	0	0	2 (18.0)	0	2 (4.1)
Ethnicity, %							
Hispanic/Latino	0	3 (30.0)	1 (12.5)	0	5 (45.5)	1 (100.0)	10 (20.4)
Not Hispanic/Latino	6 (60.0)	5 (50.0)	2 (25.0)	4 (44.4)	3 (27.3)	0	20 (40.8)
Not Reported	4 (40.0)	2 (20.0)	5 (62.5)	5 (55.6)	3 (27.3)	0	19 (38.8)
Weight, kg							
Mean (SD)	49.9 (17.1)	29.8 (11.1)	15.9 (4.7)	8.3 (2.4)	4.9 (1.7)	3.1 (-)	21.5 (19.3)
Range	32.1-80.9	19.4-47.6	10.8-25.2	4.0-11.8	3.0-8.5	-	3.0-80.9
Body Surface Area, m^2							
Mean (SD)	1.5 (0.3)	1.0 (0.2)	0.7 (0.1)	0.4 (0.1)	0.3 (0.1)	0.2 (-)	0.8 (0.5)
Range	1.2 -2.0	0.8-1.4	0.5-0.9	0.3-0.5	0.2-0.4	-	0.2-2.0
Body Mass Index, kg/m^2							
Mean (SD)	19.4 (4.5)	17.7 (4.3)	14.9 (1.8)	15.6 (2.55)	14.4 (2.35)	11.9 (-)	16.3 (3.8)
Range	14.3-27.2	13.5-26.7	11.4-17.2	10.1-17.9	10.9-17.5	-	10.1-27.2

$$BSA(m^2) = \sqrt{\frac{weight\ (\text{kg}) \times height\ (\text{cm})}{3600}}$$

[a] Enrollment/screening procedures began when subject was 9 days old; at the time study drug administration, subject was 15 days old.

Group 5: Adolescents 12 years to <18 years; Group 4: Children 6 years to <12 years Group 3: Young Children 2 years to < 6 years; Group 2A: Young Children 9 months to < 2 years; Group 2A: Young Children 9 months to < 2 years; Group 2B: Infants 28 days to < 9 months; Group 1: Neonates up to 27 days old

Source: CV185118 CSR Table S.3.1 (Summary Demography) and CV185118 CSR Table S.3.2 (Summary Physical Measurements)

Table 19: Extent of Exposure by Race and Gender (Main Phase) - Safety Analysis Set (CV185325)

	Apixaban (N=143)					
	Male		Female		Total	
Race:	Persons	Person Time (Years)	Persons	Person Time (Years)	Persons	Person Time (Years)
WHITE	43	8.832	67	15.00	110	23.84
BLACK	12	2.412	9	2.146	21	4.559
ASIAN	3	0.701	1	0.211	4	0.912
OTHER	3	0.712	5	1.144	8	1.856

Main Study Treatment Phase was defined as from Day 1 to Day 84 End of Treatment.
PFIZER CONFIDENTIAL SDTM Creation: 22AUG2022 (15:17) Source Data: adex Table Generation: 16MAR2023 (11:34)
Output File: ./Unblinded_IA/B0661037_RMP/adex_s003_rmp

Table 20: Extent of Exposure by Race and Gender (Main Phase) - Safety Analysis Set (CV185325)

	Standard Of Care (N=71)					
	Male		Female		Total	
Race:	Persons	Person Time (Years)	Persons	Person Time (Years)	Persons	Person Time (Years)
WHITE	25	4.964	28	5.807	53	10.77
BLACK	1	0.241	7	1.339	8	1.580
ASIAN	2	0.465	1	0.219	3	0.684
OTHER	2	0.479	5	1.098	7	1.577

Main Study Treatment Phase was defined as from Day 1 to Day 84 End of Treatment.
PFIZER CONFIDENTIAL SDTM Creation: 22AUG2022 (15:17) Source Data: adex Table Generation: 16MAR2023 (11:34)
Output File: ./Unblinded_IA/B0661037_RMP/adex_s003_rmp

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

Important Identified or Potential Risk	AE Follow-up Form Title
Bleeding	Adverse Event Report Questionnaire - Eliquis Bleeding Management
Liver Injury	Adverse Event Report Questionnaire - Liver Injury / Drug induced liver injury (DILI)

Follow-up Forms

Adverse Event Report Questionnaire – Eliquis Bleeding Management

Adverse Event Report Questionnaire - Liver Injury / Drug induced liver injury (DILI)

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P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

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: _____ Gender: ☐ Male ☐ Female
Ethnicity: _____
Patient's weight: _____
Patient's baseline serum creatinine (prior to bleed): _____
Country Report Origin: _____

Age Group:_____

(Age Group Definition: Neonate=0.002 years-0.077 years, Infant=0.078 years-1.999 years,Child=2 years-11.999 years, Adolescent=12 years-17.999 years, Adult=18 years-64.999 years and Elderly=65 years-199 years)

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)

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☐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: _____

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

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

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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 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): _____

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

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[Case_ID]

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.



[Case_ID]

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

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

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[Case_ID]

Adverse Event Report Questionnaire
Liver injury / Drug induced liver injury (DILI)

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

Patient Demographics:

Patient's date of birth (DD/MMM/YYYY) or age: _____ Gender: ☐ Male
Ethnicity: _____ ☐ 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			
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 details of hepatic event and if patient experienced any additional events in the table below.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (yes/no)				
Cause of Death (Y/N)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				

Does the patient have any of the following signs and symptoms related to hepatic event (If Yes, provide dates):

1. Fever?	☐ Yes	☐ No
2 Nausea?	☐ Yes	☐ No
3. Vomiting?	☐ Yes	☐ No
4. Abdominal pain?	☐ Yes	☐ No
5. Abdominal tenderness?	☐ Yes	☐ No
6. Joint pain/ arthralgia?	☐ Yes	☐ No
7. Joint swelling?	☐ Yes	☐ No
8. Rash?	☐ Yes	☐ No
9. Urticaria?	☐ Yes	☐ No
10. Mucosal inflammation or ulceration?	☐ Yes	☐ No
11. Asterixis?	☐ Yes	☐ No
12. Confusion/ disorientation?	☐ Yes	☐ No

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13. Coma?	☐ Yes	☐ No
14. Jaundice?	☐ Yes	☐ No
15. Ascites?	☐ Yes	☐ No
16. Peripheral oedema?	☐ Yes	☐ No
17. Palmar erythema?	☐ Yes	☐ No
18. Fatigue?	☐ Yes	☐ No
19. Lymphadenopathy?	☐ Yes	☐ No
20. Dark urine?	☐ Yes	☐ No
21. Other liver-related signs or symptoms?	☐ Yes	☐ No

If Yes, please specify:

Diagnostic tests (use additional pages if needed):

1. **Please provide results of imaging studies performed for the Adverse Event:**

Test Name	Pre-treatment (Baseline -with date)	At the time of AE (with date)
Magnetic resonance imaging (MRI)/ Magnetic resonance cholangiopancreatography(MRCP)		
Abdominal ultrasound		
Computerized tomography(CT) scan		
ERCP (Endoscopic retrograde cholangiopancreatography)		
Liver biopsy		
Any other imaging/diagnostic studies (please specify)		

2. **Laboratory tests (provide test unit, if applicable):**

Lab specimen collection date for the following lab tests:			___ / ___ / ___ (dd/mm/yy)		
Test Name	**Pre-treatment value (baseline)**	**AE onset value**	**AE resolution value**	**Normal low**	**Normal high**
Aspartate aminotransferase (AST)					
Alanine aminotransferase (ALT)					
Alkaline phosphatase (Alk-P)					
Liver-specific alkaline phosphatase					
Bone-specific alkaline phosphatase					
Albumin					
Prothrombin Time (PT)					
Serum bilirubin (Total/direct/ indirect)					
PT-INR					

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Test Name	Pre-treatment value (baseline)	AE onset value	AE resolution value	Normal low	Normal high
Haptoglobin					
Creatine kinase					
Aldolase					
Gamma glutamyl transferase					
Bicarbonate					
Haemoglobin					
Haematocrit					
Platelets					
Leukocytes (WBC)					
Erythrocyte count (RBC)					
Eosinophils					
Neutrophils					
Lymphocytes					
Monocyte					
Basophils					
Histopathology					
Other (please specify)					

3. Immune-histochemistry/serology tests:

Lab specimen collection date:		___/___/___(dd/mm/yy)		
Test	**Result**	**Unit**	**No unit**	**Not done**
☐ Urine ethylglucuronide				
☐ Serum phosphatidylethanol				
☐ Urine toxicology				
☐ Antinuclear antibodies				
☐ Anti-smooth muscle antibody (or anti-actin)				
☐Hepatitis B virus surface antigen				
☐ Hepatitis B virus core antibody				
☐ Hepatitis B virus DNA				
☐ Hepatitis B virus surface antibody				
☐ Hepatitis A virus antibody IgM				
☐ Hepatitis A virus antibody				
☐ Hepatitis E virus IgG antibody				
☐ Hepatitis E virus IgM antibody				
☐ Hepatitis E virus IgA antibody				
☐ Hepatitis E virus RNA				
☐ Hepatitis C virus antibody				
☐ Hepatitis C virus RNA				
☐ Other (please specify)				

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

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

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

Please mark with an "x" all that apply, and specify medication details below:

☐ NSAIDs ☐ Amiodarone ☐ Birth control pills ☐ Chlorpromazine ☐ Antibiotics ☐ Statins ☐ Halothane

☐ Herbal supplements ☐ Chemotherapy ☐ Anti-retroviral therapy ☐ Anti-TB drugs ☐ Biologics

☐ Acetaminophen(paracetamol) ☐ Dietary or nutritional supplements ☐ Other, specify:

If any of the above is checked, please provide details below:

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

Has any of the following occurred within one week before the hepatic event?

☐ Has the subject taken acetaminophen (paracetamol)? If Yes, provide details.

_____

☐ Did the subject engage in vigorous physical exercise? If Yes, provide details.

_____

☐ Did the subject eat wild mushrooms? If Yes, provide details.

_____

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):

_____

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

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[Case_ID]

Medical history:

Does the subject have a history of any of the conditions below?: a. If Yes, please give start date (dd/mm/yyyy)	**If Yes in column (a):** Is the condition/ event still ongoing? If No, please give end date (dd/mm/yyyy)
Hepato-biliary disease/Gallbladder disease (please specify; Examples: gallbladder stones, cholecystitis, bile duct stones): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Ischemic hepatitis (eg: hypotension or Congestive heart failure (CHF)): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Viral hepatitis A, B, C, D or E (please specify type): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Hyperlipidemia ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Bleeding disorders ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Haemochromatosis ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Nonalcoholic fatty liver disease(NAFLD) ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Nonalcoholic steatohepatitis (NASH) ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Alcohol-related liver disease? Examples: alcohol related cirrhosis, alcohol related hepatitis, steatosis ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Drug-induced liver injury (DILI): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Cardiovascular disease (please specify): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Neoplasm (please specify): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Autoimmune disease/ immune-compromised status, including Autoimmune hepatitis? (please specify): ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Jaundice or hyperbilirubinaemia ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
HIV infection? ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Tuberculosis? ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Right heart failure ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Seizures ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Systemic infection or sepsis? ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Herpes infection? ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Recent drop in blood pressure or shock? ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Hepatic metastasis ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___
Diabetes/Uncontrolled diabetes mellitus? ☐Yes, started: ___/___/___ ☐No	☐Yes ☐No, ended: ___/___/___ If ongoing, does the subject require: ☐Insulin? ☐Other oral or parenteral agents? ☐Dietary therapy alone?
Inflammatory bowel disease (Crohn's disease or ulcerative colitis)? ☐Yes, started: ___/___/___ ☐No	
Obesity ☐Yes, started: ___/___/___ ☐No	

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[Case_ID]

Recent vaccinations (please specify):	
Recent travel to areas at risk for viral hepatitis (A, B, C, D and E)? (Examples include: Hepatitis A–Mediterranean or South America; Hepatitis B–South-East Asia; Hepatitis E–India, Mexico) If Yes: Please specify area(s)	☐Yes _____ _____
Exposure to an environmental or industrial toxin or a chemical agent? If Yes: Check **ALL** that apply: a) Exposure date: b) Industrial solvent c) Insecticide d) Aflatoxin e) Other	☐Yes ___ / ___ / ___ (dd/mm/yy) ☐ ☐ ☐ ☐ Specify:_____
Has the subject gained or lost more than 5 lbs. (2 kg) in weight? If Yes, please provide date of assessment & Amount of weight gained or lost: in lbs. or kg.	☐Yes
Has the subject received parenteral nutrition? If Yes, provide details.	
Has the subject had significant weight loss? If Yes, provide details.	
Has the subject had a blood transfusion?	☐Yes
Has the subject obtained a tattoo(s), acupuncture, or piercing?	☐Yes
Has the subject been exposed to anyone with jaundice or hepatitis? If Yes: Check **ALL** that apply with dates: a) Hepatitis A b) Hepatitis B c) Hepatitis C d) Hepatitis E e) Jaundice	☐Yes ☐ ☐ ☐ ☐ ☐
Family history (please specify): a. Do any of the subject's first-degree relatives have alpha-1 antitrypsin deficiency? b. Do any of the subject's first-degree relatives have autoimmune disease? c. Do any of the subject's first-degree relatives have hereditary haemochromatosis?	☐ Yes ☐ Yes ☐ Yes
Recreational drugs/alcohol/tobaccoabuse (please specify amount/day, years of intake):	
Other (please specify):	

Additional questions:

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

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

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

The Marketing Authorization Holder (MAH) shall ensure that in each Member State where Eliquis is marketed, all healthcare professionals who are expected to prescribe Eliquis have access to/are provided with the following educational materials:

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

All patients and/or caregivers of paediatric patients who receive Eliquis shall be provided with a Patient Alert Card (provided within each medicine pack).

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 and/or caregivers of paediatric 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 healthcare 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 healthcare professionals that they are taking Eliquis if they need to have any surgery or invasive procedure