EU RISK MANAGEMENT PLAN (RMP)

XARELTO®

BAY59-7939
(Rivaroxaban)

No. 14.3

Date of Report:
24 AUG 2023

[redacted]

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

EU Risk Management Plan for Xarelto (Rivaroxaban)

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List of abbreviations

ABI	Ankle brachial index
ACCP	American College of Chest Physician
ACE	Angiotensin-converting enzyme
ACM	All-cause mortality
ACS	Acute Coronary Syndrome
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ALI	Acute limb ischemia
AMI	Acute Myocardial Infarction
APCC	Activated Prothrombin Complex Concentrate
aPTT	activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
aRR	Adjusted RR
ASA	Acetylsalicylic Acid
ATC	Anatomical Therapeutic Chemical
ATLAS ACS 2-TIMI 51	Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2-Thrombolysis In Myocardial Infarction 51 trial
AUC	Area Under the Curve
AUC/D	Dose-Normalised Area Under the Curve
BID	*bis in die*/Twice Daily
BMI	Body mass Index
CABG	Coronary artery bypass graft

CAD	Coronary Artery Disease
CASSINI	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, superiority study that compared the efficacy and safety of rivaroxaban with placebo for primary prophylaxis of VTE (defined as DVT and/or PE) in ambulatory adult men and women, 18 years of age and older, with various cancer types who were scheduled to initiate systemic cancer therapy as a component of their standard-of-care anticancer regimen
CCS	Chronic Coronary Syndromes
CHADS2	Score for risk estimation of stroke
CHA_2DS_2-VASc	Score for risk estimation of stroke
CEC	Clinical Endpoint Committee
CHMP	Committee for Medical Products for Human Use
CI	Confidence Interval
CIAC	Central Independent Adjudication Committee
CKD	Chronic Kidney Disease
CLI	Chronic Limb Ischemia
C_{max}	Maximum Observed Plasma Concentration
COMMANDER HF	Randomized, double-blind, event-driven, multicenter study comparing the efficacy and safety of rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an episode of decompensated heart failure
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
CRNM	Clinically Relevant Non Major
CSR	Clinical Study Report

CSVT	Cerebral Vein and Sinus Thrombosis
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	Cardiovascular
CVC	Central venous catheter
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
DDI	Drug-Drug-Interaction
DLP	Data Lock Point
DOAC	Direct oral anticoagulant
DSRU	Drug Safety Research Unit
DTE	Death or first thromboembolic events
DUS	Drug utilization and outcome study
DUSS	Drug utilization and safety study
DVT	Deep Vein Thrombosis
DVT-T	Treatment of Deep Vein Thrombosis (DVT) and Prevention of Recurrent DVT and Pulmonary Embolism (PE) in Adults
EEA	European Economic Area
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EoT	End of treatment
EINSTEIN CHOICE	Reduced-dosed rivaroxaban and standard-dosed rivaroxaban versus acetylsalicylic acid in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism

EINSTEIN Extension	Once-daily oral direct factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism
EINSTEIN Junior	Multicenter, open-label, active-controlled, randomized phase III study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism
EINSTEIN-DVT	Multicentre, randomized, open-label, assessor-blind, event-driven, non-inferiority study for efficacy of rivaroxaban compared with LMWH followed by dose-adjusted vitamin K antagonists in patients with confirmed acute symptomatic DVT without symptomatic PE
EINSTEIN-PE	Multicentre, randomized, open-label, assessor-blind, event-driven, non-inferiority study for efficacy of rivaroxaban compared with LMWH followed by dose-adjusted vitamin K antagonists in patients with confirmed acute symptomatic PE with or without symptomatic DVT
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
EU	European Union
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
F	Female
GALILEO	Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes.
GePaRD	German Pharmacoepidemiological Research Database
GI	Gastrointestinal
GRACE	Global Registry of Acute Coronary Events
GPRD	General Practice Research Database

HF	Heart failure
HFS	Hip Fracture Surgery
HIT	Heparin-induced thrombocytopenia
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRS	Heart Rhythm Society
ICOPER	International Cooperative Pulmonary Embolism Registry
INN	International Nonproprietary Names
INR	International normalised ratio
IPCD	Intermittent pneumatic compression device
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intend to treat
KID	Kid's Inpatient Database
LA	Left atrial
LAA	Left atrial appendage
LDH	Low-dose heparin
LDUH	Low-dose unfractionated heparin
LEAD	Lower extremity artery disease
LER	Lower extremity revascularization
LMWH	Low-molecular-weight heparin
LP	Last patient
M	Male

M-PEM	Modified Prescription Event Monitoring
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiovascular Events
MAGELLAN	Multicenter, rAndomized, parallel Group Efficacy and safety study in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin
MAH	Marketing Authorisation Holder
MALE	Major adverse limb events
MATS	Malmo Thrombophilia Study
MedDRA	Medical Dictionary for Regulatory Activities
MARINER	Medically Ill Patient Assessment of Rivaroxaban Versus Placebo IN Reducing Post-Discharge Venous Thrombo-Embolism Risk
Med ill	Medically Ill
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial Infarction
min	minutes(s)
MSSO	Maintenance and Support Services Organization
NAVIGATE ESUS	Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS)
NHS	National Health Service
NHSRxS	National Health Service Prescription Services
NICU	Neonatal intensive care unit
NOACs	Other Non-VKA Oral Anticoagulants
NSAID	Non-Steroidal Anti-Inflammatory Drug

NSTE-ACS	Non-ST Segment Elevation Acute Coronary Syndrome
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
NVAF	Non-Valvular Atrial Fibrillation
NYHA	New York Heart Association
OD	Once Daily
Op	Operative
OR	Odds Ratio
OSCS	Over-sulfated chondroitin sulfate
PAC	Patient Alert Card
PAD	Peripheral artery disease
PASS	Post Authorisation Safety Study
PBE	Primary bleeding event
PBRER	Periodic Benefit-Risk Evaluation Report
PCC	Prothrombin Complex Concentrate
PCI	Percutaneous Coronary Intervention
P/C	Parents/caregivers
PD	Pharmacodynamic
PDCO	Paediatric Committee
PE	Pulmonary Embolism
PEM	Prescription Event Monitoring
PE-T	Treatment of pulmonary embolism (PE) and prevention of recurrent deep vein (DVT) thrombosis and PE in adults
P-gp	P-glycoprotein
PiCT	Prothrombinase-induced Clotting Time

PIONEER	An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PL	Package Leaflet
PLATO	Study of Platelet Inhibition and Patient Outcomes
PO	*per os*/By Mouth
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	Prospective Epidemiological Study of Myocardial Infarction
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTS	Post-Thrombotic Syndrome
PV	Pharmacovigilance
PVI	Peripheral vascular interventions
QD	Per day
QoL	Quality of Life
QPPV	Qualified Person Pharmacovigilance
QT	QT interval
RBCs	Red Blood Cells
REACH	Reduction of Atherothrombosis for Continued Health
RECORD	REgulation of Coagulation in ORthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism
rFVIIa	recombinant Factor VIIa
RMP	Risk Management Plan

ROCKET	Rivaroxaban once daily oral direct Factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial
RR	Risk Ratio
SAE	Serious Adverse Event
SAPT	Single antiplatelet therapy
SCEM	Specialist Cohort Event Monitoring
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SN	Study Number
SOC	System Organ Class
SPAF	Stroke Prevention in Atrial fibrillation
SR	Sustained Release
STEMI	ST-Segment Elevation Myocardial Infarction
TAVR	Transcatheter Aortic Valve Replacement
TBD	To Be Decided
TDD	Total Daily Dose
TEAE	Treatment Emergent Adverse Event
THIN	The Health Improvement Network
THR	Total Hip Replacement
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis In Myocardial Infarction (classification)
TKR	Total Knee Replacement
UA	Unstable Angina
UFH	Unfractionated Heparin

ULN	Upper Limit of Normal
VARC	Valve Academic Research Consortium (classification)
VENTURE-AF	A prospective, randomized, open-label, active-controlled, multi-center study to explore the safety of uninterrupted rivaroxaban compared with uninterrupted VKA in adults with non-valvular AF who underwent catheter ablation
VKA	Vitamin K Antagonist
VOYAGER PAD	An international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial investigating the efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic peripheral artery disease undergoing lower extremity revascularization procedures
VTE	Venous Thromboembolism
VTE-P	Venous Thromboembolism Prophylaxis
VTE-T	Venous Thromboembolism Treatment
XAMOS	Xarelto in the prophylaxis of post-surgical venous thromboembolism after elective major orthopaedic surgery of hip or knee
XANTUS	Xarelto in prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation: A non-interventional study
XAPAEDUS	Xarelto Paediatric VTE PASS Drug Utilization Study: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism
X-TRA	A prospective, interventional, single-arm, open-label, multicenter study designed to explore once-daily oral rivaroxaban for the resolution of left atrial (LA)/left atrial appendage (LAA) thrombus in patients with nonvalvular atrial fibrillation (AF) or atrial flutter and LA/LAA thrombus confirmed by a transesophageal echocardiogram (TEE)

X-VERT	A prospective, randomized, open-label, parallel-group, active-controlled, multicentre study exploring the efficacy and safety of once daily oral rivaroxaban (BAY 59-7939) compared with that of dose-adjusted oral vitamin K antagonists (VKA) for the prevention of cardiovascular events in subjects with nonvalvular atrial fibrillation scheduled for cardioversion

Part I: Product(s) overview

Table Part I.1–Product(s) overview

Active substance(s) (INN or common name)	Rivaroxaban
Pharmacotherapeutic group(s) (ATC Code)	B01AF01
Marketing Authorisation Holder or Applicant	Bayer
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Xarelto
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Rivaroxaban is a pure (S)-enantiomer. It is an odourless, non-hygroscopic, white-to-yellowish powder. Chemical name: 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-thiophene-carboxamide Empirical formula: C19H18ClN3O5S Molecular weight: 435.85
	Summary of mode of action: Due to its direct inhibitory effect on clotting Factor Xa, rivaroxaban inhibits blood clotting in vitro and in vivo. Due to the pharmacokinetic properties of the molecule, the drug is suitable for oral administration
	Important information about its composition: *Film coated tablet*: Excipients are as follows: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium lauryl sulphate, and magnesium stearate. In addition, the film coat contains the following: macrogol 3350, hypromellose, titanium dioxide (E 171), iron oxide yellow (E172) (2.5 mg) and iron oxide red (E 172) (10 mg, 15 mg,and 20 mg). *Granules for oral suspension*: Excipients are as follows: citric acid anhydrous, flavour sweet and creamy, hypromellose 5 cP, mannitol, microcrystalline cellulose and carmellose sodium, sodium benzoate, sucralose, and xanthan gum.

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Hyperlink to the Product Information	Proposed updated Product Information as available in Module 1.3.1
Indication(s) in the EEA	Current: Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (See section 4.4 for haemodynamically unstable PE patients) Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack Xarelto co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (See sections 4.3, 4.4, and 5.1) Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least five days of initial parenteral anticoagulation treatment.
	Proposed (if applicable): None
Dosage in the EEA	Current (if applicable): *Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery* The recommended dose is 10 mg taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery provided. *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult (See section 4.4 for haemodynamically unstable PE patients)* Patients should be treated with 15 mg twice daily for the first three weeks. Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the

	patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting. When extended prevention of recurrent DVT and PE is indicated (following completion of at least six months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg once daily, a dose of Xarelto 20 mg once daily should be considered. (see sections 4.4, 5.1 and 5.2). *Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack* The recommended dose is 20 mg once daily, which is also the recommended maximum dose. For patients with moderate renal impairment (creatinine clearance 30–49 mL/min) or severe (creatinine clearance 15–29 ml/min) the recommended dose is 15 mg once daily. *Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers* The recommended dose is 2.5 mg twice daily. Patients should also take a daily dose of 75–100 mg ASA or a daily dose of 75–100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. *Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.* The recommended dose is 2.5 mg twice daily. Patients taking Xarelto 2.5 mg twice daily should also take a daily dose of 75-100 mg ASA. *Xarelto is indicated for the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.* Xarelto is available for pediatric use as a tablet or granules for oral suspension. Xarelto is dosed based on body weight using the most appropriate formulation
	Proposed (if applicable):

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Part I: Product(s) Overview

	None
Pharmaceutical form(s) and strengths	Current: • Xarelto 1 mg/mL granules for oral suspension • Film-coated tablet, 2.5 mg • Film-coated tablet, 10 mg • Film-coated tablet, 15 mg • Film-coated tablet, 20 mg
	Proposed (if applicable): None
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Xarelto is indicated for:

- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack
- Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers
- Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events
- Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

SI.1 Indication: VTE prevention in patients undergoing elective hip or knee replacement surgery

Patients undergoing major orthopaedic surgery represent the highest risk group for thromboembolism. The real incidence, prevalence and mortality rates of VTE are likely to be underestimated because the disease is often clinically silent and because autopsy data are limited.

Incidence

Table SI-1 summarizes the estimated incidence of non-fatal, symptomatic post-operative VTE in patients undergoing major orthopaedic surgery, defined as THR, TKR and HFS, without and with prophylaxis.

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Table SI-1: Estimated incidence of non-fatal, symptomatic VTE after major orthopaedic surgery (THR, TKR and HFS) (1)

Estimated incidence of nonfatal, symptomatic VTE, %	Postoperative days 0–14	Postoperative days 15–35	Postoperative days 0–35
No prophylaxis	VTE: 2.80 (PE: 1.00; DVT: 1.80)	VTE: 1.50 (PE: 0.50; DVT: 1.00)	VTE: 4.30 (PE: 1.50; DVT: 2.80)
LMWH	VTE: 1.15 (PE: 0.35; DVT: 0.80)	VTE 0.65 (PE: 0.20; DVT: 0.45)	VTE: 1.80 (PE: 0.55; DVT: 1.25)

DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.

Demographics of the population in the authorized indication and risk factors for the disease

In an international survey of 18 countries investigating TKR surgery (primary and revision), the proportion of female patients was 65.8% (range, 56.0%–72.8%), and the proportion of patients younger than 65 years of age was 30.5% (range, 19.7%–43.6%) (2).

In an observational database (The Hip and Knee Registry, US), 44% of THR patients and 38% of TKR patients were male, and 93% and 92% were white, respectively (3). In a European registry (post-2004), the mean ages of patients undergoing THR, TKR and HFS were 62, 67 and 71 years, respectively; 41% of patients undergoing THR, 29% of patients undergoing TKR and 31% undergoing HFS were male (4).

In an analysis of hip fractures in the US Medicare population (786,717), 92%–95% of patients were white, 3%–5% black and 2%–3% other races (5).

Patients undergoing surgery – in particular total hip and knee surgery (THR and TKR) – without thromboprophylaxis are at high risk of deep vein thrombosis (DVT) (incidence 40%-60%) (6). Factors that have been shown to increase the risk of VTE following major orthopaedic surgery include a history of previous VTE, current obesity, delayed mobilization, advanced age and cancer (6).

In a recent meta-analysis of 14 retrospective case–control or prospective cohort studies of patients undergoing total hip replacement or TKR surgery, three main risk factors were significantly associated with VTE: history of VTE (risk ratio [RR] >10.6), varicose vein (RR >2.7) and congestive heart failure (RR >2.0) (7). There was also an increase of VTE risk for female gender, black race, obesity, malignancy, hypertension and age ≥80 years (7).

The main existing treatment options

In patients undergoing THR or TKR, one of the following therapies is recommended for a minimum of 10–14 days for TKR: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted dose vitamin K antagonist (VKA), aspirin (all Grade 1B) or an intermittent pneumatic

compression device (IPCD) (Grade 1C). In patients undergoing HFS, LMWH, fondaparinux, LDUH, adjusted dose VKA, aspirin (all Grade 1B) or an IPCD (Grade 1C) are recommended for minimum of 10–14 days (1).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

In patients undergoing elective THR or TKR in the absence of thromboembolic prophylaxis, the rates of fatal PE were 0.1%–0.4% and 0.2%–0.7%, respectively (8-11). The 90-day mortality rate after elective THR in patients who were not receiving pharmacological thromboembolic prophylaxis was 0.98% (12).

In a UK-based study of 2448 patients undergoing HFS, mortality was 10% at 30 days and 33% at one year (13). In 4331 patients undergoing HFS in the USA between 2005 and 2010, 30-day mortality was 6% and morbidity was 30% (14).

Long-term complications of VTE include recurrent VTE, post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH) (15, 16). PTS affects approximately 30–50% of patients who have suffered from DVT and can lead to chronic leg swelling, discomfort, dermatitis and leg ulcers, significantly reducing patient quality of life (16-18). The cumulative incidence of PTS 1 year after a first DVT was 25% (7% for severe PTS) (15). CTEPH develops in 2–4% of survivors of PE (16). In a study of 223 patients with confirmed PE, the incidence of CTEPH was 1.0% at 6 months, 3.1% at 1 year and 3.8% at 2 years. The risk of CTEPH is increased with recurrent PE (OR: 19.0; 95% CI: 4.5–79.8) (19, 20), and the risk of PTS is increased with ipsilateral recurrent DVT (increase in Villalta score of +1.78; 95% CI: +0.69 to +2.87) (20, 21). Approximately 30% of VTE survivors suffer from recurrent VTE within 10 years (22, 23).

Important co-morbidities

In general, predisposing factors for VTE are factors related to venous stasis (e.g. age, obesity, immobility, plaster cast, varicose vein and trauma) and/or related to hypercoagulability (age, inherited or acquired thrombophilia, active cancer, high-dose oestrogen therapy, pregnancy/puerperium, increased blood viscosity and inflammatory disorders); predisposing factors for bleeding include acquired/inherited bleeding disorders, medical conditions associated with haemodynamic abnormalities/instability, like severe liver disease, uncontrolled severe arterial hypertension and recent gastrointestinal bleedings. The risk of peri-operative morbidity and mortality is also related to the extent of the known (and sometimes pre-operatively unknown) co-morbidities. The surgical procedure by itself may provide risk factors and an assessment on a correlation between co-morbidities and post-operative non-surgical and/or surgical complications (e.g. delayed healing, wound infections in patients with diabetes mellitus; patients with advanced liver disease and renal insufficiency) is hampered by the fact that there may be a considerable interplay between surgical procedure, various co-morbidities and individual susceptibility.

Co-morbidities in patients undergoing major orthopaedic surgery of the lower limbs are shown in Table SI-2.

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Table SI-2: Co-morbidities in patients undergoing major orthopaedic surgery of the lower limbs

Age	The incidence of first VTE increases markedly with age (24-27). No epidemiological study could be identified that describes a relationship between increased risk of bleeding and age in general.
Obesity	In general, a higher BMI increases the risk of VTE (28). In patients with BMI > 25 kg/m^2 or BMI > 29 kg/m^2 the RR of PE was 1.7 (95% CI: 1.1–2.7) and 3.2 (95% CI: 1.7–6.0), respectively. The incidence of VTE was 1.35 (95% CI: 1.09–1.67) and 2.01 (95% CI: 1.60–2.52) in patients with BMI 25–29 kg/m^2 or > 30 kg/m^2, respectively. Morbid obesity was strongly associated with prolonged wound drainage in the THR group (p = 0.001), but not in the TKR group (p = 0.590). Prolonged wound drainage resulted in a significantly longer hospital stay in both groups (p < 0.001). Each day of prolonged wound drainage increased the risk of wound infection by 42% following a THR and by 29% following a TKR (29).
Thrombophilia	See Table SI-3
Cancer	The prevalence of cancer in patients undergoing THR (9327 patients), TKR (13,846 patients) and HFS (2448 patients) was reported to be 12%, 11% and 8%, respectively (3, 13). In a database study in northern Italy, 2953 (4.2%) of 69,770 patients undergoing THR or TKR had an admission for cancer in the previous two years (30). Cancer was associated with increased mortality in patients undergoing THR (31)
Renal impairment	Patients on long-term dialysis had a cumulative incidence of THR of 35 episodes/10,000 person-years, compared with 5.3/10,000 in the general population. The strongest risk factor for THR in dialysis patients was end-stage renal disease due to systemic lupus erythematosus (adjusted RR [aRR] = 6.80, 95% CI: 4.62–10.03, in whom vascular necrosis of the hip was the most common indication, 68.4%) (32). In a US-based study of women (n = 84,620) and men (n = 28,097) aged ≥ 65 years with a hip fracture in 2003–2005, the age-adjusted prevalence of chronic renal failure was 4% and 9%, respectively (5). In a Greek study of 450 patients undergoing HFS, the incidence of kidney dysfunction after surgery was 11%; prior kidney function was regained after treatment in 73% of these cases (33).
Liver impairment	In a US-based study of women (n = 84,620) and men (n = 28,097) aged ≥ 65 years with a hip fracture in 2003–2005, the age-adjusted prevalence of moderate to severe liver disease was 0.8% and 0.3%, respectively, and the age-adjusted prevalence of chronic liver disease/cirrhosis was 0.5% and 0.7%, respectively (5). Cirrhosis was associated with 5% and 17% mortality at 1-year and during long-term follow up (> 1 year), respectively, after TKR or THR (34). Complications (including dislocations and infections, acute renal failure and gastrointestinal haemorrhage) occurred more frequently in patients with cirrhosis than in patients without cirrhosis (34).

Table SI-2: Co-morbidities in patients undergoing major orthopaedic surgery of the lower limbs

Diabetes mellitus	The prevalence of diabetes mellitus in patients undergoing THR (in studies of 660 patients and 41,744 patients) was reported to be 7% and 11%, respectively (35, 36). Patients with diabetes mellitus may have increased risk of delayed wound healing and/or wound infection (37, 38)
Congestive Heart Failure	The prevalence of congestive heart failure in patients undergoing THR (two studies of 9327 and 41,744 patients) and TKR (13,846 patients) was reported to be 2–3% and 2.5%, respectively (3, 36). In a database study in northern Italy, 859 (1.2%) of 69,770 patients undergoing THR or TKR had an admission for heart failure in the previous two years (30).
Myocardial infarction	The prevalence of MI in patients undergoing THR (9327 patients) and TKR (13,846 patients) was reported to be 7.5% and 8.6%, respectively (3), and 0.4% of 69,770 patients undergoing THR or TKR in northern Italy had been admitted for MI in the previous two years (30). The incidence of MI occurring after major orthopaedic surgery was 0.4% (10,244 patients) and 1.8% (3471 patients) (39, 40).
Hypertension	The prevalence of hypertension in total hip replacement or revision was reported to be 65% (35).
Chronic obstructive pulmonary disease (COPD)	The prevalence of COPD in patients undergoing THR (two studies of 9,327 and 41,744 patients), TKR (13,846 patients) and HFS (2,448 patients) was reported to be 5.5–13%, 5.5%, and14%, respectively (13, 36, 41). Of 69,770 patients undergoing THR or TKR in northern Italy, 1.2% had been admitted for COPD in the previous two years (30).
Gastrointestinal (GI) ulcer/recent GI haemorrhage	No epidemiological study could be identified that describes the increased risk of bleeding in patients with recent GI ulcers undergoing major orthopaedic surgery and receiving antithrombotics. GI haemorrhage was reported in 1% of patients following HFS (13)

SI.2 Indication: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Incidence

Venous thromboembolism is an acute event and therefore is better described in terms of incidence than prevalence. The reported incidence of PE (with or without DVT), ranges from 29 to 78 per 100,000 person-years and for DVT alone (without PE), from 45 to 117 per 100,000 person-years (42). In the Worcester VTE study, the age- and sex-adjusted annual event rate for recurrent VTE was 35 per 100,000 residents in 2009 (43). In two US studies, the cumulative rate of recurrence of VTE was reported as 1.4–4.8% within 30 days of the initial event, 5.6% at one year and 17.6% at 10 years (44, 45). In a study conducted in Italy, VTE recurrence rates at one, three, five and 10 years were 11.0%, 19.6%, 29.1% and 39.9%, respectively (46). In a more recent Italian registry study, the VTE recurrence rate was 3.63 per 100 patient-years (47).

Patients with unprovoked VTE have a higher risk for recurrence than those with VTE provoked by transient risk factors such as major surgery, trauma, acute medical illness and others (48). In a systematic review of available studies, the rate of VTE recurrence in the two years after discontinuing anticoagulant therapy was 7.4% per patient-year after unprovoked VTE and 3.3% per patient-year in patients with VTE provoked by a transient risk factor (49). Among patients with provoked VTE, the VTE recurrence rate was 0.7% in those with a surgical risk factor and 4.2% per patient-year in patients with a non-surgical transient risk factor. The rate ratio for unprovoked VTE versus VTE provoked by a non-surgical risk factor was 1.8 at 2 years. In a large cohort study, the hazard ratio for the risk of VTE recurrence in patients with an unprovoked first episode of VTE compared with those with provoked VTE was 2.3 (95% CI, 1.8–2.9) (46). In patients with unprovoked VTE and in those with ongoing risk factors experiencing a second event, the cumulative incidence of recurrent VTE was 11.0% (95% CI, 9.5–12.5) in the first year after discontinuation of anticoagulant therapy (46).

Demographics of the population in the authorised indication and risk factors for the disease

VTE is predominantly a disease of older age with incidence rates increasing exponentially with age for both men and women. The annual prevalence of VTE was reported as 1,382 per 100,000 in patients ≥ 65 years of age versus 231 in patients < 65 years of age (2006 data) (50). The overall age-adjusted incidence is higher for men (130 per 100,000) than women (110 per 100,000) (27). However, incidences are generally higher in women of childbearing age (< 45 years) than in men of the same age. The overall incidence of VTE may be higher in African-Americans and lower in Asians compared with individuals of European ancestry (27).

Independent risk factors for VTE include increasing age and body mass index, major surgery, hospitalization for acute medical illness, nursing home confinement, trauma/fracture, active cancer with or without concurrent chemotherapy, central vein catheterization or transvenous pacemaker, prior superficial vein thrombosis, varicose veins, neurological disease with leg paresis, urinary tract infection, elevated baseline plasma fibrin D-dimer levels and family history of VTE (27, 45, 51-56).

The risk of recurrent VTE is higher in patients with unprovoked VTE than in patients with VTE provoked by surgery, trauma, immobilization, pregnancy or female hormone intake (48). Among those with a first unprovoked VTE, factors associated with a significantly increased risk of VTE recurrence include male sex, proximal DVT and PE (versus distal DVT) and elevated levels of D-dimer (57).

The main existing treatment options

In recent years, direct oral anticoagulants (DOACs) (rivaroxaban, dabigatran, apixaban and edoxaban) have been approved for the treatment and prevention of VTE. The recent guidelines of the American College of Chest Physicians (ACCP) recommend dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy for long-term (first 3 months) treatment of patients with DVT of the leg or PE and no cancer (58). In patients with DVT of

the leg or PE and cancer, as long-term (first 3 months) anticoagulant therapy, LMWH is recommended over VKA therapy, dabigatran, rivaroxaban, apixaban or edoxaban. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a low or moderate bleeding risk, the ACCP recommends extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy. In patients with unprovoked VTE and high bleeding risk, the ACCP recommends 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (58). In patients with DVT of the leg or PE and active cancer, extended anticoagulant therapy (no scheduled stop date) is recommended over 3 months of therapy for patients with and without a high risk of bleeding (58). In patients who receive extended therapy, the ACCP suggests that there is no need to change the choice of anticoagulant after the first 3 months (58).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

VTE is associated with significant morbidity and mortality. In a Danish cohort study of 128,223 individuals with first-time VTE (1980–2011), the 30-day mortality rate in the absence of treatment was about 3% for DVT and 31% for PE (59). The risk of death in the year following DVT or PE was 13% and 20% respectively (59). Recurrent VTE is estimated to be fatal in 5% of cases overall (60).

Chronic conditions that may arise after acute VTE are PTS and CTEPH.

Important co-morbidities

In general, predisposing factors for VTE are factors related to venous stasis (e.g., recent surgery or trauma, immobility, obesity and increasing age) and/or related to hypercoagulability (e.g. use of oestrogen-containing drugs, thrombophilic conditions and active cancer). Individuals with a previous VTE are also at increased risk of further VTE episodes. The magnitude of the association with some risk factors (e.g. heart failure) varies between DVT and PE (61). Co-morbidities in patients with VTE are shown in Table SI-3.

However, many cases of VTE (20–50%) or DVT (49%) are regarded as unprovoked or idiopathic (26, 62).

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Table SI-3: Co-morbidities in patients with VTE

Age	See Table SI-2
Obesity	The prevalence of obesity (BMI ≥ 30 kg/m^2) was 21.1% among patients with a first DVT, and 19.2% among patients with a first PE (61). The combination of obesity (BMI > 30) and tall stature synergistically increased the risk of VTE. Tall (≥ 182 cm), obese men had a 5-fold (multivariable HR 5.16; 95% CI 2.39 to 11.14) increased risk of VTE compared with normal-weight men with short (≤ 172 cm) stature. Tall (≥ 168 cm), obese women had an almost 3-fold (multivariable HR 2.89; 95% CI 1.31 to 6.35) increased risk of VTE compared with normal-weight, short (≤ 159 cm) women (63).
Surgery/Trauma	19.1% of patients with a first DVT and 20.2% of patients with a first PE had surgery in the 6 months prior to the VTE event, compared with 2.1% of controls (OR: 9.4; 95% CI: 8.0–11.0 for DVT/PE overall) (61). Of patients with a first VTE, 18% had undergone surgery (64). Trauma was reported in 13% of patients with a first VTE (65).
History of VTE	The risk of VTE is considerably higher in patients who have had a previous episode of VTE than in individuals who have not had VTE (OR: 15.6; 95% CI: 6.8–35.9) (66). Studies of patients with DVT have reported a history of VTE in 17–21% of cases (66, 67). Among patients with PE, 15–27% had a previous VTE (68, 69).
Hormone therapy and use of oral contraceptives	Women receiving hormone therapy were found to be at greater risk of VTE than women not receiving therapy (OR: 1.32; 95% CI: 1.09–1.59) (61).
Thrombophilia	The prevalence of thrombophilia in the general population and in unselected patients with VTE has been reported as follows (70): • Factor V Leiden (G1691A) heterozygous: 1–15% (general population) and 10–50% (patients with VTE) • Elevated Factor VIII: 11% and 10–25% • Elevated Factor XI: 10% and 19% • Prothrombin G20210A heterozygous: 2–5% and 5–18% • Hyperhomocysteinaemia: 5–7% and 5.7–35% • Protein C deficiency: 0.2–0.4% and 3–5%
Cancer	14–20% of patients with VTE also had cancer (61, 71, 72). The prevalence of cancer was similar in patients with DVT and PE (61, 65). In a Danish study, VTE risk was higher in patients receiving chemotherapy (aRR: 18.5; 95% CI: 11.9–18.7) than in patients with cancer who were not receiving chemotherapy (aRR: 8.4; 95% CI: 6.2–11.4) (73). Hormonal therapy increased the risk of VTE 1.5-fold for patients with breast cancer (12).

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Table SI-3: Co-morbidities in patients with VTE

Pregnancy	Pregnancy is strongly associated with risk of VTE; the OR for the association was 11.4 (95% CI: 1.4–93.3) (66). The risk of VTE was increased 5-fold during pregnancy and 60-fold during the first 3 months after delivery (74). The absolute risk of VTE per 10,000 pregnancy-years increased from 4.1 (95% CI: 3.2 to 5.2) during week 1–11 of gestation to 59.0 (95% CI: 46.1 to 76.4) in week 40 and decreased in the puerperal period from 60.0 (95% CI: 47.2–76.4) during the first week after birth to 2.1 (95% CI: 1.1 to 4.2) during week 9–12 after birth. (75).
Congestive Heart Failure	Congestive heart failure was identified in 3.5% of patients with DVT (67) and 9.5% of patients with PE (76). Congestive heart failure was associated with VTE in two studies in the outpatient setting, with odds ratios of 2.9 (95% CI: 1.6–5.6) for DVT (66) and 2.5 (95% CI: 1.7–3.7) for VTE (77).
Myocardial Infarction	History of MI was reported in 6.8% of patients with first VTE, and was also identified as a risk factor for VTE (RR: 1.3; 95% CI: 1.1–1.4). The risk for VTE was strongest in the first 3 months after MI (RR: 4.2; 95% CI: 2.3–7.6) (78).
Hypertension	3.8% of patients with VTE had hypertension (range: 1.8–30.8%). A significant association was found between hypertension and the risk of VTE (OR: 1.5; 95% CI: 1.2–1.9) (Ageno et al. 2008). Of 324 patients with recurrent VTE, 29.3% had hypertension, and hypertension was an independent risk factor for recurrent VTE (HR: 1.4; 95% CI: 1.1–1.8) (79).
Diabetes Mellitus	In a recent meta-analysis that included more than 60,000 patients, 2.6% of patients with VTE had diabetes (range: 0.0–9.4%) (80). In the GPRD, the prevalence of diabetes among patients with first DVT and first PE was similar (5.6% and 6.0%, respectively) (61).
COPD	The prevalence of COPD among patients with PE was reported to be 9–14% (61, 76, 81). The prevalence of COPD among patients with first DVT was reported to be 7.1–12% (61, 82). COPD was significantly associated with mortality at 3 months (HR: 1.8; 95% CI: 1.2–2.7) (83). Mortality at 1 year was reported to be 53.3% in patients with COPD and PE (84).
Renal impairment	In the RIETE registry, 2.7% of patients with DVT had a creatinine clearance of < 30 mL/min, indicating severe renal impairment, and a further 7.5% had a creatinine clearance in the range 30–60 mL/min (moderate renal impairment) (67). Of patients with acute PE who survived the first 30 days after the event, 5.8% had CrCL < 30 mL/min; of patients who died within the first 30 days, 21% had CrCL < 30 mL/min (85). Renal impairment (CrCL < 30 mL/min) was associated with death in the first 30 days after acute PE (odds ratio 4.2 [95% CI, 3.3–5.5], $p < 0.001$) (85).
Liver Impairment	Liver cirrhosis and non-cirrhotic liver disease were present in 0.5% and 1.1%, respectively, of 99,444 patients with a first VTE; relative risks ranged from 1.7 (95% CI: 1.5–2.0) for cirrhosis to 1.9 (95% CI: 1.7–2.0) for non-cirrhotic liver disease (86).

Table SI-3: Co-morbidities in patients with VTE

GI ulcers/recent GI haemorrhage	Of 166 consecutive patients admitted with VTE, 6.0% had a gastric ulcer, and 6.6% had a duodenal ulcer (87). Of 12,294 patients with VTE enrolled in RIETE to July 2005, 116 (0.94%) patients had a recent history of major GI tract bleeding. The vast majority (99.8%) of the study participants received either anticoagulant or thrombolytic drugs as initial therapy. During the 3-month follow-up period, 10% of patients with recent major GI tract bleeding had re-bleeding (versus 2% of controls without recent bleeding), 6% (versus 0.5%) had fatal bleeding, and 17% (versus 8%) died (death from all causes). Multivariate analysis confirmed that recent GI bleeding was associated with an increased risk of both major re-bleeding (HR: 2.8; 95% CI: 1.4–5.3) and death (HR: 1.9; 95% CI: 1.2–3.1) (88).
Coagulation disorders (e.g. acquired/inherited thrombocytopenia)	The prevalence of acquired thrombocytopenia in over 10 million patients discharged from hospital following VTE between 1979 and 2005 was reported to be 0.4% (89). Patients with cancer were more likely to have thrombocytopenia than those without (0.8% versus 0.3%). In the GPRD, the prevalence of coagulation disorders has been reported to be 1.5% in patients with a first DVT (OR: 1.37; 95% CI: 0.92–2.05) and 1.8% in patients with a first PE (OR: 1.47; 95% CI: 0.98–2.22), compared with 0.8% in age- and sex-matched controls (61).

SI.3 Indication: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and a strong independent risk factor for stroke. Patients with AF have more severe strokes than patients without AF (90). There is a strong rationale for prevention of stroke and peripheral thromboembolism in these patients using anticoagulant therapy.

Incidence

The overall incidence of AF was 9.9 per 1000 person-years in women > 55 years (1.1 per 1000 person-years in those aged 55–60 years and 20.7 per 1000 person-years in patients aged 80–85 years) (91) and prevalence was 3.4% in men and 2.6% in women, and increases with age (7.9% [> 55years]; 21.9% [>85 years]) (92).

Incidence of ischaemic stroke is 5% per year in patients with non-valvular AF. When TIAs and clinically silent strokes are included, the incidence exceeds 7% per year (93). Incidence of stroke in patients with non-valvular AF during periods of not receiving warfarin is 19.7 per 1000 person-years (32,721 person-years of follow-up) (94). Incidence of a first ischaemic stroke in patients with paroxysmal or permanent AF is respectively 21 or 25 per 1000 patient-years (95).

The incidence of systemic embolism in 15,373 patients with AF in UK primary care was 1.5 per 1000 person-years (96). In patients with AF there is a 4.0-fold (men) and 5.7-fold (women) increased risk of incident thromboembolic events in the aorta (7%) and in the renal (2%), mesenteric (29%), pelvic (9%) and extremity arteries (61%) (97). In the REGARDS

cohort, age-adjusted incidence of MI was two-fold higher with AF than without (12.0 per 1000 person-years vs. 6.0 per 1000 person-years) (98).

Prevalence

In the EU, an estimated 10 million people have AF. The prevalence is projected to rise to 14–17 million by 2030 (99).

Demographics of the population in the authorised indication and risk factors for the disease

The median age of patients with AF is 75 years and approximately 70% of patients with AF are aged 65–85 years. The percentage of patients older than 75 years is higher among those with non-valvular AF and peripheral thromboembolism than those with AF and stroke (51% versus 32%, $p = 0.01$). The risk of stroke increases with age: in patients with an incident diagnosis of non-valvular AF (552,368 person-years) the incidence per 1000 person-years of first stroke for men and women respectively was 6.2 and 6.3 in patients aged 40–49 years and 40 and 46 in those aged 80–89 years.

Risk factors for AF include hypertension, congestive heart failure, coronary artery disease (CAD), diabetes mellitus, advanced age, male sex, hyperthyroidism, obesity, inflammation, sleep apnoea and excessive alcohol and caffeine intake. Genetic risk factors have also been identified (91, 93, 100, 101).

In approximately 30–45% of cases of paroxysmal AF and 20–25% of cases of persistent AF, in young patients underlying disease is not evident ('lone AF') (100).

Congestive heart failure, hypertension, age ≥ 75 years, diabetes and prior stroke are incorporated in the $CHADS_2$ AF stroke risk score. More recently, vascular disease, age ≥ 65 years and female sex have been included in the modified CHA_2DS_2-VASc risk score (102, 103).

The main existing treatment options

Antithrombotic therapy is recommended for male patients with AF who have a CHA2DS2-VASc score of 2 or more and female patients with AF who have a score of 3 or more (104).

In patients with AF who do not have mitral valve stenosis or mechanical heart valves, apixaban, dabigatran, edoxaban or rivaroxaban is recommended in preference to a vitamin K antagonist if there are no contraindications (104). Vitamin K antagonist therapy (target international normalised ratio [INR] 2.0–3.0), is recommended for stroke prevention in patients with AF who have moderate-to-severe mitral valve stenosis or mechanical heart valves. Anti-platelet therapy, including dual therapy with aspirin and clopidogrel is not recommended for stroke prevention in patients with AF (104).

For the management of patients with AF undergoing PCI and receiving a coronary stent, a short period (1–6 months) of triple therapy with oral anticoagulant (VKA antagonist or non-VKA antagonist), aspirin and clopidogrel is recommended, depending on the patient's risk of bleeding versus stent thrombosis. It is recommended that triple therapy is followed by a period of dual therapy (oral anticoagulant plus a single anti-platelet). When a DOAC is used,

the consensus recommendation is that the lowest dose effective for stroke prevention in AF should be considered (104). The use of prasugrel or ticagrelor as part of triple therapy should be avoided unless there is clear need for these agents (e.g. stent thrombosis in a patient already receiving an oral anticoagulant and aspirin plus clopidogrel) (104). Guidelines from the AHA/ACC/HRS state that following coronary revascularization in patients with CHA2DS2-VASc score of ≥ 2, it may be reasonable to use oral anticoagulants with clopidogrel, but without aspirin (105).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

All-cause mortality was three-fold higher in patients with AF compared with patients in normal sinus rhythm in a case-control study in UK primary care (n = 15,373 in each group) (96). Mortality following first stroke in patients with and without AF was 13% and 7%, respectively, at 28 days, and 43% and 25% after 3 years (106).

Mortality in patients with AF with

- Acute thromboembolic limb ischaemia: approximately 16% at 12 months (107)
- Upper vs lower extremity embolism: 4.8% vs 16.7% (108)
- Renal embolism: 11.4% at 30 days (109)
- Acute thromboembolic mesenteric ischaemia: 70% (107).

Mortality (8–365 day) in patients with ST-segment elevation myocardial infarction with (n=6721) versus without (n = 77 440) AF was 8.4% versus 2.1% ($p < 0.001$) (110).

Patients with AF in the UK spend a mean of 5 days per year in hospital (1.5 days owing to circulatory system problems) (96). Ischaemic stroke is the principal complication of AF. Six months post stroke more than half of patients still suffer from loss of motor. Stroke in patients with AF is more severe and disabling, necessitates greater resource use and more frequently recurs than stroke in patients without AF (111, 112). Complications following stroke are also more common in patients with AF compared with patients without AF (90).

Other acute thromboembolic events that can also have severe consequences in patients with AF include: limb ischaemia, which may lead to limb loss, organ failure and death (113); mesenteric ischaemia, which may lead to bowel necrosis and perforation, and subsequently peritonitis and shock (114); and renal thromboembolism, which may lead to impairment of renal function (115).

Important co-morbidities

Most patients with AF have at least one associated medical condition and a large proportion have multiple co-morbidities. Hypertension is the most prevalent concomitant disease (116-118) and other cardiac conditions, including coronary heart disease and heart failure, also commonly occur with AF. Additional co-morbidities observed in patients with AF include diabetes, obesity, metabolic syndrome, MI, cardiomyopathy, hyperthyroidism and renal disease. Cardiac surgery may also be associated with AF. Of the associated co-morbidities,

hypertension, heart failure and diabetes are established risk factors for stroke in AF. Co-morbidities in patients with non-valvular AF are shown in Table SI-4.

In a study examining cause of death and Medicare hospitalization in patients with AF, 9.9% of patients with AF also had a diagnosis of coronary heart disease (119). Approximately 954,000 percutaneous coronary intervention (PCI) procedures are performed in the United States each year (120) and 5–8% of patients who undergo PCI also have AF (121-123). Research is required to determine the optimal antithrombotic treatment strategy for the large number of patients with AF who also have the potential to require PCI, and therefore require anticoagulant treatment for two separate indications.

Table SI-4: Co-morbidities in patients with non-valvular AF

Hypertension	In a systematic review, hypertension was found to be a strong independent risk factor for stroke in patients with non-valvular AF (RR = 2.0, 95% CI: 1.6–2.5) (124). In patients diagnosed with first stroke, hypertension was found to be significantly more common in patients with AF than in patients without AF (49% versus 41%) (125). In a US claims database study, 24% of patients newly diagnosed with AF also had hypertension (126).
Hyperlipidaemia	Univariate and multivariate regression analyses have demonstrated that hyperlipidaemia is independently predictive of stroke history in patients with persistent AF (OR: 2.73–4.5) (127-129).
Coronary Artery Disease	CAD is associated with an increased risk of incident AF (HR: 1.4–3.6) (118). The prevalence of CAD in patients with AF has been reported as 25–36% (116, 117, 130). The prevalence of angina and MI was reported as 5.2–13% and 9.6–14.9%, respectively (131-133).
Heart Failure	HF is associated with an increased risk of incident AF (HR: 1.1–2.2) (118). The prevalence of heart failure in patients with AF was reported as 23–49% (116) and 24.1–45.2% (117). In a US claims database study, 9.4% of patients newly diagnosed with AF also had congestive heart failure (126). The prevalence of stroke in patients with both heart failure and AF was 14.9% (134). The incidence of stroke in patients with chronic AF and congestive heart failure was 3.48 per 100 person-years (135).
Diabetes mellitus	Diabetes is associated with an increased risk of incident AF (HR: 1.4–2.1) (118). In patients with non-valvular AF, the presence of diabetes was associated with a relative risk of stroke of 1.7 compared with the absence of diabetes (100, 124). In a US claims database study, 8.5% of patients newly diagnosed with AF also had diabetes (126).
COPD	In a cohort of patients with AF, 11.0% had a diagnosis of COPD (136). COPD was independently associated with an increase in all-cause death (136). In a study of patients with AF who had experienced a first-ever stroke event, COPD was present in 5.6% of patients with cardioembolic stroke and 13.3% of patients with atherothrombotic stroke (137).

Table SI-4: Co-morbidities in patients with non-valvular AF

Cardiomyopathy	In a study of patients with hypertrophic cardiomyopathy, the incidence of stroke over a 9-year follow-up was 8 times higher in patients with AF compared with those without AF (21% versus 2.6%; OR = 17.7, 95% CI: 4.1–75.9) (138). In addition, fatal strokes were reported in 7.5% of patients with AF.
Thyroid disease	Subclinical hyperthyroidism is associated with an increased risk of incident AF (HR: 1.9–3.1) (118). A prospective study in 160 patients with AF has shown that the presence of hyperthyroidism is a risk factor for ischaemic stroke (HR = 3.5, 95% CI: 1.15–10.42; p = 0.03) (139).
Renal disease	Patients with AF had a significantly higher prevalence of moderate Chronic Kidney Disease (CKD) (defined as eGFR < 60 mL/min/1.73 m^2 or microalbuminuria; 40.2% versus 14.0%; p < 0.01) and greater mean urinary albumin excretion (17.8 mg/L versus 12.0 mg/L; p < 0.01) than matched controls (140). A graded increased risk of stroke and other thromboembolic events has been observed with declining kidney function in patients with non-valvular AF (p = 0.0082 for trend across estimated glomerular filtration rate categories), and proteinuria has been reported to be associated with a 54% increased risk of thromboembolism (HR = 1.54, 95% CI: 1.29–1.85) after adjustment for other stroke risk factors (141).
Peripheral vascular disease	In patients with AF, the prevalence of peripheral vascular disease is 5.2–17%. In a study of patients with peripheral vascular disease, the prevalence of ischaemic stroke was 19.0% in patients with AF compared with 14.1 % in patients without AF (p < 0.01) (142, 143).

SI.4 Indication: Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS)

Differences in clinical presentation and outcomes of forms of ACS (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina [UA]), as well as the occurrence of silent MI and of sudden death outside the hospital, make estimation of the incidence, prevalence and mortality of ACS difficult. Therefore, presented data should be regarded as an estimate.

Incidence

In a large US community-based study, incidence of MI declined between 2000 and 2008 from 287 to 208 cases per 100 000 person-years, largely owing to a reduction in the incidence of STEMI (from 133 to 50 cases per 100 000 person-years between 1999 and 2008) (144).

Prevalence

In an annual Dutch health survey, 2.9% of participants reported that they had experienced a MI (145). The reported prevalence of MI in men of all ages in the UK was stable between 1988 and 2004 at about 2.3%, falling slightly to 1.7% in 2011. In British women of all ages between 1988 and 2011, prevalence peaked at 2.4% in 1996 before declining gradually to

1.0% in 2011 (146). In a large US community-based study, incidence of MI declined between 2000 and 2008 from 287 to 208 cases per 100 000 person-years, largely owing to a reduction in the incidence of STEMI (from 133 to 50 cases per 100 000 person-years between 1999 and 2008) (144).

In a global registry of patients admitted with suspected ACS, 30% had STEMI, 31% had NSTEMI, 26% had UA and 12% had another cardiac/non-cardiac final diagnosis (147). The percentage of STEMI among ACS cases varies from approximately 26% to 47% in different studies and depends heavily on the age group studied and the type of surveillance. In the USA between 2002 and 2011, the proportion of patients with acute MI who were diagnosed with NSTEMI rose from 56.1% to 73.6% in women, and from 50.4% to 65.3% in men (148).

Demographics of the population in the authorised indication and risk factors for the disease

In patients with ACS enrolled in the international Global Registry of Acute Coronary Events (GRACE) study, the median age was 65 years and 33% were women (147). In a separate GRACE analysis, 37.8% of men and 31.4% of women had STEMI.

In a national registry, 40.4% and 45.8% of patients with STEMI and NSTEMI were female, respectively. The median ages of patients with STEMI and NSTEMI were 69 and 75 years, respectively, and 83.5% and 82.4% were white. Frequencies of reinfarction, sustained ventricular arrhythmias, cardiogenic shock and stroke were higher in patients with STEMI, whereas patients with NSTEMI were more likely to develop congestive heart failure, new AF and major bleeding.

In an international case-control study, 45.2% of patients with acute MI were current smokers, compared with 26.8% of controls without heart disease (149).

Risk factors for ACS include age, male gender, hypertension, diabetes, dyslipidaemia, family history of CAD, high body mass index (BMI), poor diet, smoking, moderate alcohol intake and stress (150, 151) (152).

These risk factors also contribute to the prognosis of patients after ACS. A study of 3675 patients with ACS investigated the association between outcomes, eight traditional risk factors (age $\geq$ 65 years, male gender, family history of premature CAD, low-density lipoprotein cholesterol $\geq$ 70 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL in men and <50 mg/dL in women, systolic blood pressure > 130 mmHg, diabetes mellitus, smoking,), and four non-traditional risk factors (C-reactive protein $\geq$ 2 mg/L, triglycerides > 150 mg/dL, prediabetes [fasting glucose level 100–125 mg/dL or haemoglobin A1c > 6%] and obesity [defined as BMI $\geq$ 30 kg/m^2]). In patients who had five risk factors, which was the median, 18.25% experienced the primary end point of death, MI, UA, stroke or revascularization within 2 years (152).

In a Norwegian study, mortality from cardiovascular disease was higher in men than women and also in patients who are older vs younger, poorer vs richer and unmarried vs married. Mortality from cardiovascular disease in Norway was not influenced by which region health care was accessed from (153). In Italy however, increasing distance from a coronary care unit

and lower levels of education were both associated with lower rates of revascularization following MI (154).

The main existing treatment options

For patients with presentation of STEMI within 12 hours of symptom onset and with persistent ST-segment elevation or new or presumed new left bundle branch block, early mechanical (percutaneous coronary intervention) or pharmacological (fibrinolytic therapy [streptokinase, alteplase, reteplase, tenecteplase]) reperfusion is recommended as soon as possible (155).

Patients who have recovered from a STEMI are at high risk of new events and premature death and therefore long-term therapy is recommended, including: antiplatelet agents, oral anticoagulant in addition to antiplatelet therapy (rivaroxaban in combination with aspirin and clopidogrel), β-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and aldosterone antagonists (155).

Patients with ACS presenting without persistent ST-segment elevation may be treated with: anti-ischaemic agents (nitrates, β-blockers and calcium channel blockers [dihydropyridines only in combination with β-blockers]), oral antiplatelet agents (aspirin and a $P2Y_{12}$ inhibitor [ticagrelor, prasugrel or clopidogrel]), intravenous glycoprotein IIb/IIIa receptor inhibitors (in addition to antiplatelet agents), or anticoagulants (fondaparinux, LMWHs, UFH, bivalirudin) (156, 157).

Antiplatelet and anticoagulant therapy is recommended for all patients according to European guidelines (156). Since the publication of those guidelines, rivaroxaban has been approved for use in combination with ASA alone or with ASA plus clopidogrel or ticlopidine after an ACS in adult patients with elevated cardiac biomarkers (158).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

A US-based study showed a decline in mortality from 1950 to 1999, with overall coronary heart disease death rates decreasing by 59 (159).

In a Polish study, in-hospital mortality for NSTEMI fell from over 6% to around 3% between 2004 and 2010, in part because of improvements in pharmacotherapy and diagnosis of NSTEMI (160). In-hospital mortality rates for STEMI in the OPERA and the Zurich-Acute Coronary Syndrome registries were 4.6% (n = 1476) and 5.7% (n = 998) respectively (161, 162).

In a US-based study, the age- and sex-adjusted 30-day mortality after MI decreased from 10.5% in 1999 to 7.8% in 2008 (144), owing in part to a reduction in the case fatality rate for NSTEMI. In a Scottish registry, the 1-month case fatality rate in patients admitted with MI was 15.7% in men and 25.7% in women, and the case fatality rate among emergency admissions for angina was 2.0% in men and 1.8% in women (163). In a Polish registry, the 30-day mortality in 13,470 patients admitted with NSTEMI in 2009 was 6.6% (160).

Across Europe, in 2013, patient-based case fatality rates after acute MI ranged from a low of 7.6% in the Netherlands, to a high of 19.1% in Latvia (Estonia had the second highest reported rate at 13.1%) (164).

In the USA, the 1-year mortality after a first MI for patients ≥ 45 years of age was 19% in men and 26% in women (165). In patients admitted with acute MI in Denmark, one-year mortality was 31%, 21%, and 55% in those with NSTEMI, STEMI, and bundle branch block MI, respectively (166). In a national registry of patients with STEMI, 1-year mortality was 22.0% in women and 14.1% in men. In 13,470 Polish patients admitted to hospital with NSTEMI in 2009, one-year mortality was 14.5% (160).

ACS is a major source of mortality and morbidity both during and after hospitalisation, with up to 30% of discharged patients needing rehospitalisation within the first 6 months. Among patients with UA or NSTEMI, approximately 15% will die or have a reinfarction within 30 days of diagnosis, and about 30% of patients with UA will have an MI within 3 months (167).

The expanded GRACE study included 9557 patients with STEMI, 9783 patients with NSTEMI and 8037 with UA. The prevalence of different hospital outcomes was as follows: recurrent ischaemic symptoms, 20%; heart failure, 6% of patients with UA and 15% of patients with STEMI; MI, 1.4% of patients with UA; reinfarction, ~10–12% of patients with NSTEMI or STEMI; and major bleeding and stroke, < 2% (147). In-hospital outcomes for 24,890 Polish patients admitted with NSTEMI in 2009–2010 included major bleeding in 1.4%, stroke in 0.3% and reinfarction in 0.9% (160).

In a retrospective study of 460 patients with non-ST-elevation ACS, the incidence of death or non-fatal MI, assessed in different GRACE score categories, ranged from 3.1% to 11.2% at 30 days and from 4.2% to 27.2% at 1 year (168).

In Europe, the average length of hospital stay following AMI ranged from a low of 4.0 days (Norway, 2010) to a high of 10.3 days (Germany, 2013) (164). In a retrospective study of US Medicare beneficiaries (≥ 66 years of age), 7.4% of beneficiaries (n = 5773) who were hospitalized for AMI (N = 78,085), had ≥ 2 CHD rehospitalizations over a maximum of 10 years of follow up (169).

Important co-morbidities

Major risk factors for developing coronary heart disease and acute MI have been well established in large epidemiological studies, and include smoking, adverse lipid profiles, diabetes mellitus and elevated blood pressure (149, 170). In patients with ACS, risk factors for secondary fatal and non-fatal events include advanced age, male sex, renal disease, heart failure, cardiovascular disease, cancer and diabetes (163). Co-morbidities in patients with ACS are shown in Table SI-5.

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Table SI-5: Co-morbidities in patients with ACS

Stroke	Annual incidence of stroke after MI was 5% and increased proportionally with the number of identified risk factors present (i.e. older age, female sex, African ancestry and frailty). Comorbid conditions associated with higher stroke admission rates included prior stroke, hypertension, diabetes, atrial fibrillation, heart failure and peripheral vascular disease (171). In an Italian registry of medically managed patients with ACS, 13.0% had a history of stroke/TIA (172).
History of MI	Among people who survive the acute stage of MI, the risk of another MI, sudden death, angina pectoris, heart failure, and stroke – for both men and women – is substantial (173). Among patients aged 45–64 years with a first MI, 15% of men and 22% of women will develop a recurrent MI or fatal coronary heart disease within 5 years. In patients aged ≥ 65 years with a first MI, the corresponding percentages are 22% for both men and women. In an international registry of patients with ACS, 26% had a prior MI (147). In an Italian registry of medically managed patients with ACS, 29.0% had a history of MI (172).
Hypercholesterolaemia	Moscucci *et al.* reported that 44.3% of patients hospitalised with ACS had a medical history of hyperlipidaemia (174). Among medically managed patients with ACS, 53.0% had dyslipidaemia (172). The prevalence of hypercholesterolaemia in patients with NSTEMI in a Polish registry was 42.1–44.2% (160). Paradoxically, hypercholesterolaemia appears to be associated with reduced mortality in ACS (160, 175, 176), perhaps because patients with hypercholesterolaemia may have had medical treatment prior to admission for ACS.
Renal impairment	In a pooled analysis of patients with NSTE-ACS in three Canadian registries, 38.8% had renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) (177). Renal failure was identified as one of the most important independent comorbid factors predicting one-year mortality in NSTEMI (severe dysfunction [glomerular filtration rate < 20 vs > 50 mL/min/1.73 m^2], HR: 2.9; 95% CI: 1.5–5.9; mild dysfunction [glomerular filtration rate 20–50 vs > 50 mL/min/1.73 m^2], HR: 1.6; 95% CI: 1.1–2.6) (178). Among medically managed patients with ACS, 23.2% had renal dysfunction or were receiving dialysis (172).
Liver impairment	Patients with severe liver disease are at high risk of excessive bleeding due to the underlying coagulopathy.
Diabetes mellitus	In an international registry of patients with ACS, 26% had diabetes (147); in an Italian registry, 35.5% had diabetes (172). In 169 diabetic patients with prior MI, the sex and age-adjusted incidences (per 1,000 person-years) of myocardial

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Table SI-5: Co-morbidities in patients with ACS

	infarction (fatal or nonfatal), stroke and cardiovascular death were 78, 34 and 73, respectively (179). During 4 years of follow-up in patients aged 40–97 years with type 2 diabetes, the age-adjusted incidence of a recurrent cardiovascular event (per 1,000 person-years) was 72.7 in men and 32.5 in women. Long-standing previous cardiovascular disease, male sex, age, high triglyceride levels, and insulin use were predictors of recurrence (180).
Congestive heart failure	The incidence of heart failure after MI increased in recent times owing to a reduction in mortality. In an evaluation of trends in the incidence of heart failure after MI, heart failure occurred in 165 participants with MI (24.4%), whereas 139 participants (20.6%) died without heart failure over the 3 decades of observation. The multivariable-adjusted HR for heart failure within 30 days after MI was ≈2-fold higher in the 1990s than the 1970s. By contrast, the HR of death without heart failure within 30 days was 80% lower in the 1990s than the 1970s (181). In a recent Italian registry, 10.0% of medically managed patients with ACS had a history of heart failure (172).
Hypertension	In a Spanish registry of patients with MI, 46.0% had hypertension and mortality was 14.4% and 12.4% in those with and without hypertension, respectively (182). In an Italian registry of medically managed patients with ACS, 76.6% had a history of hypertension (172). A meta-analysis found an increased risk of death associated with antecedent hypertension in patients with MI (pooled RR: 1.5; 95% CI: 1.3–1.6). Antecedent hypertension and an increased risk of stroke, congestive heart failure and recurrent MI (183). In addition, antecedent hypertension was associated with TIMI major bleeding in a pooled analysis of clinical trials in non-ST-segment elevation [NSTE]-ACS (184). TIMI major bleeding occurred within 30 days in 4.6% and 3.2% of patients with and without hypertension, respectively (adjusted OR: 1.5; 95% CI: 1.0–2.1).
Atrial fibrillation	In an international study of patients of ACS, 8.0% had a medical history of atrial fibrillation (175). In-hospital mortality was 8.8% in those with atrial fibrillation, compared with 4.1% in those without (OR: 2.3; 95% CI: 1.8–2.9).
Coagulation disorders (e.g. those acquired/inherited such as thrombocytopenia)	The prevalence of thrombocytopenia in patients with ACS was found to be 1.6% overall (0.3% heparin-induced, 0.6% glycoprotein IIb/IIIa-associated) (185). In a US-based study, 13% of patients with NSTE-ACS developed new-onset thrombocytopenia during hospitalisation (186). In-hospital mortality increased from 2.6% in patients without thrombocytopenia to 23.4% in patients with moderate/severe thrombocytopenia. In-hospital

Table SI-5: Co-morbidities in patients with ACS

	major bleeding occurred in 10.1% of patients without thrombocytopenia, and in 53.3% of patients with moderate/severe thrombocytopenia.

SI.5 Indication: Prevention cardiovascular events in coronary artery disease and peripheral arterial disease

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, CAD was defined as those with a previous history of MI; or multi-vessel coronary disease (narrowing of ≥ 50% in two or more coronary arteries) with symptoms of stable or unstable angina; or those with previous PCI or coronary artery bypass grafting (CABG) surgery. Peripheral arterial disease (PAD) was defined as those with prior bypass or amputation surgery due to vascular disease; those with a history of intermittent claudication and ankle-brachial index (ABI) of less than 0.9 or peripheral artery stenosis ≥ 50%; or previous carotid revascularization or asymptomatic carotid artery stenosis ≥ 50% (187). These definitions are broadly similar to those provided by the European Society of Cardiology (ESC). The ESC 2013 guidelines define CAD patients as those with symptoms of CAD (including stable angina); or those who were previously symptomatic for obstructive or non-obstructive CAD and are stable on treatment; or those who present with symptoms for the first time and are judged to be in a chronic stable condition (188).

Recently, the ESC 2019 guidelines have been revised to focus on Chronic Coronary Syndromes (CCS) instead of CAD, in order to emphasize the fact that the clinical presentations of CAD can be categorized as either ACS or CCS. Thus, CCS refer to (i) patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea; (ii) patients with new onset of HF or LV dysfunction and suspected CAD; (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with recent revascularization; (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; (vi) asymptomatic subjects in whom CAD is detected at screening (189).

The ESC 2017 guidelines define PAD as all arterial disease excluding coronary arteries and the aorta, and includes the carotid and vertebral, upper extremities, mesenteric, and renal arteries. The more specific term peripheral artery disease is typically used to refer to lower extremity artery disease (LEAD) (190). In the VOYAGER PAD clinical trial, the target group was defined by those patients, aged 50 years or older; with documented moderate to severe symptomatic LEAD who underwent technically successful peripheral revascularization distal to the external iliac artery within the last 10 days prior to randomisation to the treatment (191).

Incidence

In men aged 50–59 in the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study cohort (n = 9758), the annual incidence rate of angina pectoris was 5.39 per 1000 person-years (95% CI, 4.06–6.72) and the incidence of MI or coronary death was 5.24

per 1000 person-years (95% CI, 3.93–6.55) in Ireland. In France, the annual incidence of angina pectoris was 2.61 per 1000 person-years (95% CI, 2.08–3.14) and incidence of MI or coronary death was 2.93 (95% CI, 2.38–3.48) (192). In the Multi-Ethnic Study of Atherosclerosis (META) cohort (n = 5,756), the incidence of newly detectable coronary artery calcification, a marker for atherosclerosis, was 6.6% per year in individuals aged 45–84 years old. (193). In a cohort of men and women from the Netherlands (n = 2327), incidence of intermittent claudication was 1.0 (95% CI, 0.7–7.5) per 1000 person-years at risk, but the incidence of asymptomatic LEAD was considerably higher at 9.9 (95% CI, 7.3–18.8) per 1000 person-years at risk (194).

Prevalence

In the British Regional Heart Study cohort (n = 7735) of men aged 40–59 years, 10.3% had evidence of myocardial ischemia (195). In a European cohort of individuals aged 40 years or older, the estimated prevalence of stable angina ranged from 1.4–2.5%, depending on the stringency of definition used (196). In 2010, LEAD was estimated to affect 202 million people globally, following an increase of 23.5% from 164 million affected in 2000 (197). In the Netherlands, the prevalence of LEAD was reported as 19.1% (95% CI, 18.1%–20.0%) in a cohort of 7715 men and women aged 55 years and over; however, only 6.3% of those affected reported symptoms of intermittent claudication (198). The prevalence of carotid artery stenosis (≥50% narrowing) in the general population ranges from 0.2%–7.5%, depending on age and gender (199).

Demographics of the population in the authorised indication and risk factors for the disease

Age is a major risk factor for CAD and PAD, with the prevalence increasing with increasing age. In a European cohort, the estimated prevalence of definite angina (assessed by Rose questionnaire) was 0.7% in individuals aged 40–49 years and increased to 7.1% in individuals ≥ 70 years old (196). In a US-based study, the prevalence of large-vessel LEAD was 3% in individuals younger than 60 years and over 20% in those aged 75 years or older (200). In a meta-analysis, the prevalence of asymptomatic carotid artery stenosis ≥ 50% ranged from 0.2% (95% CI, 0.0–0.4%) in men aged < 50 years to 7.5% (95% CI, 5.2–10.5%) in men aged ≥ 80 years (199).

The incidence of CAD is delayed by approximately ten years in women compared with men, therefore CAD is more prevalent in men aged below 50; however, this difference narrows with increasing age to equal prevalence rates in the seventh decade (201). In the Scottish Heart Health Study cohort (n = 10 359; aged 40–59 years), angina was present in 5.5% and a history of MI in 4.3% of men, compared with 3.3% and 1.4% of women, respectively (202). In Finland, the age-standardized annual incidence of angina was 1.89 per 100 population in women and 2.03 in men (203). In men and women aged ≥ 65 years in the Cardiovascular Health Study cohort (n = 5201), 7% of men and 5% of women had asymptomatic carotid artery stenosis ≥ 50% (204). There is no consistent sex difference in the risk of LEAD, although severe and symptomatic disease may be more common in men (205). In a European cohort, the prevalence of LEAD was 16.9% in men and 20.5% in women; however, of those

affected with LEAD, 8.7% of men reported symptoms of intermittent claudication compared with 4.7% of affected women (198).

Another recent cohort study investigating gender-related differences among patients (n=939) with PAD undergoing peripheral vascular interventions (PVI), concluded that there was not significant difference in mortality or developing MACE between men and women after a 5-year follow up. However, men had higher risk of undergoing re- PVI (HR: 1.276; 95% CI: 1.015–1.614) compared to women (206).

Risk factors for atherosclerotic disease (CAD and/or PAD) include hypertension, diabetes, smoking, depression, a history of cardiovascular disease, dyslipidemia, obesity, and chronic kidney disease (197, 205, 207-211). Diabetes and smoking are the most significant risk factors for LEAD, specifically (205).

EUCLID clinical trial, another large double-blind randomized study conducted among patients with symptomatic PAD in 28 countries (n=13885), showed that the incidence rate of myocardial infarction was 2.4 events per 100 patient-years during a median follow-up of 30 months. Patients experiencing MI were typically older (median age 69 years old), more likely to have diabetes or a previous lower extremity revascularization and also a lower ABI (212).

The main existing treatment options

In patients with CAD, the European Society of Cardiology guidelines recommend the use of at least one drug for angina/ischaemia relief (nitrates, β-blockers and/or calcium channel blockers), lipid-lowering agents (e.g statins) and long-term single antiplatelet therapy (low dose aspirin is recommended, with clopidogrel indicated as an alternative) to prevent the occurrence of an acute cardiovascular event. In some cases, revascularisation with PCI or CABG may be required (188).

For LEAD, ESC guidelines recommend firstly, to address any specific symptom of localization (limb symptoms) and also, long-term single antiplatelet therapy (aspirin or clopidogrel) in symptomatic patients and in those patients, who have undergone revascularization, in order to decrease the risk of any cardiovascular event. Revascularization, if required, is achieved by lower-extremity bypass grafting (190). Long-term single antiplatelet therapy is recommended for symptomatic patients with carotid stenosis and should be considered in those who are asymptomatic. Dual antiplatelet therapy (aspirin and clopidogrel) is recommended for at least one month after carotid artery stenosis (190).

For PAD, ESC guidelines recommend firstly, to address any specific symptom of localization (limb symptoms) and also, long-term single antiplatelet therapy (aspirin or clopidogrel) in symptomatic patients and in those patients, who have undergone revascularization, in order to decrease the risk of any cardiovascular event. Revascularization, if required, is achieved by lower-extremity bypass grafting (190). Guidelines recommend single antiplatelet therapy (SAPT) for secondary prevention in patients with PAD, and dual antiplatelet therapy (DAPT) for PAD patients after revascularization.

Guidelines recommend long-term SAPT in all PAD patients. Recommendations of DAPT(clopidogrel and aspirin) after peripheral revascularization are of Class II 2016 (213, 214).

Society	Recommendation
American College of Chest Physicians (ACCP), 2012[29]	• Long-term SAPT with aspirin or clopidogrel for symptomatic PAD before and after PTA or bypass (class Ia). • SAPT for patients undergoing PTA with or without stenting, duration not specified (class IIc).
Society for Vascular Surgery, 2015[10]	• SAPT with aspirin or clopidogrel or DAPT with aspirin and clopidogrel for patients undergoing venous or prosthetic bypass (class II). • DAPT with aspirin and clopidogrel for 1 month postinfrainguinal endovascular intervention for claudication (class II).
American College of Cardiology/American Heart Association, 2016[27]	• Effectiveness of DAPT in reducing risk of CV ischemic events is not established for patients with symptomatic PAD and low to intermediate risk of cardiovascular events (class IIb). • DAPT may be reasonable in patients with symptomatic PAD postrevascularization, duration not specified (class IIb).
European Society of Cardiology (ESC), 2017[28]	• Long-term SAPT for all symptomatic patients (class Ia) and patients who underwent revascularization (class Ic). • SAPT after infrainguinal bypass (class Ia). • Clopidogrel may be preferred over aspirin when SAPT is warranted (class IIb B). • VKA can be considered after autologous vein infrainguinal bypass (class IIb B). • DAPT with aspirin and clopidogrel for at least 1 month after infrainguinal stent implantation (class IIa C). • Consider DAPT with aspirin and clopidogrel for below-knee-bypass with a prosthetic graft (class IIb B). • Antiplatelet therapy not indicated in asymptomatic patients (class IIIa).

Abbreviations: CV, cardiovascular; DAPT, dual antiplatelet therapy; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty; SAPT, single antiplatelet therapy; VKA, vitamin K antagonists.

Long-term single antiplatelet therapy is recommended for symptomatic patients with carotid stenosis and should be considered in those who are asymptomatic. Dual antiplatelet therapy (aspirin and clopidogrel) is recommended for at least one month after carotid artery stenosis (190).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

CAD may be asymptomatic or associated with symptoms including stable angina for periods of time, interrupted with episodes of ACS (188). LEAD may be asymptomatic or cause intermittent claudication, and is associated with functional impairments in walking velocity and balance (215). Chronic occlusion of lower-limb arteries can cause critical limb ischemia, requiring major amputation in 30% of cases (216). Carotid artery stenosis is often asymptomatic, manifesting clinically as TIA or stroke. The risk of stroke in patients with carotid artery stenosis of less than 60% luminal diameter has been reported as 1.6% annually, rising to 3.2% for those with 60–99% stenosis (217).

Although often asymptomatic, individuals with CAD and/or PAD are at a higher risk of experiencing an acute CV event than the general population. In a large (n = 68 236) international cohort, 4.52% (95% CI, 4.19–4.84) of patients with CAD, 5.35% (95% CI, 4.77–5.97) of individuals with LEAD, and 6.47% (95% CI, 5.96–6.97) of patients with cerebrovascular disease experienced CV events (defined as MI, stroke or CV death) during a one year period, compared with 2.15% (95% CI, 1.84–2.46) of individuals with at least three atherosclerotic risk factors (218). In a European prospective cohort study of individuals with confirmed CAD (n = 994), the rate of all CV events (death, MI, UA, heart failure, stroke

and/or emergency revascularization) was 21.9 (95% CI, 19.1–25.2) per 100 patient years (219). In the Reduction of Atherothrombosis for Continued Health (REACH) Registry cohort (n = 23 364), individuals with carotid artery disease, followed over a four-year period, were associated with a 22% (95% CI, 14–30%) increased risk of coronary events (CV death, MI, coronary hospitalization) compared to those without (HR, 1.22; 95% CI, 1.14–1.30; adjusted for age, sex and CV risk factors) (220). In a US-based study, LEAD (identified by intermittent claudication) was associated with an all-cause mortality risk of 3.1 (95% CI, 1.9–4.9) compared to those without disease, 5.9 (95% CI, 3.0–11.4) for all deaths from cardiovascular disease, and 6.6 (95% CI, 2.9–14.9) for deaths from coronary heart disease (221). In another study, LEAD (defined as an ABI of less than 0.9) was associated with an all-cause mortality hazard ratio of 2.4 (95% CI, 1.9–2.9; adjusted for age, sex and ethnicity) (222).

In the EUCLID trial (n = 1.738), patients undergoing lower extremity revascularization (LER) appeared to be at a higher risk of MACE (HR:1.60 ; 95% CI: 1.35-1.90), all-cause mortality (HR:1.38 ; 95% CI: 1.14-1.68) and of developing major adverse limb events (MALE) including acute limb ischemia and major amputation (HR:12.0; 95% CI: 9.47-15.30) as compared to non-LER, after accounting for several potential confounders (223).

Another recent study conducted in Poland, of patients older than 45 years old, with critical limb ischemia (n=239), showed that 1 out of 4 patients experienced myocardial infarction after endovascular revascularization with > 25% mortality within the subsequent year. In addition, the hazard ratio of 1-year mortality and 1-year MACE in these patients was 2.44 (95% CI; 1.18–5.06) and 2.89 (95% CI; 1.41–5.92) respectively, compared to patients who didn't develop myocardial infarction after the revascularization (224).

In addition, another 5-year follow-up Swedish study among patients revascularized for LEAD and aged 50 years or older (n=16,889), showed that the amputation rate for IC patients was 0.4% (range 0.3%–0.5%) per year and 12.0% (95% CI 11.3–12.6) for CLI patients during the first 6 months following revascularization. Importantly, the cumulative combined incidence of death or amputation 3 years after revascularisation was 12.9% (95% CI 12.0–13.9) in IC patients and 48.8% (95% CI 47.7–49.8) in CLI patients (225).

Important co-morbidities

CAD and PAD (LEAD and carotid artery disease) share a common pathophysiological mechanism of atherosclerosis, and therefore commonly occur concurrently. In an Italian cohort of patients with LEAD (n = 200), co-morbid CAD was identified in 55% of patients and carotid artery disease in 43% (226). Patients with CAD and concomitant LEAD (n = 216) also have more extensive coronary atherosclerosis, with a greater degree of calcification, than those with CAD alone (n = 3263). They also experience more frequent cardiovascular events (26.3% LEAD+CAD vs. 19.8% CAD; p = 0.03) (227). A meta-analysis of 19 prospective studies found that 25–28% of individuals with LEAD (n = 4573) have carotid artery stenosis (228). As would be expected from their shared pathophysiology, CAD and PAD also share several co-morbidities, shown in. Table SI-6.

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Table SI-6: Co-morbidities of coronary artery disease and peripheral arterial disease

Myocardial infarction	In a European cohort of patients with confirmed angina (n = 117), 37.4% had a previous MI (196). In a Canadian cohort (n = 16 440), 18% of individuals with LEAD had history of MI (229). In a meta-analysis of patients with asymptomatic carotid artery stenosis, the incidence rate of MI was 1.8 (95% CI, 0.7–4.6; 5 studies) per 100 person-years (230).
Stroke and TIA	Prior history of stroke was present in 14% of patients with confirmed angina in a European cohort (n = 117) (196). In a cohort of patients with previous ischemic stroke (n = 151), 24.5% were found to have high-risk CAD (based on coronary calcium score, compared to 9.3% of the age- and sex-matched controls (231). In a database study (n = 16 440), stroke occurred in 13% and TIA in 14% of LEAD patients (229). In a meta-analysis of prospective cohort studies of patients with asymptomatic carotid artery stenosis (41 studies; n = 16 178), the summary incidence rate of ipsilateral stroke was 1.7 (95% CI, 1.3–2.1; 25 studies) per 100 person-years and 2.9 (95% CI, 1.9–4.3; 8 studies) for TIA (230).
Atrial fibrillation	In a US cohort of individuals diagnosed with AF (n = 17 974), 34.6% had a history of previous coronary heart disease, including 21.8% with a history of angina (232). In a Canadian cohort of individuals with LEAD (n = 16 440), 5% of individuals had AF (229).
Heart failure	In a large database study (n = 16 440), LEAD and co-morbid HF was present in 25% of individuals (229). In a British cohort of patients with HF (n = 136), 52% of patients had CAD (233).
Hypertension	In a European cohort of patients with confirmed angina (n = 117), 83.5% had a history of hypertension (196). In a cohort of patients with LEAD (n = 16 440), 58% were hypertensive (229).
Renal disease	A cross-sectional US study found CAD was present in 38% of patients with end-stage renal disese (n = 3925) (234). In a cohort of 2229 individuals, LEAD (defined as ABI < 0.9) was associated with renal insufficiency (creatinine clearance < 60 mL/min/1.73 m^2) with an odds ratio of 2.5 (95% CI, 1.2–5.1; adjusted for other comorbid conditions) (235). The prevalence of LEAD in patients with end-stage renal disease ranges from 15–46% depending on diagnostic criteria used (n = 37 218) (236).
Type 2 diabetes	Type 2 diabetes was associated with stable angina (HR, 1.62; 95% CI, 1.49–1.77) in a cohort of 34 198 individuals (237). In a database study (n = 16 440), 19% of individuals with LEAD had type 2 diabetes (229). In a cohort of 34,198 individuals with type 2 diabetes followed for 5.5 years, 16.2% developed LEAD (HR, 2.98; 95% CI, 2.76–3.22) (237).
Hypercholesterolemia	In a cohort of patients with confirmed angina (n = 117), 75.6% of individuals had hypercholesterolemia (196).

Table SI-6: Co-morbidities of coronary artery disease and peripheral arterial disease

	Hypercholesterolemia was present in 7% of a large cohort of individuals with LEAD (n = 16 440) (229).

SI.6 Indication: Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

Incidence

In children, VTE is a rare disease with an estimated incidence between 0.01 and 0.05 per 1000 children per year, which is approximately 20 to 100 times lower than in adults (238-241). As a result of better survival of children with life-threatening or chronic medical conditions and improved awareness among pediatricians, the incidence of VTE in children has significantly increased over recent years (242-246).

Pediatric VTE is an increasingly common complication amongst hospitalized children, occurring in 42–58/10 000 admissions (244, 247). The incidence of VTE in pediatric patients has increased by 70% in under a decade (244). This trend is most dramatic in children who are hospitalized, averaging 5–22 per 10 000 pediatric inpatients (238, 248-250), but community-acquired pediatric VTE is also increasing (0.1–0.5 per 10 000 children) (238, 249).

In a US study using data from annual Nationwide Inpatient Sample databases from the Healthcare Cost and Utilization Project from 2009 to 2011, incidence rates for VTE were 32.4 per 10 000 at-risk patients aged 1–17 years (251). The increased incidence of VTE in the pediatric population is likely due to both enhanced awareness and recognition of VTE, as well as increased prevalence of thromboembolic associated risk factors (252).

Prevalence

Using the Kid's Inpatient Database (KID) 2006, which included over 2.4 million eligible discharges, VTE was identified in 188 per 100 000 discharges for children ≤18 years of age (246).

Several studies have reported changing rates of VTE with time, for example, from 34 to 58 cases per 10 000 admissions from 2001–2007 (244), or from 0.3 to 28.8 per 10 000 admissions from 1992–2005 (243). Most studies report a bimodal peak distribution, in which infants less than 1 year of age and adolescents are at the greatest risk for development of VTE (253). In another study, overall, the age-adjusted rate of VTE-associated hospitalization increased from 4.7 per 100 000 during 1994 to 9.5 per 100 000 during 2009 (254). Teenage girls have twice the rate of VTE compared with teenage boys; this is associated with the use of oral contraceptives and pregnancy (249).

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Demographics of the population in the authorised indication and risk factors for the disease

A Canadian registry published in 1994 highlighted that central venous lines were the single most important predisposing cause of VTE in children (33%), whereas inherited coagulation disorders accounted for 9%. VTE was associated with cancer (23%), congenital heart disease (15%), and trauma (15%) (238).

VTE in children is often provoked by a variety of risk factors and rarely is unprovoked in nature (255). Expressions of VTE that usually require anticoagulant therapy include venous thrombosis of the lower extremity, caval vein, renal vein, portal vein, right side of the heart, lungs, upper extremity, subclavian vein, jugular vein, and cerebral vein and sinuses.

The main existing treatment options

The most recent American College of Chest Physicians (ACCP) management guidelines of 2012 (256) recommend for the initial treatment of VTE in children adjusted-dose unfractionated heparin (UFH), bodyweight-adjusted low-molecular-weight heparin (LMWH) or fondaparinux. For subsequent treatment, either INR-titrated vitamin K antagonist (VKA) or bodyweight-adjusted LMWH is recommended. Suggested treatment durations are 3 months for children with provoked VTE in whom the risk factor has resolved and continued anticoagulant therapy in children who have ongoing risk factors. For children with idiopathic VTE, the suggested treatment duration has a minimum of 3 months and a maximum of 6 to 12 months. For catheter-related VTE, the ACCP guidelines suggest a total duration of anticoagulation of between 6 weeks and 3 months (257). Although the suggested treatment duration in CVC-VTE is from 6 weeks to 3 months, many physicians treat young children with CVC-VTE for periods shorter than 6 weeks.

Although there is no documentation in the medical literature about adherence to the international guidelines for children with VTE, the impression is that the guidelines are generally followed, especially in older children (258). However, for neonates and infants with VTE, anticoagulation is often not given or given for a short duration only because of the presence of serious illnesses, apprehension of bleeding risk in the neonatal period, the presentation with minimal clots, and the practice of repeat ultrasound imaging to guide duration of treatment, with continuation of anticoagulation only if recanalization has failed (259). Whether resolution on ultrasound represents true cure and abolition of risk of recurrence for catheter-related or non-catheter-related VTE remains to be determined.

No anticoagulants are approved for use in children and there is limited research on their use in the pediatric population (260). Despite this, use of anticoagulants in children is widespread (261). Owing to limited data, little is known regarding the optimal dosing regimens, duration of treatment and the efficacy and safety profiles (including bleeding risk) of these anticoagulants in children (253). Treatment decisions are therefore based on extrapolation from adult data and the experience of the treating physician (260, 262).

Unfractionated heparin (UFH) is a commonly used anticoagulant that is administered by continuous intravenous infusion in hospitalized children. The benefits of UFH include a short half-life and the availability of a reversal agent (protamine). However, dosing of UFH is

complicated by the high degree of inter- and intra-patient variability (261). This is compounded in young children due to variability in the plasma concentration of thrombin and antithrombin, resulting in heparin resistance or sensitivity (263). An additional concern with the use of UFH therapy is the rare but serious side effect of heparin-induced thrombocytopenia (HIT)(261). In addition, as UFH is derived from animal tissue, there is a potential risk of contamination with over-sulfated chondroitin sulfate (OSCS) (264).

A common alternative to UFH is low-molecular-weight heparin (LMWH) which has a more predictable dose-response and longer half-life than UFH. LMWH can be administered subcutaneously in an outpatient setting, although twice daily dosing is necessary. LMWH has a lower risk of OSCS contamination and HIT than UFH; however, LMWH may have a negative effect on bone metabolism (261).

The low-molecular-weight heparin (LMWH) dalteparin sodium (FRAGMIN) has been approved in the US on 16 MAY 2019 for treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older (265).

Treatment with fondaparinux, a synthetic polysaccharide is another potential alternative to UFH. Fondaparinux is not associated with a risk of OSCS contamination or HIT and has no known effects on bone metabolism. In a small open-label clinical trial, once daily fondaparinux demonstrated an acceptable safety profile for the treatment of VTE in children (266, 267). However, unlike LMWH, the effects of an overdose of fondaparinux cannot be reversed with protamine (253).

VKAs are an acceptable alternative to heparin-based anticoagulants, particularly for older children owing to their oral route of administration (253). However, VKAs have several drug interactions which may preclude their use in children who are receiving concomitant medication (261). Moreover, VKAs require frequent dose monitoring and adjustment to achieve and maintain the target INR. However, an optimal INR has not been directly determined in children, but rather has been extrapolated from adult data. There is also some evidence to suggest that long-term warfarin therapy in children may be associated with the development of osteoporosis (253).

The parenteral direct thrombin inhibitors argatroban (268, 269) and bivalirudin (263, 270) have also been investigated for the treatment of VTE in children. Unlike heparin-based anticoagulants, these agents are unaffected by low or fluctuating concentrations of antithrombin and do not cause HIT (263). Only a few small, single-arm, open-label trials have been published in children; therefore, only limited conclusions can be drawn regarding their efficacy and safety (263, 268-270). In the pediatric population, these drugs are used predominantly in the context of suspected or confirmed HIT (271).

Clinical trials of other non-VKA oral anticoagulants (NOACs) including rivaroxaban are ongoing for the treatment and/or prevention of VTE in children (272).

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The reporting of thromboembolic events in children and neonates has been on the increase, owing to improvements in the diagnosis and care of children with congenital heart disease, cancer, and prematurity.

In two studies, the mortality rate for children directly attributable to VTE was reported as 2.2% and 3.7%, respectively (273, 274). Pediatric VTE is an increasingly common complication amongst hospitalized children, occurring in 42–58/10 000 admissions (244, 247).

The only randomized study on the treatment of venous thrombosis in children conducted so far (the REVIVE study) confirmed that cancer and infections, followed by congenital heart disease, were the most frequently reported risk factors (257, 275). In the REVIVE study, children with cerebral vein and sinus thrombosis were excluded due to lack of consensus on the need for anticoagulation. Risk factors for recurrent VTE in the European collaborative pediatric database on cerebral venous thrombosis include age at onset, absence of anticoagulant treatment, persistent venous occlusion, or presence of the prothrombin gene mutation (257).

Important co-morbidities

Approximately 95% of venous thromboembolisms (VTEs) in children are associated with serious disease (253), e.g. children with congenital heart disease, cancer, and prematurity, with central venous catheter (CVC) being the most important acquired trigger for development of VTE in children, contributing to >90% of all neonatal cases of venous thrombosis and to >50% of all cases in other age groups (238, 239, 276, 277). The incidence of VTE in pediatric patients has increased by 70% in under a decade (244).

For antithrombotic treatment of cerebral vein and sinus thrombosis (CSVT), consensus-based guidelines are discordant regarding use of anticoagulation. The most recent American College of Chest Physician (ACCP) guidelines (256, 260) suggest therapeutic anticoagulation for children without significant intracranial hemorrhage, while the American Heart Association (AHA) guidelines published in 2008 (278) suggest anticoagulants only in case of evidence of thrombus propagation, multiple cerebral or systemic emboli or if a severe prothrombotic state is present.

Part II: Module SII - Non-clinical part of the safety specification

SII.1 Key safety findings from non-clinical studies and relevance to human usage:

A comprehensive non-clinical programme has been conducted to characterise the toxicological and toxico-kinetic profile of rivaroxaban according to current testing guideline standards and regulatory requirements to support the intended use of rivaroxaban.

In accordance with the use in humans, the chosen route of administration in the animal studies was oral. Single-dose toxicity studies were performed in rats and mice. Repeat-dose toxicity to support long-term administration in patients was covered by studies with daily treatment up to 6 months in rats and up to 12 months in dogs. The dog was selected as a non-rodent species, as metabolism and kinetic data available have shown that the dog can be considered as human-like with regard to the metabolic and kinetic profile. Furthermore, repeat-dose toxicity data from mice for up to 13 weeks of treatment are available. In addition, the standard battery of genotoxicity studies as well as the complete package of reproduction toxicity studies in rats and rabbits was performed. Two-year carcinogenicity studies were performed in rats and mice. Due to structural similarities to linezolid, in vitro and in vivo investigations assessing potential effects on mitochondrial protein synthesis and function were performed.

Key safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity	
• Low acute toxicity in rats and mice. • In all species tested, as a consequence of the pharmacological mode of action, prolongation of coagulation time was observed, starting already at the lowest dose tested. • No major difference in the qualitative or quantitative toxicological response in male and female animals. • Body weight gain reduction in rats and dogs without impaired general condition or any signs of toxicity at high exposure levels. • Exaggerated pharmacological activity (inhibition of blood coagulation) in dogs, leading to severe potentially life-threatening haemorrhages with secondary anaemia in individual animals. • Up to the highest dose tested, no intrinsic organ-specific toxicity of rivaroxaban was revealed in mice, rats or dogs.	• Single- and repeat-dose toxicity studies in rats, mice and dogs, species considered appropriate for the non-clinical safety evaluation, revealed no organ-specific toxicity of rivaroxaban. The non-clinical safety profile is mainly characterised by exaggerated pharmacological activity of rivaroxaban resulting in subclinical and clinically relevant bleeding events. • As haemorrhages and potential sequelae thereof (e.g. post-surgical anaemia) are addressed in the RMP and covered by routine pharmacovigilance monitoring there is no need for further clinical measures.

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Key safety findings (from non-clinical studies)	Relevance to human usage
Reproductive and developmental toxicity	
• Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-fetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.	• As intra-uterine bleeding is considered the primary cause of maternal and fetal toxicity, and this effect is related to the mode of action of rivaroxaban, relevance for humans has to be expected. Effects on pregnancy and lactation were not addressed in clinical studies and hence to avoid any harm to pregnant women, and unborn and newborn children, rivaroxaban is contraindicated to pregnant or nursing women, and women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.
• [^{14}C]Rivaroxaban-related radioactivity penetrates the blood–placenta barrier in rats. The average exposure in the fetuses, based on the area under the plasma concentration–time curve from 0 h to 24 h [$AUC_{(0-24\ h)}$], reached about 20% of the exposure in maternal blood. In the mammary glands of rats an approximately blood-equivalent AUC indicating secretion of radioactivity into milk was found. In the milk of lactating rats a low amount of [^{14}C] rivaroxaban-related radioactivity was seen.	
Nephrotoxicity	
• Up to the highest dose tested, no intrinsic organ-specific toxicity of rivaroxaban was revealed in mice, rats or dogs.	• Non-clinical safety studies showed no risk of rivaroxaban-related nephrotoxicity.
Hepatotoxicity	
• Minimal non-dose-related increases in total bilirubin levels in mice, rats and dogs, which are considered to be due to an increased haemoglobin turnover secondary to clinical or subclinical haemorrhages.	• Non-clinical safety studies showed no risk of rivaroxaban-related hepatotoxicity.
• Non-dose-related, minimal increase in alanine aminotransferase (less than 2-fold) in rats. As the increase was isolated (no corresponding findings in other liver-related parameters and no morphological correlate) and transient (increase vanished despite continuous treatment), it was considered neither adverse and indicative for evidence of liver toxicity of rivaroxaban nor biologically relevant. No comparable findings in mice and dogs.	

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Key safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity	
• No evidence for genotoxicity in the standard International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) battery of *in vitro* and *in vivo* genotoxicity tests.	• Genotoxicity studies did not reveal any risk to humans.
Carcinogenicity	
• No evidence for a carcinogenic effect.	• Carcinogenicity studies did not reveal any risk to humans.
General safety pharmacology	
• Prolongation of coagulation time, resulting in prolonged bleeding time at supratherapeutic doses. • Additive effects after co-administration with non-steroidal anti-inflammatory drugs and other antithrombotic drugs (acetylsalicylic acid, clopidogrel). • Activated charcoal given together or shortly after rivaroxaban administration reduces or prevents intestinal absorption of rivaroxaban.	• Safety pharmacology studies did not reveal any risk to humans.
• Pharmacological effects of rivaroxaban are partly antagonised by the administration of recombinant FVIIa (rFVIIa) and prothrombin complex concentrate (PCC). The effects of recombinant rVIIa (NovoSeven, Novo Nordisk), a PCC (Beriplex) or an activated PCC (APCC; FEIBA NF 1000E) on the prolongation of the bleeding time induced by high doses of intravenous rivaroxaban were tested in the mesenteric artery bleeding model in rats. rFVIIa, a PCC and an APCC each partially reversed the prolonged bleeding time in rats treated with rivaroxaban when administered before or after the induction of bleeding. The effects of rFVIIa and APCC were also tested in baboons anticoagulated with a high dose of rivaroxaban, and each shortened the prolonged bleeding time.	• The data suggest that rFVIIa, a PCC or an APCC may have potential as a possible reversing agent to rivaroxaban.
• A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available (details available in the Summary of Product Characteristics of andexanet alfa).	• If bleeding cannot be controlled by the above measures (rFVIIa, a PCC or an APCC), the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises

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Key safety findings (from non-clinical studies)	Relevance to human usage
	the pharmacodynamic effect of rivaroxaban should be considered.
• No evidence for cardiovascular (including QT prolongation), pulmonary, renal or central nervous system safety risk.	
Mechanisms for drug interactions	
• See general safety pharmacology.	
Other toxicity-related information or data	
• Non-phototoxic.	• Phototoxicity studies did not reveal any risk to humans.
• Rivaroxaban shows a structural relationship to linezolid, an antimicrobial drug.	• As rivaroxaban is inactive in terms of antibacterial effects, there is no risk of resistance formation and pharmacodynamic drug–drug interaction, and thus no specific measures are needed.
• After long-term administration, linezolid reveals clinically relevant side effects (in particular aplastic anaemia) that are believed to be a consequence of an inhibition of mitochondrial protein synthesis. In order to exclude the possibility that rivaroxaban could induce a similar kind of mitochondrial toxicity, *in vitro* and *in vivo* investigations specifically addressing mitochondrial protein synthesis and mitochondrial function were performed. Under the conditions of these assays, and in contrast to linezolid, rivaroxaban showed no evidence of mitochondrial toxicity *in vitro* and *in vivo*. This assessment is further supported by the non-clinical safety profile of rivaroxaban, which does not indicate any linezolid-like non-specific side effects. The first and most prominent side effect that would be expected from linezolid-like mitochondrial toxicity would be aplastic anaemia. No such toxicity was observed in the non-clinical safety studies.	• Rivaroxaban showed no evidence for mitochondrial toxicity in preclinical studies. As haemorrhages and potential sequelae thereof (e.g. post-surgical anaemia) are addressed in the RMP and covered by routine pharmacovigilance monitoring there is no need for further clinical measures.

Rivaroxaban was tested in a comprehensive non-clinical safety package and was thoroughly investigated on potential reprotoxicity. In order to support the use of rivaroxaban in the paediatric population non-clinical safety studies in juvenile rats were performed. Juvenile rat toxicity testing did not reveal any new toxicological findings or targets.

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SII.2 Conclusions on non-clinical data

In summary, single- and repeat-dose toxicity studies in rats, mice and dogs, species considered appropriate for the non-clinical safety evaluation, revealed no organ-specific toxicity of rivaroxaban. The non-clinical safety profile is mainly characterised by exaggerated pharmacological activity of rivaroxaban resulting in subclinical and clinically relevant bleeding events. Non-clinical safety studies showed no risk of rivaroxaban-related hepatotoxicity or nephrotoxicity. The slight increase of total bilirubin is considered to be secondary to an increased haemoglobin turnover secondary to haemorrhages. Safety pharmacology studies as well as studies on genotoxicity, carcinogenicity and phototoxicity did not reveal any risk to humans.

Due to the mode of action, the administration of rivaroxaban results in an increased bleeding risk, which is clearly evident in studies on developmental toxicity and pre- as well as post-natal development. Embryo-fetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams. In addition, there is evidence that rivaroxaban passes the placenta and that rivaroxaban is secreted into the milk. To avoid any harm to pregnant women, and unborn and newborn children, rivaroxaban is contraindicated to pregnant or nursing women, and women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Safety concerns

Important identified risks (confirmed by clinical data)

- Haemorrhage

Important potential risks (not refuted by clinical data or which are of unknown significance)

- Embryo-fetal toxicity

Missing information

- None

Part II: Module SIII - Clinical trial exposure

Clinical trials with rivaroxaban have been conducted to assess safety and efficacy in prevention and treatment of thromboembolic events in different patient populations and at different strengths.

Along with the latest application for a new indication, in term neonates, infants and toddlers, children, and adolescents aged less than 18 years, the respective clinical trial data on exposure were presented, therefore, the data specific to this application are presented at the start of this module.

The main differences between the pediatric studies are in the dosing scheme, the study duration, the formulation(s) used, whether a comparator arm was included and in the number of children. Studies 12892 and 17992 are single-dose studies with only one day of treatment (pool 3 in the integrated analysis statistical analysis plan). All multi-dose studies, i.e. 17618, 14372, 14373 and 14374 are included in pool 1 in the integrated analysis statistical analysis plan. Pool 2 of the integrated analysis statistical analysis plan includes all active-controlled studies, i.e. 14372, 14373 and 14374 and is a subset of pool 1 used for identification of ADRs.

Changes based on data from the EINSTEIN Junior study program submission and the proposed new liquid formulation and the newly proposed indication for Xarelto in the pediatric population are included in Table SIII-1 to Table SIII-9. The following tables show patient's exposure based on data from completed phase 2 and phase 3 clinical trials in the adult population (DLP 15 NOV 2020).

SIII.1 Data on exposure based on completed pediatric population

Table SIII-1: Duration of exposure to study medication: Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children birth to < 18 years (Pediatric Population, Pool of SN 12892, 17992, 17618, 14373, 14374, 14372)

Duration of study medication	Patients	Person time (years)
At least 1 day	528	134
At least 28 days	382	132
At least 80 days	290	122
At least 300 days	31	30
Total person time for indication		**134**

365.25 days = 1 Patient year.
Treatment duration = date of last study medication - date of first study medication + 1.
The treatment start date as reported by the investigator is used for calculation.

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Table SIII-2: Exposure by age group and gender: Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children birth to < 18 years (pool 1: 17618, 14373, 14374, 14372)

	Patients		Person time (years)	
Age group	**Male**	**Female**	**Male**	**Female**
12 - <18 years	86	105	40.279	39.354
6 - <12 years	64	35	18.653	7.658
2-<6 years	36	35	8.348	10.834
Birth -< 2 years	32	29	4.928	3.236
0.5-<2 years	17	19	3.094	2.472
Birth -< 0.5 years	15	10	1.834	0.764
Total	**218**	**204**	**72.208**	**61.081**

365.25 days = 1 Patient year.
Treatment duration = date of last study medication - date of first study medication + 1.
The treatment start date as reported by the investigator is used for calculation.

Table SIII-3: Exposure by age group and gender: Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children birth to <18 years (pool 3: 12892, 17992)

	Patients		Person time (years)	
Age group	**Male**	**Female**	**Male**	**Female**
12 - <18 years	4	5	0.011	0.014
6 - <12 years	25	15	0.068	0.041
2-<6 years	16	13	0.044	0.036
Birth -< 2 years	17	11	0.047	0.03
0.5-<2 years	16	10	0.044	0.027
Birth -< 0.5 years	1	1	0.003	0.003
Total	**62**	**44**	**0.17**	**0.12**

365.25 days = 1 Patient year.
Treatment duration = date of last study medication - date of first study medication + 1.
The treatment start date as reported by the investigator is used for calculation.

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Table SIII-4: Exposure by study and dose (all enrolled subjects pool 1: 17618, 14373, 14374, 14372)

Study Identifier	Treatment group	Patients	Person time (years)
14372	Rivaroxaban OD (tablet)	117	56.383
	Rivaroxaban OD (suspension)	91	31.973
	Rivaroxaban BID (tablet)	8	2.196
	Rivaroxaban BID (suspension)	75	27.754
	Rivaroxaban TID (suspension)	38	8.386
14373	Rivaroxaban OD (tablet)	24	1.851
	Rivaroxaban BID (suspension)	19	1.498
14374	Rivaroxaban BID (suspension)	40	3.066
17618	Rivaroxaban BID (suspension)	5	0.099
	Rivaroxaban TID (suspension)	5	0.085
Total		**422**	**133.29**

365.25 days = 1 Patient year.
Treatment duration = date of last study medication - date of first study medication + 1.
The treatment start date as reported by the investigator is used for calculation.
Children who changed dose regimen during treatment are presented under their initial dose regimen.
For study 17618 Rivaroxaban BID (suspension): Granules For Oral Suspension = 1, Ready-to-use Oral Suspension = 4.
For consistency reasons, label of treatment group was adapted in comparison to label specified in corresponding SAP.

Table SIII-5: Exposure by study and dose (all enrolled subjects pool 3: 12892, 17992)

Study Identifier	Treatment group	Patients	Person time (years)
12892	Rivaroxaban Tablet Low Dose - Single dose	8	0.022
	Rivaroxaban Tablet High Dose - Single dose	9	0.025
	Rivaroxaban Suspension Low Dose - Single dose	28	0.077
	Rivaroxaban Suspension High Dose - Single dose	14	0.038
17992	Group A: Rivaroxaban Suspension Phase I (12892) Low Dose - Single dose	22	0.06
	Group B: Rivaroxaban Suspension Phase II (14373/14374) - Single dose	23	0.063
	Group C: Rivaroxaban Suspension (0.4 mg/kg body weight) - Single dose	2	0.005
Total		**106**	**0.29**

365.25 days = 1 Patient year.
Treatment duration = date of last study medication - date of first study medication + 1.
The treatment start date as reported by the investigator is used for calculation.
Children who changed dose regimen during treatment are presented under their initial dose regimen.
For consistency reasons, label of treatment group was adapted in comparison to label specified in corresponding SAP.

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Table SIII-6: Exposure by race (safety analysis set, pool 1: 17618, 14373, 14374, 14372)

Race	Patients	Person time (years)
White	345	112.151
Black or African American	18	4.444
Asian	23	5.498
Native Hawaiian or Other Pacific Islander	1	0.296
Not Reported	31	10.097
Multiple	4	0.805
Total	**422**	**133.29**

365.25 days = 1 Patient year.
Multiple: Subjects who reported that they belong to more than one race.
Treatment duration = date of last study medication - date of first study medication + 1.
The treatment start date as reported by the investigator is used for calculation.

Table SIII-7: Exposure by race (safety analysis set, pool 3: 12892, 17992)

Race	Patients	Person time (years)
missing	4	0.011
White	81	0.222
Black or African American	3	0.008
Asian	3	0.008
American Indian or Alaska Native	1	0.003
Not Reported	10	0.027
Multiple	4	0.011
Total	**106**	**0.29**

365.25 days = 1 Patient year.
Multiple: Subjects who reported that they belong to more than one race.
Treatment duration = date of last study medication - date of first study medication + 1. The treatment start date as reported by the investigator is used for calculation.

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Table SIII-8: Exposure for special populations (safety analysis set, pool 1: 17618, 14373, 14374, 14372)

Special population	Patients	Person time (years)
Hepatic Impairment at Baseline		
No	409	129.489
Yes	13	3.8
Baseline eGFR category		
Moderate kidney dysfunction (30 to < 50 mL/min/1.73m2)	3	0.378
Mild kidney dysfunction (50 to < 80 mL/min/1.73m2)	30	6.552
Normal kidney function (>= 80 mL/min/1.73m2)	383	124.446
missing	6	1.914

365.25 days = 1 Patient year.
A subject is defined to have a medical history of hepatic impairment, if a preferred term included in the MedDRA SMQ Hepatic disorders (excluding sub-SMQs Liver-related coagulation and bleeding disturbances and Liver related investigations, signs and symptoms) is reported.
Since in children younger than 1 year the eGFR cannot be calculated, it was assumed that those in the <90th percentile, 90-97.5th percentile, and >97.5th percentile group taken from the publication of Boer at al. for Serum Creatinine had an estimated GFR of >80 mL/min/1.73m2,
50-80 mL/min/1.73m2, and 30-50 mL/min/1.73m2 group, respectively.
Reference: Boer DP, de Rijke YB, Hop WC, et al. Reference values for serum creatinine in children younger than 1 year of age.
Treatment duration = date of last study medication - date of first study medication + 1. The treatment start date as reported by the investigator is used for calculation.

Table SIII-9: Exposure for special populations (safety analysis set, pool 3: 12892, 17992)

Special population	Patients	Person time (years)
Hepatic Impairment at Baseline		
No	103	0.282
Yes	3	0.008
Baseline eGFR category		
Moderate kidney dysfunction (30 to < 50 mL/min/1.73m2)	5	0.014
Mild kidney dysfunction (50 to < 80 mL/min/1.73m2)	6	0.016
Normal kidney function (>= 80 mL/min/1.73m2)	95	0.26

365.25 days = 1 Patient year.
A subject is defined to have a medical history of hepatic impairment, if a preferred term included in the MedDRA SMQ Hepatic disorders (excluding sub-SMQs Liver-related coagulation and bleeding disturbances and Liver related investigations, signs and symptoms) is reported.
Since in children younger than 1 year the eGFR cannot be calculated, it was assumed that those in the <90th percentile, 90-97.5th percentile, and >97.5th percentile group taken from the publication of Boer at al. for Serum Creatinine had an estimated GFR of >80 mL/min/1.73m2,
50-80 mL/min/1.73m2, and 30-50 mL/min/1.73m2 group, respectively.
Reference: Boer DP, de Rijke YB, Hop WC, et al. Reference values for serum creatinine in children younger than 1 year of age.
Treatment duration = date of last study medication - date of first study medication + 1. The treatment start date as reported by the investigator is used for calculation.

SIII.2 Data on exposure based on completed phase 2 and phase 3 clinical trials in the adult population

Table SIII-10: CAD/PAD (SN 15786)

Duration of study medication	Patients	Person time (years)
>1 to 7 days	67	1
>1 to 2 weeks	73	2
>2 to 4 weeks	138	8
>4 to 8 weeks	263	28
>8 to 12 weeks	175	33
>3 to 6 months (180 days)	611	216
>6 to 12 months (360 days)	1503	1178
>12 to 18 months (540 days)	3512	4237
>18 to 24 months (720 days)	3866	6689
>24 to 30 months (900 days)	3594	7865
>2.5 to 3 years (1080 days)	2407	6484
>3 years	2035	6512
Total person time for indication		**33255**

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Table SIII-11: ESUS (SN 16573)

Duration of study medication	Patients	Person time (years)
1 day	24	0
>1 to 7 days	64	1
>1 to 2 weeks	43	1
>2 to 4 weeks	112	7
>4 to 8 weeks	240	27
>8 to 12 weeks	195	37
>3 to 6 months (180 days)	555	201
>6 to 12 months (360 days)	931	667
>12 to 18 months (540 days)	725	882
>18 to 24 months (720 days)	487	826
>24 to 30 months (900 days)	177	380
>2.5 to 3 years (1080 days)	9	23
Total person time for indication		**3051**

Table SIII-12: ESUS (SN 16573)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	9	7	13	7
>40 to <65 years	1035	395	892	337
Elderly people				
65–74 years	763	522	678	414
75–84 years	351	367	309	311
≥85 years	47	66	33	56
Total	**2205**	**1357**	**1925**	**1126**

Table SIII-13: ESUS (SN 16573)

Dose of exposure (TDD)	Patients	Person time (years)
15 mg TDD: 15 mg OD	3562	3051
Total	**3562**	**3051**

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Table SIII-14: ESUS (SN 16573)

Race or ethnic origin	Patients (N)	Person time (years)
White	2582	2188
Black	50	45
Asian	709	642
American Indian or Alaska Native	25	14
Native Hawaiian or other Pacific Islander	3	1
Not reported	188	154
Multiple	5	6
Total	**3562**	**3051**

Table SIII-15: ESUS (SN 16573)

Special populations	Patients (N)	Person time (years)
Is patient lactating?		
Missing	3562	3051
Renal impairment		
<30 mL/min	1	1
30-<50 mL/min	214	176
50-≤80 mL/min	1746	1526
>80 mL/min	1600	1348
Missing	1	1
Hepatic disorder at baseline		
No	3501	3002
Yes	61	49
Total	**3562**	**3051**

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Table SIII-16: Pool of SN 12839 and 17261

Duration of study medication	Patients	Person time (years)
1 day	116	0
>1 to 7 days	449	6
>1 to 2 weeks	403	12
>2 to 4 weeks	348	20
>4 to 8 weeks	8660	983
>8 to 12 weeks	1	0
missing	2	0
Total person time for indication		**1021**

Table SIII-17: Pool of SN 12839 and 17261

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	18	14	2	1
>40 to <65 years	1871	1223	195	127
Elderly people				
65–74 years	1756	1422	180	150
75–84 years	1445	1576	142	162
≥85 years	249	405	23	39
Total	**5339**	**4640**	**542**	**479**

Table SIII-18: Pool of SN 12839 and 17261

Dose of exposure (TDD)	Patients	Person time (years)
7.5 mg TDD: 7.5 mg OD	1092	127
10 mg TDD: 10 mg OD	8887	894
Total	**9979**	**1021**

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Table SIII-19: Pool of SN 12839 and 17261

Race or ethnic origin	Patients (N)	Person time (years)
missing	179	13
White	8509	900
Black	158	13
Asian	801	63
American Indian or Alaska Native	21	2
Not reported	3	0
Multiple	6	1
Total	**9979**	**1021**

Table SIII-20: Pool of SN 12839 and 17261

Special populations	Patients (N)	Person time (years)
Is patient lactating?		
Missing	8209	881
No	1770	140
Renal impairment		
<30 mL/min	81	4
30-<50 mL/min	1872	184
50-≤80 mL/min	3908	406
>80 mL/min	4040	422
Missing	78	5
Hepatic disorder at baseline		
No	9492	976
Yes	487	45
Total	**9979**	**1021**

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Table SIII-21: COMMANDER HF (SN 16302)

Duration of study medication	Patients	Person time (years)
1 day	12	0
>1 to 7 days	31	0
>1 to 2 weeks	30	1
>2 to 4 weeks	50	3
>4 to 8 weeks	73	8
>8 to 12 weeks	59	12
>3 to 6 months (180 days)	170	61
>6 to 12 months (360 days)	455	352
>12 to 18 months (540 days)	470	579
>18 to 24 months (720 days)	345	596
>24 to 30 months (900 days)	259	570
>2.5 to 3 years (1080 days)	134	365
> 3 years	411	1497
Total person time for indication		**4044**

Table SIII-22: COMMANDER HF (SN 16302)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	15	1	26	3
>40 to <65 years	871	168	1520	327
Elderly people				
65–74 years	659	191	1011	311
75–84 years	365	162	507	256
≥85 years	40	27	46	36
Total	**1950**	**549**	**3112**	**932**

Table SIII-23: COMMANDER HF (SN 16302)

Dose of exposure (TDD)	Patients	Person time (years)
5 mg TDD: 2.5 mg BID	2499	4044
Total	**2499**	**4044**

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Table SIII-24: COMMANDER HF (SN 16302)

Race or ethnic origin	Patients (N)	Person time (years)
missing		
White	2056	3476
Black	29	36
Asian	361	468
American Indian or Alaska Native	11	10
Native Hawaiian or other Pacific Islander	2	3
Not reported	5	7
Other	31	40
Multiple	4	4
Total	**2499**	**4044**

Table SIII-25: COMMANDER HF (SN 16302)

Special populations	Patients (N)	Person time (years)
Is patient lactating?		
Missing	2499	4044
No		
Renal impairment		
<30 mL/min	80	90
30-<50 mL/min	478	661
50-≤80 mL/min	1233	2084
>80 mL/min	708	1209
Missing		
Hepatic disorder at baseline		
Missing	2499	4044
Total	**2499**	**4044**

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Table SIII-26: CASSINI (SN 18262)

Duration of study medication	Patients	Person time (years)
1 day	1	0
>1 to 7 days	18	0
>1 to 2 weeks	7	0
>2 to 4 weeks	16	1
>4 to 8 weeks	31	4
>8 to 12 weeks	34	6
>3 to 6 months (180 days)	172	73
>6 to 12 months (360 days)	126	63
Total person time for indication		**148**

Table SIII-27: CASSINI (SN 18262)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	5	10	2	4
>40 to <65 years	122	95	45	37
Elderly people				
65–74 years	58	62	20	23
75–84 years	27	24	7	8
≥85 years	0	2		1
Total	**212**	**193**	**75**	**73**

Table SIII-28: CASSINI (SN 18262)

Dose of exposure (TDD)	Patients	Person time (years)
10 mg TDD: 10 mg OD	405	148
Total	**405**	**148**

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Table SIII-29: CASSINI (SN 18262)

Race or ethnic origin	Patients (N)	Person time (years)
White	342	126
Black	11	3
Asian	6	2
American Indian or Alaska Native	1	1
Native Hawaiian or other Pacific Islander	1	0
Not reported	37	12
Other	7	3
Total	**405**	**148**

Table SIII-30: CASSINI (SN 18262)

Special populations	Patients (N)	Person time (years)
Is patient lactating?		
Missing	405	148
Renal impairment		
<30 mL/min	1	0
30-<50 mL/min	30	7
50-≤80 mL/min	107	38
>80 mL/min	259	99
Missing	8	3
Hepatic disorder at baseline		
No	375	136
Yes	30	11
Total	**405**	**148**

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Table SIII-31: GALILEO (SN 17938)

Duration of study medication	Patients	Person time (years)
1 day	2	0
>1 to 7 days	24	0
>1 to 2 weeks	19	1
>2 to 4 weeks	21	1
>4 to 8 weeks	39	4
>8 to 12 weeks	23	4
>3 to 6 months (180 days)	78	26
>6 to 12 months (360 days)	117	92
>12 to 18 months (540 days)	218	270
>18 to 24 months (720 days)	194	332
>24 to 30 months (900 days)	66	139
Total person time for indication		**871**

Table SIII-32: GALILEO (SN 17938)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
>40 to <65 years	14	10	18	15
Elderly people				
65–74 years	70	37	77	40
75–84 years	212	219	247	233
≥85 years	117	122	111	130
Total	**413**	**388**	**452**	**418**

Table SIII-33: GALILEO (SN 17938)

Dose of exposure (TDD)	Patients	Person time (years)
10 mg TDD: 10 mg OD	801	871
Total	**801**	**871**

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Table SIII-34: GALILEO (SN 17938)

Race or ethnic origin	Patients (N)	Person time (years)
White	673	752
Black	9	12
Asian	2	1
Not reported	117	106
Total	**801**	**871**

Table SIII-35: GALILEO (SN 17938)

Special populations	Patients (N)	Person time (years)
Is patient lactating?		
Missing	801	871
Renal impairment		
<30 mL/min	5	3
30-<50 mL/min	112	129
50-≤80 mL/min	415	444
>80 mL/min	269	294
Hepatic disorder at baseline		
No	777	842
Yes	24	29
Total	**801**	**871**

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Table SIII-36: VOYAGER PAD (SN 17454)

Duration of study medication	Patients	Person time (years)
1 day	11	0
>1 to 7 days	56	1
>1 to 2 weeks	41	1
>2 to 4 weeks	46	3
>4 to 8 weeks	76	9
>8 to 12 weeks	54	11
>3 to 6 months (180 days)	182	64
>6 to 12 months (360 days)	191	133
>12 to 18 months (540 days)	144	175
>18 to 24 months (720 days)	518	936
>24 to 30 months (900 days)	741	1623
>2.5 to 3 years (1080 days)	622	1677
> 3 years	574	1882
Total person time for indication		**6513**

Table SIII-37: VOYAGER PAD (SN 17454)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
>40 to <65 years	1096	247	2327	505
Elderly people				
65–74 years	918	334	1841	655
75–84 years	366	225	674	409
≥85 years	37	33	48	54
Total	**2417**	**839**	**4890**	**1623**

Table SIII-38: VOYAGER PAD (SN 17454)

Dose of exposure (TDD)	Patients	Person time (years)
5 mg TDD: 2.5 mg BID	3256	6513
Total	**3256**	**6513**

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Table SIII-39: VOYAGER PAD (SN 17454)

Race or ethnic origin	Patients (N)	Person time (years)
White	2626	5298
Black	82	157
Asian	480	945
American Indian or Alaska Native	1	3
Not reported	66	108
Multiple	1	2
Total	**3256**	**6513**

Table SIII-40: VOYAGER PAD (SN 17454)

Special populations	Patients (N)	Person time (years)
Is patient lactating?		
Missing	3256	6513
Renal impairment		
<30 mL/min	14	20
30-<50 mL/min	322	576
50-≤80 mL/min	1370	2723
>80 mL/min	1426	2954
Missing	124	240
Hepatic disorder at baseline		
No	3140	6303
Yes	116	210
Total	**3256**	**6513**

Table SIII-41: CAD/PAD (SN 15786)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	39	5	62	8
>40 to <65 years	3358	925	5967	1551
Elderly people				
65–74 years	8029	2097	15041	3836
75–84 years	2665	941	4794	1691
≥85 years	125	60	205	100
Total	**14216**	**4028**	**26070**	**7185**

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Table SIII-42: CAD/PAD (SN 15786)

Dose of exposure (TDD)	Patients	Person time (years)
5 mg TDD: 2.5 mg BID	9134	16698
10 mg TDD: 5 mg BID	9110	16556
Total	**18244**	**33255**

Table SIII-43: CAD/PAD (SN 15786)

Race or ethnic origin	Patients (N)	Person time (years)
White	11330	20852
Black or African American	170	303
Asian	2863	5498
Total	**14363**	**26653**

Table SIII-44: CAD/PAD (SN 15786)

Special populations	Patients (N)	Person time (years)
Lactating women		
Yes		
No		
Missing	18244	33255
Renal impairment		
<30 mL/min	157	241
30-<50 mL/min	1759	3047
50-≤80 mL/min	8920	16401
>80 mL/min	7402	13558
Missing	6	8
Hepatic disorder at baseline		
No	18002	32814
Yes	242	441
Total	**18244**	**33255**

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Table SIII-45: Duration of exposure

Across indications (All completed rivaroxaban phase II and III studies)		
Duration of study medication	**Patients**	**Person time (years)**
1 day	437	1
>1 to 7 days	2803	40
>1 to 2 weeks	4661	140
>2 to 4 weeks	1733	102
>4 to 8 weeks	14418	1571
>8 to 12 weeks	1919	378
>3 to 6 months (180 days)	6069	2290
>6 to 12 months (360 days)	13246	9497
>12 to 18 months (540 days)	11309	13371
>18 to 24 months (720 days)	9138	15764
>24 to 30 months (900 days)	7418	16180
>2.5 to 3 years (1080 days)	4093	11005
>3 years	3161	10326
Missing	32	0
Total person time		**80666**

Table SIII-46: VTE prevention in patients undergoing THR and TKR (Pool of SN 10942, 10944, 10945, 11527, 11354, 11355, 11356, 11357, 14397 and 14398)

Duration of study medication	**Patients**	**Person time (years)**
1 day	51	0
>1 to 7 days	1489	25
>1 to 2 weeks	3662	110
>2 to 4 weeks	217	10
>4 to 8 weeks	3413	327
Missing	19	0
Total person time for indication		**472**

Table SIII-47: VTE treatment (Pool of SN 11223, 11528, 13238, 11702 DVT, 11702 PE, 11899, 14568, 15960 and 16416)

Duration of study medication	Patients	Person time (years)
1 day	17	0
>1 to 7 days	131	2
>1 to 2 weeks	68	2
>2 to 4 weeks	122	7
>4 to 8 weeks	132	14
>8 to 12 weeks	437	97
>3 to 6 months (180 days)	1904	711
>6 to 12 months (360 days)	3967	2837
>12 to 18 months (540 days)	980	993
>18 to 24 months (720 days)	13	20
Missing	4	0
Total person time for indication		**4684**

Table SIII-48: SPAF/PCI (Pool of SN 11390, 11866, 12024, 11630, 12620, 15572, 15693, 15694, 16320 and 16523)

Duration of study medication	Patients	Person time (years)
1 day	119	0
>1 to 7 days	156	2
>1 to 2 weeks	130	4
>2 to 4 weeks	305	20
>4 to 8 weeks	899	107
>8 to 12 weeks	600	111
>3 to 6 months (180 days)	535	189
>6 to 12 months (360 days)	942	753
>12 to 18 months (540 days)	2651	3082
>18 to 24 months (720 days)	1612	2763
>24 to 30 months (900 days)	1592	3494
>2.5 to 3 years (1080 days)	910	2429
>3 years	141	435
Missing	7	0
Total person time for indication		**13388**

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Table SIII-49: ACS (Pool of SN 11898, 13194 and 17896)

Duration of study medication	Patients	Person time (years)
1 day	82	0
>1 to 7 days	307	3
>1 to 2 weeks	178	5
>2 to 4 weeks	311	19
>4 to 8 weeks	541	56
>8 to 12 weeks	300	58
>3 to 6 months (180 days)	1677	692
>6 to 12 months (360 days)	4949	3375
>12 to 18 months (540 days)	2596	3140
>18 to 24 months (720 days)	2103	3601
>24 to 30 months (900 days)	989	2109
>2.5 to 3 years (1080 days)	11	28
Total person time for indication		**13086**

Table SIII-50: VTE prevention in Med ill (SN 12839 and 17261)

Duration of study medication	Patients	Person time (years)
1 day	116	0
>1 to 7 days	449	6
>1 to 2 weeks	403	12
>2 to 4 weeks	348	20
>4 to 8 weeks	8660	983
>8 to 12 weeks	1	0
Missing	2	0
Total person time for indication		**1021**

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Table SIII-51: Age group and gender

Across indications (All completed rivaroxaban phase II and III studies)				
Age group	**Patients**		**Person time (years)**	
	M	**F**	**M**	**F**
Birth -< 0.5 years	15	10	2	1
0.5 - <2 years	17	19	3	2
2 - <6 years	36	35	8	11
6 - <12 years	64	35	19	8
12 - <18 years	86	105	40	39
Adults				
18–40 years	1071	854	665	440
>40 to <65 years	21325	9024	21524	6269
Elderly people				
65–74 years	19359	9953	24943	8835
75–84 years	9170	7200	10341	6022
≥85 years	982	1077	772	722
Total	**52125**	**28312**	**58316**	**22350**

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Table SIII-52: VTE prevention in patients undergoing THR and TKR (Pool of SN 10942, 10944, 10945, 11527, 11354, 11355, 11356, 11357, 14397 and 14398)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	131	105	10	8
>40 to <65 years	1602	2218	94	120
Elderly people				
65–74 years	1117	2030	60	102
75–84 years	503	1062	25	49
≥85 years	30	53	1	3
Total	**3383**	**5468**	**190**	**282**

Table SIII-53: VTE treatment (Pool of SN 11223, 11528, 13238, 11702 DVT, 11702 PE, 11899, 14568, 15960 and 16416)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	583	686	334	386
>40 to <65 years	2176	1330	1376	799
Elderly people				
65–74 years	959	766	593	476
75–84 years	511	598	288	341
≥85 years	74	92	43	47
Total	**4303**	**3472**	**2635**	**2049**

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Table SIII-54: SPAF/PCI (Pool of SN 11390, 11866, 12024, 11630, 12620, 15572, 15693, 15694, 16320 and 16523)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	46	8	40	7
>40 to <65 years	2103	655	2413	831
Elderly people				
65–74 years	2421	1237	3008	1651
75–84 years	2116	1579	2811	2145
≥85 years	236	198	239	243
Total	**6922**	**3677**	**8511**	**4876**

Table SIII-55: ACS (Pool of SN 11898, 13194 and 17896)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	225	18	175	15
>40 to <65 years	7077	1758	6677	1620
Elderly people				
65–74 years	2609	1255	2432	1177
75–84 years	609	447	536	416
≥85 years	27	19	22	15
Total	**10547**	**3497**	**9842**	**3244**

Table SIII-56: VTE prevention in Med ill (SN 12839)

Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	12	7	1	1
>40 to <65 years	784	520	65	43
Elderly people				
65–74 years	678	466	53	38
75–84 years	620	586	47	45
≥85 years	129	195	9	14
Total	**2223**	**1774**	**175**	**140**

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Table SIII-57: Dose

Across indications (All completed rivaroxaban phase II and III studies)		
Dose of exposure (TDD)	**Patients**	**Person time (years)**
5 mg TDD: 2.5 mg BID	21998	34019
5 mg TDD: 5 mg OD	455	82
5–15 mg TDD: 2.5 mg BID -> 10/15 mg OD	706	602
7.5 mg TDD: 7.5 mg OD	1267	137
10 mg TDD: 10 mg OD	18509	3729
10 mg TDD: 5 mg BID	15083	22185
15 mg TDD: 15 mg OD	6397	6439
15 mg TDD: 7.5 mg BID	175	74
15–20 mg TDD: 10 mg BID 3 weeks -> 15 mg OD	21	12
15–30 mg TDD: 15 mg BID 3 weeks -> 15 mg OD	52	30
20 mg TDD: 10 mg BID	775	166
20 mg TDD: 20 mg OD	8886	10472
20–30 mg TDD: 15 mg BID 3 weeks -> 20 mg OD	3960	2425
30 mg TDD: 15 mg BID	173	4
30 mg TDD: 30 mg OD	364	33
40 mg TDD: 20 mg BID	437	30
40 mg TDD: 40 mg OD	394	59
40–60 mg TDD: 30 mg BID 3 weeks -> 40 mg OD plus strong CYP3A4 inducer	20	5
60 mg TDD: 30 mg BID	343	30
Pediatric: Individual dosing scheme	422	133
Total	**80437**	**80666**

Table SIII-58: VTE prevention in patients undergoing THR and TKR (Pool of SN 10942, 10944, 10945, 11527, 11354, 11355, 11356, 11357, 14397 and 14398)

Dose of exposure (TDD)	Patients	Person time (years)
5 mg TDD: 2.5 mg BID	308	6
5 mg TDD: 5 mg OD	300	13
7.5 mg TDD: 7.5 mg OD	175	11
10 mg TDD: 10 mg OD	6414	410
10 mg TDD: 5 mg BID	318	6
20 mg TDD: 10 mg BID	304	6
20 mg TDD: 20 mg OD	139	3
30 mg TDD: 30 mg OD	230	4
40 mg TDD: 20 mg BID	309	6
40 mg TDD: 40 mg OD	137	2
60 mg TDD: 30 mg BID	217	4
Total	**8851**	**472**

Table SIII-59: VTE treatment (Pool of SN 11223, 11528, 13238, 11702 DVT, 11702 PE, 11899, 14568, 15960 and 16416)

Dose of exposure (TDD)	Patients	Person time (years)
10 mg TDD: 10 mg OD	1127	905
15–20 mg TDD: 10 mg BID 3 weeks -> 15 mg OD	21	12
15–30 mg TDD: 15 mg BID 3 weeks -> 15 mg OD	52	30
20 mg TDD: 10 mg BID	120	26
20 mg TDD: 20 mg OD	1668	1144
20–30 mg TDD: 15 mg BID 3 weeks -> 20 mg OD	3960	2425
30 mg TDD: 15 mg BID	173	4
30 mg TDD: 30 mg OD	134	29
40 mg TDD: 20 mg BID	117	23
40 mg TDD: 40 mg OD	257	56
40–60 mg TDD: 30 mg BID 3 weeks -> 40 mg OD plus strong CYP3A4 inducer	20	5
60 mg TDD: 30 mg BID	126	26
Total	**7775**	**4684**

Table SIII-60: SPAF/PCI (Pool of SN 11390, 11866, 12024, 11630, 12620, 15572, 15693, 15694, 16320 and 16523)

Dose of exposure (TDD)	Patients	Person time (years)
5 mg TDD: 2.5 mg BID	24	2
5–15 mg TDD: 2.5 mg BID -> 10/15 mg OD	706	602
10 mg TDD: 10 mg OD	348	274
10 mg TDD: 5 mg BID	26	2
15 mg TDD: 15 mg OD	2657	3309
20 mg TDD: 10 mg BID	49	4
20 mg TDD: 20 mg OD	6778	9195
40 mg TDD: 20 mg BID	11	1
Total	**10599**	**13388**

Table SIII-61: ACS (Pool of SN 11898, 13194 and 17896)

Dose of exposure (TDD)	Patients	Person time (years)
5 mg TDD: 2.5 mg BID	6777	6755
5 mg TDD: 5 mg OD	155	69
10 mg TDD: 10 mg OD	527	227
10 mg TDD: 5 mg BID	5629	5620
15 mg TDD: 15 mg OD	178	79
15 mg TDD: 7.5 mg BID	175	74
20 mg TDD: 10 mg BID	302	131
20 mg TDD: 20 mg OD	301	130
Total	**14044**	**13086**

Table SIII-62: VTE prevention in Med ill (SN 12839)

Dose of exposure (TDD)	Patients	Person time (years)
10 mg TDD: 10 mg OD	3997	316
Total	**3997**	**316**

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Table SIII-63: Race or ethnic origin

Across indications (All completed rivaroxaban phase II and III studies)		
Race or ethnic origin	**Patients (N)**	**Person time (years)**
White	60553	58444
Black	1187	942
Asian	11262	12602
American Indian or Alaska native	85	53
Native Hawaiian or other Pacific Islander	23	14
Other	5414	7496
Multiple	26	16
Not reported	768	639
Missing	1119	461
Total	**80437**	**80666**

Table SIII-64: VTE prevention in patients undergoing THR and TKR (Pool of SN 10942, 10944, 10945, 11527, 11354, 11355, 11356, 11357, 14397 and 14398)

Race or ethnic origin	**Patients (N)**	**Person time (years)**
White	6972	363
Black or African American	177	9
Asian	1143	66
American Indian or Alaska native	6	0
Other	366	22
Missing	187	12
Total	**8851**	**472**

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Table SIII-65: VTE treatment (Pool of SN 11223, 11528, 13238, 11702 DVT, 11702 PE, 11899, 14568, 15960 and 16416)

Race or ethnic origin	Patients (N)	Person time (years)
White	5610	3356
Black or African American	253	140
Asian	828	505
American Indian or Alaska native	5	4
Native Hawaiian or other Pacific Islander	6	3
Other	62	20
Multiple	1	1
Not reported	261	222
Missing	749	432
Total	**7775**	**4684**

Table SIII-66: SPAF/PCI (Pool of SN 11390, 11866, 12024, 11630, 12620, 15572, 15693, 15694, 16320 and 16523)

Race or ethnic origin	Patients (N)	Person time (years)
White	8360	10569
Black or African American	119	145
Asian	1832	2338
American Indian or Alaska native	9	15
Native Hawaiian or other Pacific Islander	4	2
Other	218	303
Multiple	5	1
Not reported	51	12
Missing	1	1
Total	**10599**	**13388**

Table SIII-67: ACS (Pool of SN 11898, 13194 and 17896)

Race or ethnic origin	Patients (N)	Person time (years)
White	11148	10452
Black or African American	111	73
Asian	2214	2067
American Indian or Alaska native	6	5
Native Hawaiian or other Pacific Islander	6	4
Other	547	477
Not reported	9	6
Missing	3	2
Total	**14044**	**13086**

Table SIII-68: VTE prevention in Med ill (SN 12839)

Race or ethnic origin	Patients (N)	Person time (years)
White	2749	218
Black or African American	89	6
Asian	793	63
American Indian or Alaska native	12	1
Other	175	15
Missing	179	13
Total	**3997**	**316**

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Table SIII-69: Special populations (totals)

Across indications (All completed rivaroxaban phase II and III studies)		
Total population	**Persons**	**Person time**
Is patient lactating		
Yes	1	0
No	9709	1778
Missing	70727	78887
Renal impairment		
<30 mL/min	496	421
30-<50 mL/min	8624	8293
50-≤80 mL/min	32241	35591
>80 mL/min	38426	35893
Missing	677	467
Hepatic disorder at baseline		
No	75527	74585
Yes	2411	2037
Missing	2499	4044
Total	**80437**	**80666**

Table SIII-70: VTE prevention in patients undergoing THR and TKR (Pool of SN 10942, 10944, 10945, 11527, 11354, 11355, 11356, 11357, 14397 and 14398)

Special populations	**Patients (N)**	**Person time (years)**
Lactating women		
Yes		
No	5451	281
Missing	3400	191
Renal impairment		
<30 mL/min	34	2
30-<50 mL/min	539	27
50-≤80 mL/min	3097	161
>80 mL/min	5090	278
Missing	91	4
Hepatic disorder at baseline		
No	8563	456
Yes	288	16
Total	**8851**	**472**

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Table SIII-71: VTE treatment (Pool of SN 11223, 11528, 13238, 11702 DVT, 11702 PE, 11899, 14568, 15960 and 16416)

Special populations	Patients (N)	Person time (years)
Lactating women		
Yes	1	0
No	2357	1206
Missing	5417	3477
Renal impairment		
<30 mL/min	19	7
30-<50 mL/min	529	287
50-≤80 mL/min	2002	1179
>80 mL/min	5145	3177
Missing	80	34
Hepatic disorder at baseline		
No	7431	4470
Yes	344	214
Total	**7775**	**4684**

Table SIII-72: SPAF/PCI (Pool of SN 11390, 11866, 12024, 11630, 12620, 15572, 15693, 15694, 16320 and 16523)

Special populations	Patients (N)	Person time (years)
Lactating women		
Yes		
No	131	149
Missing	10468	13238
Renal impairment		
<30 mL/min	20	13
30-<50 mL/min	1944	2486
50-≤80 mL/min	4766	6254
>80 mL/min	3806	4583
Missing	63	51
Hepatic disorder at baseline		
No	10034	12604
Yes	565	783
Total	**10599**	**13388**

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Table SIII-73: ACS (Pool of SN 11898, 13194 and 17896)

Special populations	Patients (N)	Person time (years)
Lactating women		
Yes		
No		
Missing	14044	13086
Renal impairment		
<30 mL/min	57	40
30-<50 mL/min	822	714
50-≤80 mL/min	4647	4368
>80 mL/min	8298	7846
Missing	220	119
Hepatic disorder at baseline		
No	13803	12852
Yes	241	234
Total	**14044**	**13086**

Table SIII-74: VTE prevention in Med ill (SN 12839)

Special populations	Patients (N)	Person time (years)
Lactating women		
Yes		
No	1770	140
Missing	2227	175
Renal impairment		
<30 mL/min	81	4
30-<50 mL/min	780	57
50-≤80 mL/min	1487	120
>80 mL/min	1571	129
Missing	78	5
Hepatic disorder at baseline		
No	3721	295
Yes	276	21
Total	**3997**	**316**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
1) Hypersensitivity	Hypersensitivity to rivaroxaban or to any of the excipients is a contraindication	No	Hypersensitivity will remain a contraindication
2) Active bleeding or high risk of bleeding contraindicating treatment with LMWH (or VKA)	Since rivaroxaban may increase the risk of bleeding, it is contraindicated in patients who are actively bleeding.	No	Active bleeding or high risk of bleeding contraindicating treatment will remain a contraindication
3) Lesion or condition, if considered to be a significant risk for major bleeding	Use of rivaroxaban is contraindicated in individuals with a lesion or condition that poses a significant risk of major bleeding as outlined	No	Use of rivaroxaban will remain contraindicated in individuals in patients with a lesion or condition that poses a significant risk of major bleeding
4) Concomitant treatment with any other anticoagulants	Concomitant treatment of rivaroxaban with any other anticoagulants is contraindicated except from specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.	No	Concomitant treatment with any other anticoagulants will remain contraindicated (except from specific circumstances)

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Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

5) Prior ischaemic stroke or transient ischaemic attack (TIA) in patients who were planned to receive acetylsalicylic acid (ASA) plus thienopyridine in the ATLAS ACS 2–TIMI 51 study	Use of concomitant treatment with antiplatelet therapy in patients with a prior stroke or TIA is a contraindication.	No	Patients following diagnosis with ACS, concomitant treatment with antiplatelet therapy in patients with a prior stroke or TIA will remain a contraindication
6) Significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis) (In ROCKET and EINSTEIN-DVT/PE and Ext.: an additional exclusion criterion was ALT >3xULN; In children (EINSTEIN Junior program) hepatic disease which was associated either: with coagulopathy leading to a clinically relevant bleeding risk, or ALT >5x ULN, or total bilirubin >2x ULN with direct bilirubin >20% of the total were exclusion criteria)	The use of rivaroxaban in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C remains contraindicated.	No	Labeling is considered adequate and experience from exposure over time did not identify a safety concern (see Procedure number: EMEA/H/C/PSR/S/0027).

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Part II: Module SIV - Populations not studied in clinical trials

Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

7) Pregnancy and breast-feeding	Pregnancy and breast-feeding remain contraindications and women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.	No	Pregnant and breast-feeding women were not included in the clinical development program. The contraindication will remain unless any potential risk can clearly be excluded. Labeling is considered adequate and experience from exposure over time did not identify a safety concern (see Procedure number: EMEA/H/C/PSR/S/0027).
8) CrCl < 30 mL/min; in children younger than one year, serum creatinine results above 97.5th percentile); Estimated glomerular filtration rate (eGFR)<15 mL/min (COMPASS)	In patients with severe renal impairment (CrCl< 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk.	No	Addressed in the SmPCs (Section 4.4 Special warnings and precautions for use and in section 4.2 Posology and method of administration)
9) Patients younger than six months with: • Gestational age at birth of less than 37 weeks, or • Oral feeding/ (naso)gastric for less than 10 days, or • Body weight less than 2600 g	Dosing of rivaroxaban cannot be reliably determined in this patient populations and was not studied	No	Addressed in the SmPC Xarelto 1 mg/mL granules for oral suspension (Section Special warnings and precautions for use)
10) Concomitant use of drugs that influence the coagulation system e.g. NSAIDs/antiplatelet drugs	Concomitant use of rivaroxaban with NSAIDs/ platelet aggregation inhibitors may lead to an increased bleeding risk.	No	Addressed in the SmPCs (Section 4.5 Interaction with other medicinal products and other forms of interaction NSAIDs/platelet aggregation inhibitors)

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Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

11) CYP3A4 and P-gp inhibitors	Concomitant use of rivaroxaban with strong inhibitors of both CYP3A4 and P-gp may increase blood plasma concentrations of rivaroxaban which may lead to an increased bleeding risk.	No	Addressed in the SmPCs (Section 4.4 Special warnings and precautions for use) Labeling is considered adequate and experience from exposure over time did not identify a safety concern (see Procedure number: EMEA/H/C/PSR/S/0027).
12) CYP3A4 inducers	Concomitant use of rivaroxaban with strong CYP3A4 inducers led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects.	No	Addressed in the SmPCs (Section 4.5 Interaction with other medicinal products and other forms of interaction)
13) Patients with valvular heart disease (exclusion criterion for ROCKET programme)	Patients with artificial heart valves may require dose adjustment; exposure data in this population are not available, therefore patients with artificial heart valves have been excluded from the ROCKET clinical trial programme.	No	Addressed in the SmPC for 2.5 mg/10 mg/15 mg/ 20 mg (Section 4.4 Special warnings and precautions for use) Labeling is considered adequate and experience from exposure over time did not identify a safety concern (see Procedure number: EMEA/H/C/PSR/S/0027).

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Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

14) Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE (exclusion criterion in EINSTEIN programme)	Patients with PE who are haemodynamically unstable patients or may receive thrombolysis or pulmonary embolectomy may require dose adjustment; exposure data in this population are not available, therefore these patients have been excluded from the EINSTEIN clinical trial programme.	No	Addressed in the SmPC for 10 mg/15 mg/ 20 mg (VTE-T, SPAF) (Section 4.4 Special warnings and precautions for use)
15) Stroke within one month or any history of hemorrhagic or lacunar stroke (COMPASS)	Use of concomitant treatment (ASA) was considered a risk for bleeding;	No	Addressed in the SmPCs (Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use)
16) Severe heart failure with known ejection fraction <30% or New York Heart Association (NYHA) class III or IV symptoms (COMPASS)	Patients with stable CAD/PAD were to be investigated.	No	Addressed in the SmPCs (Section 4.4 Special warnings and precautions for use)
17) Known non-cardiovascular disease that is associated with poor prognosis (e.g., metastatic cancer) or that increases the risk of an adverse reaction to study interventions. (COMPASS)	Increased risk for adverse events and/or adverse reactions to study interventions.	No	Addressed in the SmPCs (Section 4.3 Contraindications)

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Part II: Module SIV - Populations not studied in clinical trials

Table SIV.1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

18) Any medically documented history of intracranial hemorrhage, stroke, or transient ischemic attack (TIA) (VOYAGER PAD);	Use of concomitant treatment (ASA) was considered a risk for bleeding;	No	Addressed in the SmPCs (Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use) as under CAD/PAD indication.

Exclusion criteria from pivotal studies not resulting in a registration or not relevant in real life settings (e.g. participation in other clinical studies) have not been considered.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical 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, due to the limited period of exposure, and the inclusion and exclusion criteria applied to the studies.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Pregnant or breastfeeding women were not included in the clinical development program, incl. the pre-authorization program; no relevant data on exposure can be presented
Patients with relevant comorbidities:	Across all completed rivaroxaban phase II and III studies [n= 80,437 (100%)]:
• Patients with hepatic impairment	Exposure in patients with hepatic impairment under treatment with rivaroxaban was: 2,411 with hepatic disorder at baseline.
• Patients with renal impairment	Exposure in patients with renal impairment under treatment with rivaroxaban was: 33,241 patients with eGFR 50 - <=80 ml/min 8,264 patients with eGFR 30 - <50 ml/min 469 patients with eGFR <30 ml/min

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Part II: Module SIV - Populations not studied in clinical trials

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
• Patients with cardiovascular impairment	Exposure in patients with cardiovascular impairment under treatment with rivaroxaban was: Indication SPAF/PCI 13,388 patient-years Indication ACS 13,086 patient-years Indication CAD/PAD 33,255 patient-years Indication HF n=2,499 (4,044 patient-years) Indication TAVR n=801 (871 patient years) Indication PAD (revasc) n=3,256 (6,513 patient-years)
• Patients with history of prior stroke	Cerebral ischemic infarction and stroke n=8537 (10.6%) Cerebral and intracranial hemorrhage n=102 (0.1%)
• Immunocompromised patients	Not applicabe/included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	Indication VTE prevention in cancer n=401 (CASSINI) and active cancer at baseline n=379 (EINSTEIN programme) and n=294 (MAGELLAN) with active cancer
Population with relevant different ethnic origin	Not applicable/included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not applicable/included in the clinical development program
Other	
No other special population under-represented in clinical trials which are relevant for the targeted indication if the safety profile is expected to be different to the general population.	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Patient exposure has been estimated by calculation from company distribution data. Estimates of exposure are based upon finished product.

It should be noted that the calculation is based on distribution rather than consumption of Xarelto; there is a delay between the time when a medication is distributed and the time when it is consumed by a patient.

From the time of first marketing authorisation of Xarelto for the VTE-P indication, other indications have been approved which entail chronic use of different strengths of rivaroxaban. A crude patient–time exposure can be estimated based on the assumption that one tablet is taken as the total daily dose in the majority of treatments. For the ACS indication as well as the CAD and PAD indication, the 2.5 mg tablet is used in a twice-daily regimen, which is reflected in the calculations below. In order to present an overall estimate of patients' exposure to all approved dosages, person-months and person-years were calculated independently of the different dosing schedules and approved dosages. For the 10 mg tablets (the approved dose for the VTE-P indication), the number of estimated patient-months will roughly correspond to the number of patients receiving Xarelto for VTE-P in major orthopaedic surgery, because the duration of treatment is close to one month (on average 24.5 days, depending on the type of major orthopaedic surgery). However, one has to note that the 10 mg dose is also approved for chronic use for SPAF in Japan. For the 2.5 mg, 15 mg and 20 mg formulations, it is not possible to determine reliably how many patients were exposed, because the duration of use varies.

SV.1.2 Exposure

Based on the available sales data, the estimated worldwide patient exposure (for all dosages: 2.5 mg, 10 mg, 15 mg, and 20 mg) from launch to 15 SEP 2022[1] (this DLP is taken from the recent PSUR/PBRER No 23.1,) is >57 million patient-years. From the DLP of the PSUR and the DLP of this EU RMP no safety concern has arisen.

All exposure estimates (2.5 mg, 10 mg, 15 mg and 20 mg Tablet, 1 mg/mL Granules for oral suspension) exclude use in clinical trials and observational studies.

[1] The date range of the sales period is slightly earlier than the reporting period (01 SEP 2008 to 31 AUG 2022 versus 15 SEP 2008 to 15 SEP 2022), while its duration is the same. The date selection is intended to allow for the use of more complete, rather than preliminary sales data. No significant impact on the overall safety analysis is expected.

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Part II: Module SV - Post-authorisation experience

Table SV.1: Cumulative Worldwide Post Marketing Exposure Estimate for Xarelto (covering period from 15 SEP 2008 to 31 AUG 2022)

Strength	Tablets	Patient -Years
1 mg/ml granules kit	11,907	Cannot be estimated[a]
2,5 mg[b]	481,355,811	668,550
10 mg	2,566,054,402	7,127,929
15 mg	5,625,983,524	15,627,732
20 mg	12,136,651,615	33,712,921
Total	**20,810,057,259**	**57,137,132**

[a] Treatment duration in pediatric patients varies considerably between 1 month and 12 months for VTE treatment and Xarelto was studied for 12 months in children with CHD who have undergone the Fontan procedure for thromboprophylaxis. Therefore, it is impossible to reliably estimate pediatric patient exposure in patient years. Asa guesstimate, between 1,000 and 5,000 patients may have been exposed world-wide.
[b] Used at a daily dose of 5 mg (2.5 mg BID)

No new information has emerged during the reporting interval that would change the overall evaluation of benefit-risk for Xarelto in the approved indications. The company's assessment of the benefit-risk balance for Xarelto remains favourable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Limited pack sizes for Xarelto and a controlled distribution (prescription only medicine) will limit any potential risk of misuse for illegal purposes. At present no potential for misuse or illegal use has been identified according to the most recent PBRER/PSUR No. 23.1.

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Part II – Modules SVII: Identified and Potential Risks

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The 'Risk Management Plan (RMP) for Rivaroxaban', version no. 1.3, for the indication 'Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs', signed on 14 JUL 2008 presented the following summary in part 5 of the document:

Safety concern:	
Important identified Risks	Haemorrhage
Important Potential Risks	Increase in LFTs, bilirubin
	Transient increase of lipase and amylase
	Renal impairment – increase in creatinine
Important missing information	Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery
	Patients with severe renal impairment (CrCl <30ml/min)
	Remedial pro-coagulant therapy for excessive haemorrhage
	Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole-antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir)
	Pregnant or breast-feeding women

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

As Rivaroxaban was registered in 2009 the format and requirements for the RMP changed over time. Risks which after thorough evaluation have not been included in the list of safety concern cannot be recapitulated.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

In general, ADRs listed in section 4.8 of the CCDS, which are no safety concerns dealt with in this module, are considered as such. These AEs had been identified as ADR from pooled safety data from pivotal studies, and not been classified a safety concern upon further review and evaluation.

Known ADRs that do not impact the benefit-risk profile:

- very common: in children from birth to <18 years: fever, headache
- common: dyspepsia, nausea, fever, headache, dry mouth, feeling unwell (incl. malaise), dizziness, contusion (postprocedural)

Risks (ADRs) with minimal clinical impact on patients (in relation to the severity of the indication treated:

- very common: in children from birth to <18 years: vomiting
- common: gastrointestinal and abdominal pains, constipation, diarrhea, vomiting, decreased general strength and energy (incl. fatigue and asthenia), pain in extremity, pruritus (incl. generalized pruritus), rash, urticaria, hypotension, edema peripheral, increase in transaminases, anemia (incl. respective laboratory parameters) (as consequence of haemorrhage, what is an important identified risk),
- uncommon: wound secretion
- rare: localized edema

Adverse drug reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- common: in children from birth to <18 years: thrombocytosis (incl. platelet count increased), tachycardia, increase in bilirubin, thrombocytopenia
- uncommon: thrombocytosis (incl. platelet count increased), tachycardia, allergic reaction, dermatitis allergic, syncope, increase in bilirubin, increase in blood alkaline phosphatase, increase in LDH, increase in lipase, increase in amylase, increase in γGT, hepatic impairment
- uncommon: in children from birth to <18 years: bilirubin conjugated increased (with or without concomitant increase of ALT)
- rare: bilirubin conjugated increased (with or without concomitant increase of ALT), jaundice, vascular pseudoaneurysm (postprocedural)
- very rare: eosinophilic pneumonia

Known risks that require no further characterisation and are namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- common: renal impairment

AEs from PMS surveillance to be inserted into the undesirable effects section of the CCDS upon authority request followed up via routine pharmacovigilance (frequency categories as estimated from pivotal studies):

- uncommon: angioedema, allergic oedema, thrombocytopenia
- rare: cholestasis, hepatitis (incl. hepatocellular injury)
- not known, anticoagulant-related nephropathy

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Part II – Modules SVII: Identified and Potential Risks

Frequency categories in the above paragraph:

very common	(≥1/10)	≥10%
common	(≥1/100 to <1/10)	≥1.0%-<10%
uncommon	(≥1/1,000 to <1/100)	≥0.1% - <1.0%
rare	(≥1/10,000 to <1/1,000)	<0.1%

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk:

Safety Concern: Important identified risks	
1. Haemorrhage	
Reasons for classification	Expectedly, due to the pharmacological mode of action, haemorrhages have been observed in patients treated with rivaroxaban. As haemorrhages have an impact on the benefit-risk balance of rivaroxaban, it was classified as important identified risk.
Seriousness	Haemorrhages can become serious, as they may well lead to hospitalization (e.g. circulatory breakdown due to blood loss), as they require intervention (e.g. surgical treatment to stop bleeding, substitution of blood (pRBC), remedial pro-coagulant therapy), may become life-threatening or lead to a fatal outcome.
Frequency	The frequency of haemorrhage under treatment with rivaroxaban is depending on dosage, scenario (e.g. surgery, intervention), co-morbidities, co-medication, treatment duration, etc. In pivotal studies bleeding incidence was determined between 3.20% ('stable' patients at non-surgical site) to 31.95% in adults (patients with PCI intervention (arterial puncture)) and to 39.5% (adjudicated bleedings) in children from birth to less than 18 years as assessed by adjudication committees based on predefined adjudication criteria (Table SVII-1)
Severity	Overall, in pivotal studies performed the majority of treatment-emergent bleeding events were mild to moderate in severity [Source: Clinical Study Reports (see Reference list)]

Important potential risk:

Safety Concern: Important potential risks	
1. Embryo-fetal toxicity	
Reasons for classification	Pregnant women were/are excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC. Toxic potential may lead to severe organ damage or serious harm to the unborn. Therefore, toxicity towards the unborn definitely would have an impact on the benefit-risk balance of rivaroxaban. Consequently, it was classified as important potential risk.
Seriousness	Severe organ damage, bleeding, toxic potential may lead to a congenital anomaly/birth defect, resulting in persistent or significant disability or

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Safety Concern: Important potential risks	
	incapacity, may lead to (imminent) abortion what may be life-threatening or result in death Table SVII-2).
Frequency	Cannot be estimated; pregnant women were/are excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC.
Severity	Cannot be estimated; there are no data on toxic potential to human embryo or fetus.
2. Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	
Reasons for classification	The drug-device combination product including the pharmaceutical form 1 mg/mL granules for oral suspension needs to be prepared by the child's caregiver using the drug-device combination kit. Errors in the preparation of the suspension, as well as its subsequent application, may result in over- or underdosing.
Seriousness	Overdose Haemorrhages can become serious, as they may well lead to hospitalization (e.g. circulatory breakdown due to blood loss), as they require intervention (e.g. surgical treatment to stop bleeding, substitution of blood (pRBC), remedial pro-coagulant therapy), may become life-threatening or lead to a fatal outcome. Overall, in pivotal studies performed the majority of treatment-emergent bleeding events were mild to moderate. Underdose Lack of drug effect; recurrence of VTE
Frequency	Cannot be estimated; very few events of accidental over- or underdosing of study drug were recorded in the pivotal phase III study EINSTEIN Junior; this does not allow deriving a pattern or trend leading to either sporadic or systematic overdosing or underdosing of study drug with the liquid formulation of rivaroxaban.
Severity	Cannot be estimated; none of the reported events of accidental overdosing or underdosing of study drug in the pivotal phase III study EINSTEIN Junior were reported as directly associated with other adverse events.

Missing information:

Safety Concern: Missing information	
1. Remedial pro-coagulant therapy for excessive haemorrhage	
Reasons for classification	The use of drugs to promote clotting of the blood (procoagulants) may be required in the event of excessive bleeding. However, there is limited information on the use of procoagulants in patients receiving rivaroxaban.
Data required	Adequate recommendation on treatment with procoagulants.

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Safety Concern: Missing information	
2. Patients with atrial fibrillation (AF) and a prosthetic heart valve	
Reasons for classification	Evidence suggests that patients with artificial (prosthetic) heart valves may require greater levels of anticoagulants to stop their blood from clotting than those without artificial heart valves. However, the safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves and no data are available to suggest that rivaroxaban provides sufficient coagulation in this patient population. Therefore, treatment with Xarelto is not recommended for these patients.
Data required	Adequate recommendation on treatment in patients with prosthetic heart valves, if applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concern or reclassification taken within this RMP update.

The following safety concerns had been classified previously as 'Missing information' and were removed from the list of safety concerns. The reasons for the removal from the list of safety concerns were the changes in the level of evidence in the benefit-risk evaluation and the limited impact on populations exposed (Procedure number: EMEA/H/C/PSR/S/0027):

- Patients with severe renal impairment (CrCl < 30 mL/min):

  Category 1 PASS program (conclusion): The limited use of rivaroxaban observed in patients with severe kidney impairment and the observed incidence of bleeding outcomes indicate that the label instructions work well. The use in this subgroup appears to be associated with only slight increase of bleeding risk which in combination with the low utilization is not considered a safety concern.

- Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir):

  Category 1 PASS program (conclusion): The DUS data provide reassurance that concomitant use of these potential DDI drugs and rivaroxaban is low overall, and the few cases that are observed do not indicate any safety concerns.

- Pregnant or breast-feeding women:

  Category 1 PASS program (conclusion): Data do not give rise to safety concerns, including an analysis on congenital malformation reports. In addition, the most recent PBRER No. 19.0 no adverse events (AEs) were reported on the vast majority of rivaroxaban exposure via breastfeeding. Moreover, with the recent authorisation of rivaroxaban use in patients aged 18 years or younger, there is no indication of direct toxicity of rivaroxaban to neonates and young children, even at therapeutic doses that presumably exceed the amounts of rivaroxaban that can be ingested via breastfeeding.

- Patients with atrial fibrillation (AF) and a prosthetic heart valve:

  Category 1 PASS program (conclusion): The rivaroxaban label includes the indication for patients with NVAF and does not recommend use in patients with mechanical heart valves since these patients were not included in the clinical trial program. The data from the DUS support the assessment that the label restricts the use of rivaroxaban efficiently.

  In September 2021 the ESC guidelines were updated for patients with AF and valve disorders to recommend NOACs.

- Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting:

  Category 1 PASS program (conclusion): Rivaroxaban appeared to be well tolerated and safe in long-term use. The MAH proposes to remove the topic of "Missing Information", because data from the past decade from the PASS DUS programme, other studies (e.g. non-interventional studies in real life setting), and post-marketing surveillance did not point to a safety concern for patients under long-term treatment with rivaroxaban.

- Patients with significant liver diseases (severe hepatic impairment/Child Pugh C):

  Category 1 PASS program (conclusion): The MAH concludes that only few patients with significant liver disease were exposed to rivaroxaban, indicating that the contraindication in the EU SmPC is effective; the slight to moderate increased risks seen in patients with significant liver disease were not unexpected and are likely due to the underlying liver disease, even if some influence of rivaroxaban plasma concentration cannot be excluded. Overall, these results do not indicate a safety concern.

SVII.3 Details of important identified risks, important potential risks, and missing information

General information

In the EU RMP version 13.4 data from the following studies were added, none of which was submitted as an application for a new indication in the EU:

NAVIGATE ESUS phase III study (SN 16573): Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS),

MARINER phase III study (SN 17261): Medically Ill Patient Assessment of Rivaroxaban Versus Placebo IN Reducing Post-Discharge Venous Thrombo-Embolism Risk,

COMMANDER HF phase III study (SN 16302): A Randomized, Double-blind, Event-driven, Multicenter Study Comparing the Efficacy and Safety of Rivaroxaban with Placebo for Reducing the Risk of Death, Myocardial Infarction or Stroke in Subjects with Heart Failure

and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure,

CASSINI phase III study (SN 18262): Multicenter, randomized, double-blind, placebo-controlled, parallel-group, superiority study that compared the efficacy and safety of rivaroxaban with placebo for primary prophylaxis of VTE (defined as DVT and/or PE) in ambulatory adult men and women, 18 years of age and older, with various cancer types who were scheduled to initiate systemic cancer therapy as a component of their standard-of-care anticancer regimen,

GALILEO phase III study (SN 17938): Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes, and

VOYAGER PAD phase III study (SN17454): An international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial investigating the efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic peripheral artery disease undergoing lower extremity revascularization procedures.

Regarding spontaneous post marketing ADR reports, the DLP for the data presented in this section was 15 SEP 2020 (note: this DLP was taken from the PSUR/PBRER No. 19) unless stated otherwise.

In the following, the important identified risk is defined as the most important identified adverse event / adverse reaction which is serious or frequent, and that might have an impact on the balance of benefits and risks for rivaroxaban, and for which there is a high level of evidence for a causal association with rivaroxaban.

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important Identified: Haemorrhage

Potential mechanisms:

Bleeding is the major complication of anticoagulant therapy. The increased risk for bleeding under treatment with an anticoagulant compound is contributable to its pharmacodynamic property in preventing blood from clotting (pharmacological mode of action is dose dependent inhibition of factor Xa). Treatment with an anticoagulant must be understood as relevant influence on haemostasis in an individual.

Evidence source(s) and strength of evidence:

Evidence was mainly taken from pivotal studies and can therefore be considered valid.

MRR-00150 (Module 5.3.5.4), MRR-00218 (Module 5.3.5.1), MRR-00223 (Module 5.3.5.4), MRR-00233 (Module 5.3.5.1), MRR-00234 (Module 5.3.5.1), MRR-00273 (Module 5.3.5.1), MRR-00292 (Module 5.3.5.1), MRR-00300 (Module 5.3.5.3), MRR-A41857 (Module 5.3.5.1), MRR-A49701 (Module 5.3.5.1), MRR-A51599 (Module 5.3.5.4), A53042 (Module

5.3.5.1), R-8568 (Module 5.3.5.1), R-8570 (Module 5.3.5.1), PH-35415 (Module 5.3.5.3), PH-35843 (Module 5.3.5.3), PH- 36312 (Module 5.3.5.3), PH-36633 (Module 5.3.5.3), PH-36709 (Module 5.3.5.3), PH-36892, PH-37587, PH-36746, PH-38665, Module 5.3.5.1/16523, CTD Module 5.3.5.1, CTD Module 5.3.5.3; PH39589; EU RMP version 12.4.; COMPASS, PH-39342, NAVIGATE ESUS PH-39740, MARINER R-12741, COMMANDER HF R-12742, CASSINI R-12891, GALILEO PH-40182, EINSTEIN Junior phase III PH 40166, Technical Report PH-41010, VOYAGER PAD PH-40164, Technical Reports PH-41518 and PH-41520, PBRER/PSUR No. 19.0.

Characterisation of the risk:

As expected, due to the pharmacological mode of action, haemorrhages (i.e. surgical and extra-surgical site bleeding events, fatal and critical organ bleedings) have been observed in patients treated with rivaroxaban and in patients receiving comparator (e.g. enoxaparin/VKAs/platelet aggregation inhibitors) and/or placebo.

The variability in the rate of bleeding across the rivaroxaban programme may be due to differences in baseline characteristics of individuals, concomitant medication, or underlying and/or concomitant diseases. The risk of haemorrhage may be facilitated by the medical condition, e.g. intra-articular within the context of a surgical procedure; concomitant administration of other anticoagulants and/or uncontrolled arterial hypertension may facilitate the occurrence of intracranial bleedings. Pulmonary haemorrhage may be clinical sign of pre-existing lung diseases such as bronchiectasis. An increased bleeding risk (e.g. menorrhagia) for rivaroxaban treated women aged < 55 years could be observed when compared to enoxaparin/vitamin K antagonist (VKA) treatment. Anticoagulant agents may be associated with an increased risk of upper GI bleedings because of an exacerbation of pre-existing (clinically silent) lesions in the GI tract associated e.g. with non-steroidal anti-inflammatory drugs (NSAIDs), acetyl salicylic acid (ASA) or H. pylori infection.

Unless stated otherwise, adverse event (AE) frequencies from clinical trials are based on clinical pooled data from all completed pivotal Phase III clinical studies in the approved EU indications as well as from the completed phase III studies of rivaroxaban (see above). In addition, this chapter contains data from phase IIIb study X-VeRT and phase IIIb studies VENTURE AF as well as data from post marketing non-interventional studies XAMOS (comparing rivaroxaban with any other pharmacological standard treatment for the prophylaxis of VTE after major orthopaedic surgery), XANTUS (describing the use of rivaroxaban in a broad NVAF patient population) and XALIA (comparing rivaroxaban with standard anticoagulation treatment in patients with deep vein thrombosis [DVT]). All results are displayed for patients valid for safety.

Bleeding Event Committees adjudicated clinical bleeding events according to standardised criteria as outlined in the respective Committees' Manuals and study protocols (e.g. ISTH or TIMI guidelines for major bleeds).

In Table SVII-1 the incidence of treatment-emergent bleeding events in Phase III studies is presented under treatment with rivaroxaban:

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Table SVII-1: Incidence of treatment-emergent bleeding events in Phase III studies (as assessed by respective CIAC based on pre-defined adjudication criteria or number of AEs, see footnotes)

	Any bleeding				Major bleeding			
	Rivaroxaban		Comparator		Rivaroxaban		Comparator	
RECORD	6.30%	(384/6,097)	5.81%	(355/6,109)[A]	0.36%	(22/6,097)	0.16%	(10/6,109)[A]
Surgical site	3.40%	(207/6,097)	3.04%	(186/6,109)	0.21%	(13/6,097)	0.10%	(6/6,109)
Extra-surgical site	3.20%	(195/6,097)	2.96%	(181/6,109)	0.15%	(9/6,097)	0.07%	(4/6,109)
Pooled EINSTEIN-DVT and -PE	28.30%	(11,69/4,130)	28.00%	(1,153/4,116)[B]	1.0%	(40/4,130)	1.7%	(72/4,116)[B]
EINSTEIN Extension	17.39%	(104/598)	10.68%	(63/590)[C]	0.67%	(4/598)	0.00%	(0/590)[C]
EINSTEIN Choice	16.11%	(360/2,234)	13.62%	(154/1,131)[D]	0.49%	(11/2,234)	0.27%	(3/1,131)[D]
Pooled ROCKET and J-ROCKET	22.68%	(1,758/7,750)	22.00%	(1,708/7,764)[E]	5.43%	(421/7,750)	5.36%	(1,708/7,764)[E]
PIONEER AF-PCI	31.95%	448/1,402	40.03%	279/697[FG]	1.85%	(26/1,402)[E]	2.87%	(20/697)[FG]
MAGELLAN (up to day 35)	12.5%	(501/3,997)	8.5%	(341/4,001)[A]	1.1%	(43/3,997)	0.4%	(15/4,001)[A]
ATLAS ACS 2–TIMI 51	22%	(2,252/10,225)	12.5%	(643/5,125)[C]	1.5%	(153/10,225)[E]	0.5%	(27/5,125)[CF]
COMPASS	10.7%	(1,953/18,244)	6.7%	(613/9,107)	2.7%	(488/18,244)	1.6%	(144/9,107)
EINSTEIN Junior Phase III[J]	39.5%	(130/329)	30.2%	(49/162)[H]	0%	0/329	1.2%	(2/162)
NAVIGATE ESUS	12.4%	(442/3,562)	7.8%	(279/3,559)	1.7%	(62/3,562)	0.6%	(23/3,559)
MARINER	3.0%	(177/5,982)	2.0%	(119/5,980)	0.28%	(17/5,982)	0.15%	(9/5,980)
COMMANDER HF	11.5%	(287/2,499)	6.7%	(167/2,509)	3.3%	(82/2,499)	2.9%	(50/2,509)
CASSINI	20.5%	(83/405)	12.9%	(52/404)	1.98%	(8/405)	0.99%	(4/404)
GALILEO	25.1%	(201/801)	16.7%	(135/807)	3.2%	(26/801)	1.5%	(12/807)[SAF]
VOYAGER PAD	16.8%	(546/3,256)	10.9%	(354/3,248)	1.9%	(62/3,256)	1.4%	(44/3,248)[SAF]

[A] Enoxaparin; [B] enoxaparin/VKA; [C] placebo; [D] acetylsalicylic acid; [E] VKA, [F] TIMI major bleeding, [G] VKA plus dual antiplatelet therapy, [H] Standard of care with either subcutaneous low molecular weight heparin (LMWH), subcutaneous fondaparinux, intravenous unfractionated heparin (UFH) and/or oral vitamin K antagonist (VKA); [J] numbers used for EINSTEIN Junior are from the confirmed bleeding table

CIAC, central independent adjudication committee; AF, atrial fibrillation; DVT, deep vein thrombosis; PCI, percutaneous coronary intervention; PE, pulmonary embolism

Treatment-emergent is defined as the event occurred after randomisation and up to 2 days after the last dose of study drug; in EINSTEIN Choice, all bleeding events are investigator reported.

Pooled RECORD studies [Source: PH-35415; Module 5.3.5.3, Table 14.3.1/11.1.1.5/11.3.1.5/11.4.1.5]

EINSTEIN DVT, PE and Extension [Source: PH-36746, Table 14.3.1, MRR-00273, Module 5.3.5.1, Table 14.3.1 /38]

EINSTEIN Choice [Source: PH-39589 Amendment 1, Table 14.1.8 /1, PH-38665, Table 14.3.1.3 /1]

ROCKET Pool [Source: R-8568, Module 5.3.5.3]

PIONEER AF-PCI [Source: R- 11826, Table 15, Table 29]

Magellan [Source: A51599, Module 5.3.5.4, Table 14.3.1/120, Table 14.3.1/139, Table 14.3.1/142]

ATLAS [Source: R-8673, Module 5.3.5.1, Table 40 (TBL021)]

COMPASS [Source: PH-39342, Table 14.3.1/4, Table 14.3.1/200]

EINSTEIN Junior Phase III [Source: PH-40166, Table 14.3.2.3/1]

COMMANDER HF [Source: PH-41518, Table 14.2/2; Clinical Study Report R-12742, Table 30]

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GALILEO [Source PH-41518, Table 14.2/2; PH-40182, Table 10-1, Table 10-10]
MARINER [Source PH-41518, Table 14.2/2; Clinical Study Report R-12741, Table 27]
NAVIGATE ESUS [Source PH-41518, Table 14.2/2; PH-39740, Table 10-11]
CASSINI [Source PH-41518, Table 14.2/2; R-12891, Table 27]
VOYAGER PAD [Source PH-41518, Table 14.2/2; PH-40164, Table 14.3.1.3/1]
(Please note that all data from Table 14.2/2 in PH-41518 and PH-39859 are based on 'SMQ haemorrhages' and therefore not only considering adjuciated events)

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In the RECORD program (VTE prevention in patients undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery) the focus was on extra-surgical site bleeding events, which allows a better assessment of clinically important events because haemoglobin decreases and blood transfusions are expected and occur frequently after surgery, as does some bleeding from the surgical wound. Therefore, most surgical site bleeding events associated only with haemoglobin decreases and blood transfusions do not lead to any changes in patient management and are not considered "major" in nature by orthopaedic surgeons.

In the EINSTEIN, ROCKET and MAGELLAN clinical trials as well as in the post-marketing non-interventional cohort studies XANTUS (SN 15914) and XALIA (SN 15915) a major bleeding event was defined according to ISTH guidelines (fatal bleeding, overt bleeding associated with a fall in haemoglobin of 2 g/dL or more; led to a transfusion of two or more units of packed red blood cells or whole blood; occurred in a critical site [intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal]).

In PIONEER AF-PCI (SN 16523), major bleeding was defined according to Thrombolysis In Myocardial Infarction (TIMI) criteria (any symptomatic intracranial haemorrhage or clinically overt signs of haemorrhage [including imaging] associated with a drop in haemoglobin of $\geq$ 5 g/dL [or when the haemoglobin concentration was not available, an absolute drop in haematocrit of $\geq$ 15%]).

The primary safety endpoint of ATLAS ACS 2–TIMI 51 (SN 13194) was the incidence of TIMI major bleeding events not associated with coronary artery bypass graft (CABG) surgery (i.e., non-CABG TIMI major bleeding).

The primary safety outcome in COMPASS (SN 15786) is Modified ISTH major bleeding, defined as: i) fatal bleeding, and/or ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding into the surgical site requiring re-operation and/or iii) bleeding leading to hospitalization.

The primary safety outcome in phase III EINSTEIN Junior (SN 14372) is the composite of overt major bleeding and clinically relevant non-major bleeding. Other safety outcomes include all deaths and other vascular events (myocardial infarction, cerebrovascular accident, non-CNS systemic embolism). Major bleeding is defined as overt bleeding associated with a fall in hemoglobin of 2 g/dL or more or leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults, or occurring in a critical site, e.g. intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal, or contributing to death. Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, or unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or discomfort for the child such as pain or impairment of activities of daily life (such as loss of school days or hospitalization).

All other overt bleeding episodes not meeting the criteria for clinically relevant bleeding were classified as trivial bleed.

Most frequent treatment-emergent bleeding events:

In the pooled RECORD studies (SN 11354, 11355, 11356, 11357), the majority of bleeding events were most commonly confined to the surgical site; non-surgical bleeding events relate to gastrointestinal (GI) and urogenital tract, and epistaxis. The majority of bleeding events occurred within the first 2 weeks after surgery; thereafter only minor increases in event rates for GI tract bleeding, epistaxis, haematuria and menorrhagia had been observed, thus extended prophylaxis (up to 35 days in THR) did not lead to an important increase in bleeding.

In the rivaroxaban groups from the EINSTEIN-DVT, -PE and Ext studies (SN 11702-DVT, SN 11702-PE and SN 11899), the most frequently reported bleeding events were epistaxis, contusion, haematuria, menorrhagia and gingival bleeding. Compared with the other rivaroxaban studies, the higher proportion of younger (pre-menopausal) female patients contributed to the higher frequency of menorrhagia observed in the EINSTEIN programme. Women with major bleeding events from the uterus had significant pathology of the genital tract (4 women out of 5 with major bleeding events) or thrombocytopenia (1 out of 5). Most women with trivial or clinically relevant non-major bleeding events continued their treatment with rivaroxaban. In the rivaroxaban groups from the EINSTEIN Choice study [Source: PH-39589; Table 14.1.8 /2], the most frequently reported bleeding events were epistaxis, subcutaneous haematoma, gingival bleeding and menorrhagia, consistent with results from the other EINSTEIN studies [Source: PH-38665].

In the pooled ROCKET studies (SN 11630, SN 12620), the most frequently reported bleeding events were epistaxis, haematuria, gingival bleeding, contusion and haematoma [Source: R-8568, Module 5.3.5.3]. Bleeding sites for the principal safety endpoint (a composite of major and non-major clinically relevant bleeding) differed by treatment group: rivaroxaban was more often associated with bleeding at sites throughout the GI tract as well as haematuria and epistaxis, whereas warfarin was more often associated with critical organ bleeding (e.g. intracranial) as well as haematoma and skin bleeding. The higher frequency of intracerebral haemorrhage compared to the other phase III clinical trial programmes seen in this programme is expected due to the studied population.

In the PIONEER AF-PCI study (SN 16523), the most frequently reported treatment-emergent bleeding-related adverse events were epistaxis (10.3%), haematoma (5.5%), contusion (3.3%), haematuria (2.6%) and gingival bleeding (2.4%) [Source: R- 11826].

Study X-VeRT (SN 15693) explored the efficacy and safety of rivaroxaban od for the prevention of cardiovascular events in patients with non-valvular AF who were scheduled for cardioversion compared with dose-adjusted oral vitamin K antagonists. Adjudicated treatment-emergent bleeding was reported for 124/1487 (8.3%) patients overall. Major bleeding occurred in 6/988 (0.6%) patients receiving rivaroxaban and 4/499 (0.8%) of patients receiving VKA. The most frequently occurring major bleed was gastrointestinal haemorrhage lower, which occurred in 2/988 (0.2%) patients receiving rivaroxaban and 1/499 (0.2%)

patients receiving VKA. A total of 3/1487 (0.2%) fatal bleeds were recorded [Source: PH-37587, Table 14.3.1/85].

VENTURE (SN 15694) enrolled a total of 123 patients in the rivaroxaban arm and 121 patients in the VKA arm receiving at least one dose of study drug. In the rivaroxaban arm, there were no patients with major bleeding events in the post-ablation period. There was one ISTH major bleeding event of vascular pseudoaneurysm reported for a patient randomized to the VKA arm. Any treatment-emergent post-ablation bleeding was reported in 14 and 13 patients in the rivaroxaban and VKA treatment arms, respectively [Source: R-9627].

X-TRA (SN 16320) enrolled 60 patients who received at least one dose of study drug. No major bleeding events (ISTH criteria) were reported. Non-major bleeding events were reported in five patients (8.3%; mild gingival bleeding, moderate ear haemorrhage, moderate epistaxis, mild gastrointestinal haemorrhage, and mild petechiae) [Source: PH-38027].

In MAGELLAN (SN 12839), the most frequently reported bleeding adverse events in the rivaroxaban group were epistaxis, haematuria, ecchymosis, haemoptysis, and GI tract bleedings [Source: PH-36499, Module 5.3.5.4, Table 14.3.1 /2].

In ATLAS ACS 2–TIMI 51 (SN 13194) the most frequently reported bleeding events were epistaxis, gingival bleeding, and haematoma [Source: PH-36650, Module 5.3.5.3, Table 14.3.4 /2]. The most frequently reported treatment-emergent bleeding-related serious adverse events in the rivaroxaban group (pooled doses and strata) were: GI haemorrhage (50/10,225 [0.5%]) and haematuria (28/10,225 [0.3%]). [Source: PH-36650, Module 5.3.5.3, Table 14.3.4 /4].

In COMPASS (SN 15786) the most frequently reported bleeding events were those from the GI tract (680/18,244) [3.7%], from the respiratory tract (464/18,244) [2.5%], and epistaxis, (403/18,244) [2.2%]). In Table SVII-2 the incidence of treatment-emergent adverse events and bleeding events as reported by investigator from the COMPASS study is presented:

Table SVII-2: Incidence of treatment-emergent adverse events and bleeding events as reported by investigator (COMPASS) MedDRA V20.0 SMQ Haemorrhages, System Organ Class or Preferred Terms occurring in ≥2% of patients

SOC (≥2.0%) PT (≥2.0%)	Rivaroxaban 2.5 mg bid, ASA 100mg od N=9,134 (100%)	Rivaroxaban 5mg bid N=9,110 (100%)	ASA 100mg od N=9,107 (100%)
Any Event	1,149 (12.6%)	1,027 (11.3%)	183 (2.0%)
Gastrointestinal disorders	361 (4.0%)	319 (3.5%)	30 (2.7%)
Respiratory, thoracic and mediastinal disorders	248 (2.7%)	216 (2.4%)	139 (1.5%)
Epistaxis	216 (2.4%)	187 (2.1%)	118 (1.3%)

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Table SVII-2: Incidence of treatment-emergent adverse events and bleeding events as reported by investigator (COMPASS) MedDRA V20.0 SMQ Haemorrhages, System Organ Class or Preferred Terms occurring in ≥2% of patients

SOC (≥2.0%) PT (≥2.0%)	Rivaroxaban 2.5 mg bid, ASA 100mg od N=9,134 (100%)	Rivaroxaban 5mg bid N=9,110 (100%)	ASA 100mg od N=9,107 (100%)

Source: PH-39963 Table 14.8 /3

In phase III EINSTEIN Junior (SN 14372) the most frequently reported bleeding events were epistaxis (42/329) [12.8%], menorrhagia (23/329) [7.0%], subcutaneous hematoma (15/329) [15/329) [4.6%], gingival bleeding (13/329) [4.0%] and wound hemorrhage (13/329) [4.0%] [Source: PH-40166, Table 14.3.2.1/21].

Table SVII-3: Study 14372: Principal safety outcome during the main treatment period; Safety Analysis Set (adjudicated bleedings)

Bleeding events	Bleeding site grouping	Rivaroxaban N=329 (100%)	Comparator N=162 (100%)
Any confirmed bleeding	Any	119 (36.2%)	45 (27.8%)
Principal safety outcome *	Any	10 (3.0%)	3 (1.9%)
Major bleeding	Any	0	2 (1.2%)
	Intracranial	0	1 (0.6%)
	Respiratory tract	0	1 (0.6%)
Clinically relevant non-major bleeding	Any	10 (3.0%)	1 (0.6%)
	Gastrointestinal tract	4 (1.2%)	0
	Genital	1 (0.3%)	0
	Injection site	1 (0.3%)	0
	Nasal	2 (0.6%)	1 (0.6 %)
	Oral cavity	1 (0.3%)	0
	Urinary tract	1 (0.3%)	0

* Composite of (i) treatment-emergent major bleeding and (ii) clinically relevant non-major bleeding
Source: Report PH-40166, Tables 14.3.2.3/6, 14.3.2.3/56, 14.3.2.3/60

Onset of bleeding events – cumulative incidences (Kaplan–Meier):

In the RECORD studies, the majority of any treatment-emergent surgical site bleeding events occurred within the first week after surgery, namely 203 from 246 surgical site bleedings for patients receiving rivaroxaban and 173 from 223 for enoxaparin patients. Almost 50% of extra-surgical site bleeding (n = 95) developed within the first 4 days after surgery [Source: PH-35415, Module 5.3.5.3].

In the pooled data from EINSTEIN-DVT and -PE (SN 11702-DVT and -PE), the Kaplan-Meier cumulative incidence rate for all confirmed treatment-emergent bleeding events (determined by CIAC) at day 359 was 34.9% (95% CI: 32.9-36.9) for rivaroxaban and 34.5% (95% CI: 32.5-36.4) for enoxaparin/VKA group. In both treatment groups, approximately half

of all confirmed treatment-emergent bleeding events occurred in the first 30 days of treatment, which includes the time period that patients received a TDD of rivaroxaban 30 mg (cumulative number of events [Kaplan-Meier] at day 30, rivaroxaban: n = 642/1169; enoxaparin/VKA: n = 654/1153) [Source: PH-36746, Figure 14.3.1/17].

In the EINSTEIN-Ext study (SN 11899 [N = 598]), the Kaplan-Meier cumulative incidence rate for all confirmed treatment-emergent bleeding events (determined by CIAC) at day 360 was 24.92% (95% CI: 18.94-30.90) for rivaroxaban and 14.19% (95% CI: 10.08-18.30) for placebo [Source: MRR-00273, Module 5.3.5.1]. The majority of all confirmed treatment-emergent bleeding events occurred in the first 3 months of treatment (cumulative number of events [Kaplan–Meier] at day 90, rivaroxaban: n = 74/104; placebo: n = 42/63). [Source: MRR-00273, Module 5.3.5.1].

In EINSTEIN Choice, the Kaplan-Meier cumulative probability of treatment-emergent first major bleeding events at day 360 was 0.5% (95% CI: 0.2-1.1), 0.7% (95% CI: 0.3-1.5) and 0.4% (95% CI: 0.1-1.1) in the rivaroxaban 10 mg, rivaroxaban 20 mg and ASA 100 mg groups, respectively [Source: PH-38665; Table 14.3.1.3 / 31]. The Kaplan-Meier cumulative probability of treatment-emergent first event of the composite of major bleeding event or clinically relevant non-major bleeding at day 360 was 1.7% (95% CI: 1.1-2.8), 2.3% (95% CI: 1.5-3.4) and 1.4% (95% CI: 0.8-2.4) in the rivaroxaban 10 mg, rivaroxaban 20 mg and ASA 100 mg groups, respectively [Source: PH-38665; Table 14.3.1.3 / 55].

For the pooled ROCKET studies (SN 11630 and SN 12620) the Kaplan-Meier cumulative incidence rate for the principal safety endpoint (composite of major and non-major clinically relevant bleeding events, adjudicated by CEC, at day 360 while on treatment was 15.77% (95% CI: 14.94-16.64) for rivaroxaban and 15.67% (95% CI: 14.84-16.54) for warfarin and at day 1290 was 32.58% (95% CI: 30.13-35.17) for rivaroxaban and 32.64% (95% CI: 27.66-38.26) for warfarin [Source: R-8568, Module 5.3.5.3].

In the PIONEER AF-PCI study (SN 16523), the Kaplan-Meier cumulative probability rate for treatment-emergent TIMI clinically significant bleeding (CEC adjudicated) at day 360 was 17.41% (95% CI: 15.44-19.61) for the combined rivaroxaban groups and 26.73% (95% CI: 23.41-30.42) for the VKA + dual antiplatelet therapy (DAPT) group [Source: R-11826 Attachment TENDPKM02a].

In the X-VeRT study (SN 15693) the incidence risk of the treatment-emergent principal safety outcome was similar in the 2 treatment groups and the hazard ratio for the interval from first treatment with study drug to the last dose + 2 days (rivaroxaban versus VKA) was 0.74 (95% CI: 0.21, 2.64) [Source: PH-37587, Table 14.3.1/142].

In the MAGELLAN study (SN 12839), the Kaplan–Meier cumulative event rate of treatment-emergent all confirmed bleeding events (central adjudication) by Day 10 was 7.84% (95% CI: 7.00–8.69) for rivaroxaban and 5.86% (95% CI: 5.12–6.60) for enoxaparin by Day 35 was 12.52% (95%CI: 11.44–13.60) for rivaroxaban and 8.24% (95% CI: 7.35–9.13) for enoxaparin/placebo [Source: A51599, Module 5.3.5.4].

In the ATLAS ACS 2–TIMI 51 study (SN 13194), the Kaplan–Meier cumulative risk of treatment-emergent non-CABG-related TIMI major bleeding events (as adjudicated by the

CEC) at day 720 was 2.13% (95% CI: 1.77–2.57) for rivaroxaban and 0.61% (95% CI: 0.37-0.99) for placebo [Source: R-8673, Module 5.3.5.1, Output DBL05A].

In the COMPASS study (SN 15786), the Kaplan-Meier cumulative risk of treatment-emergent modified ISTH major bleeding at day 900 (30 months) was 3.77% (95% CI: 3.31-4.30) for rivaroxaban 2.5mg bid/ASA 100mg od, 3.23% (95% CI: 2.80-3.73) for rivaroxaban 5 mg bid and 2.09% (95% CI: 1.74-2.51) for ASA 100mg od [Source PH-39342, Table 14.3.1/47].

In the EINSTEIN Junior phase III study (SN 14372) the majority of events of the principal safety outcome (composite of treatment-emergent major bleeding and CRNM bleeding) in both treatment groups occurred during the first month of randomized treatment. During the main treatment period of Study 14372, no major bleeding was recorded in any of the 329 children treated with rivaroxaban, while among the 162 children in the comparator group, two major bleedings occurred. CRNM bleeding during the main treatment period was recorded in 10 children (3.0%) in the rivaroxaban group and in 3 children (1.9%) in the comparator group.

Treatment extension was started by 149 children randomized to rivaroxaban and by 69 children randomized to comparator.

Table SVII-4Study 14372: Incidences of Principal Safety outcome during extended treatment periods

Principal Safety outcome = composite of treatment-emergent major bleeding and CRNM bleeding
Safety analysis set

Extension	Age group	Rivaroxaban		Comparator	
period	(years)	Incidence	95% CI	Incidence	95% CI
Extension 1	12 to < 18	1.1% (1 / 93)	0.1% - 5.3%	0.0% (0 / 46)	0.0% - 6.9%
Extension 2	12 to < 18	2.6% (1 / 38)	0.1% - 13.4%	5.3% (1 / 19)	0.3% - 24.4%
	< 2	11.1% (1 / 9)	0.6% - 44.3%	0.0% (0 / 5)	0.0% - 50.0%
Extension 3		*no Principal Safety outcome recorded*			

CI = confidence interval; CRNM = clinically relevant non major
Incidence = number of subjects having the event in the time window / number at risk
number at risk = number of subjects in reference population.
Confidence Intervals calculated by applying the method of Blyth-Still-Casella.
Source: Report PH-40166, Tables 14.3.2.3/77, 14.3.2.3 /78, 14.3.2.3/79 (279)

Post-marketing data:

1) Non-interventional cohort study XAMOS (SN 13802) – VTE prevention in THR and major orthopaedic surgery

The incidence of major bleeding in the safety population (rivaroxaban, N = 8,778; standard of care, N = 8,635) was low, with no significant difference seen between rivaroxaban and standard of care using the RECORD (0.4% vs 0.3%; odds ratio [OR]: 1.19; 95% confidence interval [CI]: 0.73–1.95) and EMA (1.7% vs 1.4%; OR: 1.19; 95% CI: 0.93–1.51) definitions of major bleeding. The proportion of patients with any treatment-emergent bleeding event was significantly different between the rivaroxaban (4.7%) and standard of care (3.2%) groups

(OR: 1.46 [95% CI: 1.25–1.71]; hazard ratio: 1.437 [95% CI: 1.232–1.677]) [Source: PH-36892, Table 16.1.1.2/6.1, Table 16.1.1.2/8.1].

The most frequently reported treatment-emergent bleeding-related AEs leading to study drug discontinuation were as follows: operative haemorrhage (rivaroxaban, n = 3 (< 0.1%); standard of care, n = 1 (< 0.1%)); wound haemorrhage (rivaroxaban, n = 2 (< 0.1%); standard of care, n = 5 (0.1%)) and haematoma (rivaroxaban, n = 10 (0.1%); standard of care, n = 6 (0.1%)) [Source: PH-36892, Table 16.1.1.1/9.17.2.1]

The vast majority of treatment-emergent bleeding-related AEs reported in patients receiving rivaroxaban resolved. No fatal treatment-emergent bleeding events were reported in the rivaroxaban group [Source: PH-36892, Tables 16.1.1.1/10.1.2.1 and 16.1.1.1/9.24.2.1].

Most frequently, bleeding events were in the SOC 'injury, poisoning and procedural complications', reported in 355 (2.0%) patients overall. Within this SOC, 'operative haemorrhage' and 'wound haemorrhage' were reported in 103 (0.6%) and 77 (0.4%) patients, respectively. There were no relevant differences between the treatment groups.

In a *post hoc* sub-analysis of XAMOS data the observed incidences of major bleeding events in rivaroxaban-treated patients who underwent non-elective procedures of the lower limb (n = 790) are comparable to those from the overall XAMOS study as well as the RECORD studies. Within this subset, the incidence of treatment-emergent major bleeding was 0.6% in the rivaroxaban group versus 0.7% in the standard of care group using the RECORD definition, and 1.1% in the rivaroxaban group versus 1.0% in the standard of care group using the EMA definition. Any treatment emergent bleeding events occurred in 2.8% and 1.0% of the rivaroxaban and standard of care groups, respectively [Source: PH-37908, Table 9.1.2.2].

2) Non-interventional cohort study XANTUS (SN 15914) – prevention of stroke and non-central nervous systemic embolism in patients with non-valvular atrial fibrillation

There were 142 adjudicated treatment-emergent major bleeding events reported in 128 (1.9%) patients. The major bleeding incidence rate was 2.1 (95% CI: 1.8–2.5) per 100 patient-years. The reasons for events to be adjudicated as major bleedings were: transfusion of ≥ 2 units of packed RBCs or whole blood in 53 (0.8%) patients, fall in haemoglobin of ≥ 2 g/dL in 52 (0.8%) patients, occurrence at a critical site in 43 (0.6%) patients (including intra-cranial in 26 [0.4%] patients), and death in 12 (0.2%) patients. Major bleeding was most prominent in the gastrointestinal system (52, 0.8%). Overall 60 (0.9%) patients discontinued treatment due to an adjudicated major bleeding event. The incidence rate of major bleeding was slightly higher among patients with prior antithrombotic therapy (2.2 per 100 patient-years, 95% CI: 1.8–2.7) than among patients without prior antithrombotic therapy (1.7, 95% CI 1.2–2.5).

There were 1133 non-major treatment-emergent bleeding events reported in 878 (12.9%) patients. The incidence rate of non-major bleeding was 15.4 (95% CI: 14.4–16.5) per 100 patient-years. By far the most common PT was epistaxis, reported in 292 (4.3%) patients. The most commonly reported PTs were gingival bleeding (74 patients, 1.1%) and rectal haemorrhage (45 patients, 0.7%) [Source: PH-38797].

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3) Non-interventional cohort study XALIA (SN 15915) – VTE treatment in patients with acute DVT with or without PE

The safety population in XALIA study comprised of 4768 patients (2619 rivaroxaban vs. 2149 standard of care) who received study medication for treatment of acute DVT with or without PE.

Treatment emergent major bleeding was reported in 19 patients (0.73%, 95% CI: 0.44%-1.13%) in the rivaroxaban group and 48 patients, 2.23%, 95% CI: 1.65%–2.95% in the standard anticoagulation. The incidence rate was 1.23 (95% CI: 0.74–1.92) per 100 patient-years in the rivaroxaban group and 3.39 (95% CI: 2.50–4.49) in the standard anticoagulation group. In the rivaroxaban group no fatal bleeding events were reported.

The most frequently reported treatment-emergent bleeding-related PTs in the rivaroxaban group were epistaxis and gingival bleeding while haematoma and haematuria were more frequently reported in the standard anticoagulation group. The incidences of TEAEs of increased or prolonged menstrual or abnormal vaginal bleeding in younger females (age < 55) were higher for the rivaroxaban group (12.4%) compared to the standard anticoagulation group (3.9%). The major imbalance was driven by the PT menorrhagia (rivaroxaban: 7.8%; standard anticoagulation: 2.0%). The majority of menorrhagia (>90%) was reported as non-serious; in approx. 70% of menorrhagia the outcome was reported as recovered/recovering [Source: PH- 38879].

Overall, the majority of treatment-emergent bleeding events were mild to moderate in severity.

Risk factors and risk groups:

Patients with certain pre-existing conditions (e.g. active cancer, previous stroke, bronchiectasis, history of bleeding, anaemia, uncontrolled hypertension, renal impairment, known GI ulcerations), those receiving concurrent antithrombotics, or the elderly, may be at higher risk of bleeding. Post-operative patients are generally at high risk of bleeding, especially during treatment with anticoagulants. Pre-menopausal women may be at risk for menorrhagia.

Preventability:

No data on preventability of (occult and overt) haemorrhage are available. Predictive factors may include patients with a higher risk of haemorrhage due to co-morbidities and/or concomitant anticoagulation and/or other co-medications. Appropriate treatment of risk factors for haemorrhage as applied to the general population as well as careful choice of co-medications may reduce the risk of developing these events whilst receiving rivaroxaban. See the respective section in Part V of this RMP regarding additional risk minimization measures.

Impact on the risk-benefit balance of the product:

The impact of increased bleeding risk under treatment with rivaroxaban is countered by routine pharmacovigilance measures as well as additional risk minimization measures.

Public health impact:

No specific analyses of quality of life were performed in the subgroup of patients with haemorrhage. Haemorrhage in patients receiving rivaroxaban generally resolves with dose interruption or discontinuation, but major bleeding events/bleeding into critical organs may present a significant issue in terms of loss of function and quality of life. The impact of haemorrhage on the individual patient is dependent on the site and severity of the bleeding event. Significant haemorrhage may be life-threatening or potentially fatal.

No public health impact of safety concern was identified.

Critical Organ Bleedings (according to respective guidelines (ISTH / TIMI) and other relevant treatment-emergent bleeding sites:

Overall, the incidence of critical organ bleeding was low.

In the pooled EINSTEIN-DVT and -PE studies (SN 11702-DVT and -PE), there were more major non-fatal critical organ bleeding events in the enoxaparin/VKA group (0.7% [29/4116]) than in the rivaroxaban group (0.3% [7/4130]). The higher incidence rate of major non-fatal non-critical organ bleeding events was related to the site uterus (0.2% [8/4130]) in the rivaroxaban treatment group versus none in the enoxaparin/VKA treatment group. In all of the patients study medication was discontinued and patients recovered [Source: PH-36746; Table 14.3.1/175].

In the EINSTEIN Extension (SN 11899), treatment-emergent major bleeding events occurred in four patients receiving rivaroxaban (three GI bleeding events and one menometrorrhagia) and no patients in the placebo group. All of the events were medically manageable and resolved after cessation of the study drug and appropriate medical treatment [Source: MRR-00273, Module 5.3.5.1].

In EINSTEIN Choice (SN 16416), treatment-emergent major bleeding events occurred in five patients (0.4%) receiving rivaroxaban 10 mg once daily (OD) (one intracranial, one intramuscular with compartment syndrome, two in the GI tract and one intra-abdominal), six patients (0.5%) receiving rivaroxaban 20 mg OD (one pericardial [fatal], three intracranial, one pulmonary, and one in the GI tract), and three patients (0.3%) receiving ASA 100 mg OD (two intracranial [one of which was fatal] and one in the GI tract) [Source: PH-38665; Table 14.3.1.3 / 1].

In the pooled ROCKET studies (SN 11630 and SN 12620), the event rates of critical organ bleeding intracranial haemorrhage and death were significantly lower in the rivaroxaban group than in the warfarin group ($p = 0.010$, $p = 0.019$ and $p = 0.002$, respectively). The event rate of haemoglobin drop (≥2 g/dL) was significantly higher in the rivaroxaban group than the warfarin group ($p = 0.036$).

In the PIONEER AF-PCI study (SN 16523), the incidence of treatment-emergent critical organ bleeding was 0.78% (11/1402) in the combined rivaroxaban groups and 1.58% (11/697) in the VKA + DAPT group (log-rank $p = 0.070$) [Source: R-11826 /Attachments TBE14391 and TBEHR01b].

In the MAGELLAN study (SN 12839), the rivaroxaban-enoxaparin/placebo treatment phase, the most prominent difference in the incidence of bleeding events was reported (rivaroxaban vs enoxaparin) for the intracranial bleeding site (4 [0.1%] vs 2 [< 0.1%] patients), retroperitoneal bleeding site (3 [< 0.1%] vs 0 patients), and pulmonary bleeding site (3 [< 0.1%] vs 0 patients). The incidence of intraocular bleeding and pericardial bleeding was in one patient each in both rivaroxaban and enoxaparin groups, whereas the incidence of GI bleeding was in one patient only in the rivaroxaban group and of tracheal bleeding in one patient only in the enoxaparin group.

In ATLAS ACS 2–TIMI 51 (SN 13194), the incidence of bleeding into a critical organ was balanced between the 2.5 mg bid (all strata) (25/5115 [0.5%]) and placebo (21/5125 [0.4%]) groups, and was numerically higher in the 5 mg bid group (all strata) (41/5110 [0.8%]). [Source: R-8673, Module 5.3.5.1, Table 45].

In COMPASS (SN 15786) the incidence of non-fatal critical organ bleeding was 0.6% (58/9134) for rivaroxaban 2.5mg bid/ASA100 mg od, 0.7% (63/9110) for rivaroxaban 5 mg bid and 0.5% (43/9107) for ASA 100mg od. [Source: PH-39342, Table 14.3.1/4].

Outcome:

Overall, the majority of the bleeding events resolved [EU RMP vs 11.4].

Fatal bleedings

In the pooled RECORD, ROCKET, EINSTEIN-DVT/PE/Ext, MAGELLAN and ATLAS, the incidence of fatal treatment-emergent bleeding events for rivaroxaban is 0.17% (54/32,625). The main bleeding sites are the GI tract and brain. In the RECORD programme, there was one fatal GI bleeding (in a patient with gastric ulcers).

The incidence of fatal bleeding events in the pooled EINSTEIN-DVT and -PE studies (SN 11702-DVT and -PE) was <0.1% (3/4,130) in the rivaroxaban (2 intracranial, 1 gastrointestinal bleeding) and 0.2 % (8/4,116) in the enoxaparin/VKA group (4 intracranial, 1 retroperitoneal, 2 gastrointestinal, and one thorax-related bleeding event) [Source: PH-36746, Table 14.3.1 /175]. In the EINSTEIN Extension study (SN 11899), no fatal bleeding events were reported

In the EINSTEIN Choice, 2 patients had fatal bleeding events [Source PH-38665, Table 14.3.1.3 /13]. One fatal bleeding in the rivaroxaban 20 mg group was due to pericardial bleeding following a dissection of the aorta. The second event was due to a spontaneous intracranial bleeding in the ASA 100 mg group [Source PH-38665, Table 14.3.2 /1].

In the pooled ROCKET programme (SN 11630, SN 12620), less than 1% of all patients experienced a fatal bleeding event while on treatment, and the incidence of fatal bleeding was lower for the rivaroxaban group (0.28% [22/7,750]) than the warfarin group (0.58% [45/7,764]). The most common type of fatal bleeding event was intracranial for both rivaroxaban (0.26%) [Source: R-8568, CTD Module 5.3.5.3, Module 2.7.4].

In the PIONEER AF-PCI study (SN 16523), a total of 9 patients had fatal treatment-emergent bleeding events; 3 were gastrointestinal bleeding events (1 in each treatment strategy group), 1 was an intra-abdominal bleeding event (VKA group), and 5 were intracranial bleeding

events (1 in rivaroxaban 15 mg once daily group, 1 in rivaroxaban 2.5 mg twice daily/15 mg once daily group, and 3 in the VKA group) [Source: R-11826 /Table 19].

In the MAGELLAN study (SN 12839), during the rivaroxaban-enoxaparin/placebo treatment phase (Day 1 to Day 35), a total of 8 (0.1%) patients were reported with treatment-emergent fatal bleeding events, 7 in the rivaroxaban group (2 intracranial, 1 retroperitoneal, 1 GI, 3 pulmonary) and 1 in the enoxaparin group (tracheal) [Source: A51599, Module 5.3.5.4]. In the rivaroxaban group three cases (Patients [redacted]) of treatment-emergent pulmonary haemorrhage with fatal outcome had been reported in patients with concomitant bronchiectasis, history of previous haemoptysis, lung cancer or tuberculosis.

The frequency of fatal bleeding events in the ATLAS ACS 2–TIMI 51 study was numerically lower for the rivaroxaban 2.5 mg group compared with placebo (0.1% vs. 0.2%) and numerically higher for the rivaroxaban 5 mg dose (0.3%) compared with the 2.5 mg dose and placebo [Source: R-8673, Module 5.3.5.1, Table 44].

In COMPASS (SN 15786) 12 (0.1%) patients in the rivaroxaban 2.5mg bid/ASA 100mg od group,13 (0.1%) in the rivaroxaban 5mg bid group, and 8 (<0.1%) in the ASA 100mg od group had a treatment-emergent bleeding that was fatal [Source: PH-39342, Table 14.3.1/4].

In the phase III study EINSTEIN Junior (SN 14372) during the entire trial period 2 deaths occurred, both in the age cohort 12 to < 18 years of the rivaroxaban group. 1 death occurred during the main treatment period (femoral myofibrosarcoma), while the other death occurred during follow-up (Hodgkin's lymphoma). Both deaths were adjudicated as related to cancer progression, and not related to study drug. Details can be found in the respective subject narratives (Report PH-40166, Section 15 (279)).

SVII.3.1.1.1 Update on the completed Phase III program

In the recently completed phase III program, in the NAVIGATE ESUS study, the MARINER study, the COMMANDER HF study, the CASSINI study, the GALILEO study, and the VOYAGER PAD study the defined safety outcome was 'bleeding'.

In NAVIGATE ESUS the safety objective was to document the incidence of clinically relevant bleeding. The primary safety variable was the time from randomization to time of first occurrence of a major bleeding (ISTH) defined as a bleeding event.

In MARINER the 'principal safety outcome' was major bleeding by ISTH criteria. Bleeding events were categorized into major bleeding events (principal safety outcome), non-major clinically relevant bleeding events, and other bleeding events.

In COMMANDER HF the principal safety outcome was the time to the first occurrence of fatal bleeding or bleeding into a critical space with a potential for permanent disability based on the safety analysis set and on-treatment observation period.

In CASSINI the primary safety objective of this study was to assess the incidence of major bleeding (defined by ISTH). In addition, clinically relevant non-major bleeding, minor

bleeding, and composite bleeding (defined as major, clinically relevant non-major, and minor bleeding) were assessed.

In GALILEO the primary safety endpoint was a primary bleeding event (PBE), defined according to VARC definitions as the adjudicated composite of: life-threatening or disabling bleeding, major bleeding. (Valve Academic Research Consortium (classification))

In VOYAGER PAD the primary safety outcome was major bleeding events according to the TIMI classification.

NAVIGATE ESUS study (SN 16573):

Evidence source and strength of evidence: PH-41518, PH-39740 (280), randomized clinical trail.

The primary objective was to evaluate whether rivaroxaban is superior to ASA in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS.

Subjects who met all inclusion criteria and none of the exclusion criteria were randomly allocated to either rivaroxaban 15 mg OD or ASA 100 mg OD in a 1:1 ratio.

Incidence of treatment-emergent bleeding events:

In the rivaroxaban arm 442/3,562 (12.4%) compared to 279/3,559 (7.8%) in the comparator arm experienced a bleeding event (excluding lab value events) among the safety analysis set.

The incidence rate of adjudicated ISTH major bleeding events in the ITT population was significantly higher in the rivaroxaban group compared with the ASA group (Table 10–11). ISTH major bleeding events occurred in 62 subjects (1.82/100 patient-years) in the rivaroxaban group and 23 subjects (0.67/100 patient-years) in the ASA group (HR 2.72; 95% CI 1.68-4.39; p = 0.00002.

Most frequent major bleeding events:

Major Bleeding events in the rivaroxaban group and the ASA group, respectively, listed by decreasing frequency were most frequently located in the (apart from the unknown site) gastrointestinal tract (22 events for rivaroxaban, 4.4% vs. 2.1%), gingival (1.4%, 0.3%), or rectal - hemorrhoidal (0.9%, 0.5%). Bleeding events were frequent at the nasal site (2.6%, 1.9%), the skin (other than injection site) (1.9% in both treatment groups), with ecchymosis (0.7%, 0.5%), and hematoma (0.4%, 0.8%), and in the urinary tract (1.5%, 0.6%).

Onset of bleeding events – cumulative incidences (Kaplan–Meier)

The Kaplan-Meier curves for ISTH major bleeding separated early and continued to separate over time. At 1 year (365 days) post-randomization, the Kaplan-Meier cumulative incidence risk for ISTH major bleeding events for subjects randomized to rivaroxaban was 2.0%; and for ASA it was 0.6%.

Fatal Bleeding

Per adjudication of ISTH major bleeding events the primary safety outcome was n=62 (1.7%) versus n=23 (0.6%) HR 2.72 (CI 95% 1.68;4.39), p=0.00002, and for fatal bleeding it was n=4 (0.1%) versus n=1 (<0.1%) HR 4.01 (CI 95% 0.45;35.86), p=0.17895.

Critical Organ Bleedings and other relevant bleeding sites

For the following criteria of ISTH major bleeding events, the number of subjects with such bleeding events was generally higher in the rivaroxaban group compared with the ASA group. For symptomatic bleeding in a critical area or organ (excluding intracranial) there were 9 vs. 4 events/subjects, for symptomatic intracranial hemorrhage there were 20 vs. 5 events/subjects, for clinically overt bleeding associated with a recent decrease in the hemoglobin level of ≥ 2 g/dL compared to the most recent hemoglobin value available before the event there were 19 vs. 10 events/subjects, and for clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood there were 31 vs. 13 events/subjects.

Post-marketing data

There is no registered indication for treatment to reduce the risk of recurrent stroke and systemic embolism in patients with a recent ESUS.

Overall conclusion

Treatment with rivaroxaban was associated with a (known) higher risk of bleeding. A similar adverse event (non-bleeding) profile was observed between the 2 treatment groups. No new safety signals were uncovered for rivaroxaban.

No CSR was submitted upon agreement with EMA, results were presented in PBRER/PSUR No. 16.0 on the early stop and summary of the study, and results of the study in No. 17.0 (Procedure no.: EMEA/H/C/PSUSA/00002653/201809, period covered by the PSUR: 15 SEP 2017 – 15 SEP 2018.

MARINER study (SN 17261):

Evidence source and strength of evidence: PH-41518, R-12741 (281), randomized clinical trial

The primary objective of this study was to assess the efficacy and safety of rivaroxaban, compared with placebo in the prevention of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE could not be ruled out as the cause) post-hospital discharge in high-risk, medically ill subjects.

Subjects received double-blind treatment (oral rivaroxaban or matching placebo QD). Those subjects with a baseline CrCl of ≥50 mL/min were to receive rivaroxaban 10 mg once daily (QD) or placebo QD. A dose adjustment to rivaroxaban 7.5 mg QD was to be implemented for subjects with a baseline CrCl of ≥30 to <50 mL/min. Study drug started at randomization (Day 1) and continued until Day 45 (inclusive). The subject was assessed 30 days later for safety follow-up.

Incidence of treatment-emergent bleeding events:

In the rivaroxaban arm 177/5,982 (3.0%) compared to 119/5,980 (2.0%) in the placebo arm experienced a bleeding event (excluding lab value events) in the safety analysis set.

The number (and incidence) of the first occurrence of major bleeding was 17 (0.28%) subjects in the rivaroxaban group compared with 9 (0.15%) subjects in the placebo group, a risk difference of 0.13% (HR: 1.88; 95% CI: 0.84, 4.23; p=0.124).

A greater proportion of subjects receiving rivaroxaban had each type of major bleeding than placebo subjects. When evaluated by bleeding type, a greater proportion of subjects in the rivaroxaban group than in the placebo group had a major bleeding event of fall in hemoglobin ≥2 g/dL (14 [0.23%] subjects in the rivaroxaban group compared with 6 [0.10%] subjects in the placebo group) and transfusion of ≥2 units of packed RBCs (or whole blood) (11 [0.18%] subjects in the rivaroxaban group compared with 3 [0.05%] subjects in the placebo group).

Most frequent treatment-emergent bleeding events:

Major bleeding at a non-critical site was was most frequently reported as upper and lower gastrointestinal bleeding (hematemesis or melena), 5 (0.08%) events in the rivaroxaban group and 6 (0.10%) for upper GI bleeding in the placebo group, and 5 (0.08%) events in the rivaroxaban group and 1 (0.02%) event for lower GI bleeding in the placebo group. The most frequent non-major clinically relevant bleeding was epistaxis with 33 (0.55%) events in the rivaroxaban group, and 14 (0.23%) in the placebo group.

Onset of bleeding events – cumulative incidences (Kaplan–Meier)

Throughout the treatment period, and especially after Day 10, the cumulative risk of the first occurrence of major bleeding was higher with rivaroxaban compared with placebo. Kaplan-Meier estimates of cumulative incidences of major bleeding at day 10 were 0.12% cumulative incidence (95% CI 0.06, 0.25) for rivaroxaban and 0.10% cumulative incidence for placebo (95% CI 0.05, 0.23), and at day 45 for rivaroxaban 0.29% cumulative incidence (95% CI 0.18, 0.47) and 0.15% cumulative incidence (95% CI 0.08, 0.30) for placebo.

Fatal Bleeding

Fatal bleeding occurred in 2 subjects, both in the rivaroxaban 10 mg dose stratum. One of these fatal bleeding events was due to epistaxis, which began on Day 3, and met major bleeding criteria for a fall in hemoglobin of ≥2 g/dL. The other fatal bleeding event was due to intracranial, intraparenchymal critical site bleeding, which began on Day 38.

Critical Organ Bleedings and other relevant treatment-emergent bleeding sites

Major bleeding at a critical site was reported for 3 (0.05%) subjects in the rivaroxaban group and 2 (0.03%) subjects in the placebo group. All critical site bleeding was intracranial, including 2 subjects (1 subject in each treatment group) with intraparenchymal bleeding, 1 placebo subject with intraparenchymal and intra-ventricular bleeding, 1 rivaroxaban subject with subarachnoid bleeding, and 1 rivaroxaban subject with subdural bleeding.

Post-marketing data

There is no registered indication in the EU for treatment in high-risk medically ill patients.

Overall conclusion

A numerically greater incidence in most bleeding categories was seen in the rivaroxaban group compared with placebo. Rivaroxaban was associated with a statistically significant increase in NMCR bleeding and Other bleeding events compared with placebo. The incidence of major bleeding, major bleeding at a critical site, and fatal bleeding were all generally low with both rivaroxaban dose strata and not significantly different from placebo.

The benefit-risk analyses showed that treatment with rivaroxaban would prevent more harmful events (ie, efficacy outcome events) than it would cause (ie, bleeding events). These results suggest an overall favorable benefit-risk balance for rivaroxaban compared with placebo. This was especially true when focused on major thrombotic events that were fatal or caused potentially irreversible harm compared with critical site or fatal bleeding, particularly for subjects treated with rivaroxaban 10 mg. No new safety signals were uncovered for rivaroxaban.

No CSR was submitted upon agreement with EMA, results were presented in PBRER/PSUR No. 17.0 and No. 18.0 (Procedure no.: EMEA/H/C/PSUSA/00002653/201909, Period covered by the PSUR: 15 SEP 2018 - 15 SEP 2019).

COMMANDER HF study (SN 16302):

Evidence source and strength of evidence: PH-41518, R-12742 (282), randomized clinical trial.

The primary objective was to demonstrate that rivaroxaban is superior to placebo in subjects with heart failure (HF) and significant coronary artery disease (CAD), who were receiving standard care, in reducing the risk of the composite of all-cause mortality (ACM), myocardial infarction (MI), or stroke following an index event.

Incidence of treatment-emergent bleeding events:

In the rivaroxaban arm 287/2,488 (11.5%) patients compared to 167/2,509 (6.7%) in the placebo arm experienced a bleeding event (excluding lab value events) in the safety analysis set.

The bleeding events associated with the principal safety outcome (ie, the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability) occurred in relatively few subjects (41 subjects) and there was no statistically significant differences between the 2 treatment groups: 18 subjects in the rivaroxaban group and 23 subjects in the placebo group (incidence rate per 100 patient-years: 0.44 vs 0.55; HR 0.80; 95% CI: 0.43 to 1.49; p=0.484).

Subjects in the rivaroxaban group had more bleeding events requiring hospitalization than subjects in the placebo group (incidence rate per 100 patient-years: 1.52 vs 1.16, HR: 1.30; 95% CI: 0.89 to 1.90, p=0.170), but there was no statistically significant difference between

the groups. The most frequent site of bleeding was upper GI with an incidence rate of 0.8% in the rivaroxaban group and 0.5% in the placebo group.

Most frequent treatment-emergent bleeding events:

The most frequent bleeding events were epistaxis with 51 (2.0%) for rivaroxaban and 26 (1.0%) for placebo, Skin (Ecchymosis Other Than Instrumented Site) with 48(1.9%) for rivaroxaban and 30(1.2%) for placebo and GI-tract bleeding with 30 (1.2%) upper GI-tract bleedings (hematemesis/melena) for rivaroxaban, and 14 (0.6%) for placebo.

Onset of bleeding events – cumulative rates (Kaplan–Meier)

The Kaplan-Meier cumulative risk of treatment-emergent bleeding (principal safety outcome: fatal bleeding or bleeding into a critical space with a potential for permanent disability) for the safety analysis set and on-treatment observation period at day 360 was 0.54% (95% CI: 0.30, 0.98), and 0.76% (95% CI: 0.47, 1.25) for the placebo arm.

Fatal Bleeding

The overall incidence of on-treatment fatal bleeding events was low with 9 fatal bleeding events in each treatment group (0.4%) [event rate per 100 patient-years: 0.22 vs 0.22; HR: 1.03; 95% CI: 0.41 to 2.59; p= 0.951]) but fewer critical space bleeding events occurred in the rivaroxaban group compared with the placebo group (event rate per 100 patient-years: 0.32 vs 0.48; HR: 0.67; 95% CI: 0.33 to 1.34; p=0.253).. There were 10 fatal bleeding events, in Category 1 (Any ISTH major bleeding event considered to be the primary cause of death by the investigator): (3 [0.1%] in the rivaroxaban group and 7 [0.3%] in the placebo group). Bleeding sites associated with these fatal events included intracranial, retroperitoneal and other for the rivaroxaban group and upper GI and intracranial for the placebo group. Fatal bleeding events in Category 2 (Any ISTH major bleeding event not considered to be the primary cause of death by the investigator but results in death within 7 days) included 6 [0.2%] in the rivaroxaban group (bleeding sites: bleeding associated with non-cardiac surgery, upper GI, lower GI and intracranial) and 2 (0.1%) in the placebo group (bleeding sites: intracranial and puncture site).

Critical Organ Bleedings

The incidence of bleeding into a critical space with the potential for permanent disability by bleeding site for the safety analysis set and on-treatment observation period was low. The majority of the critical space bleeding events were intracranial (27/33, 82%). There were fewer intracranial bleeding events in the rivaroxaban group (n=9) compared with the placebo group (n=18). There were 9 (0.4%) intracranial, 3 (0.1%) intraocular and 1 (<0.1%) retroperitoneal bleedings in the rivaroxaban group, compared to 18 (0.7%) intracranial, and 2 (0.1%) intraocular bleedings in the placebo group.

Post-marketing data

There is no registered indication for treatment in subjects with heart failure and significant CAD following an episode of decompensation.

Overall conclusion

There was no statistically significant difference between the 2 treatment groups for the principal safety outcome of fatal or critical organ bleeding (event rate per 100 patient-years: 0.44 vs 0.55, HR 0.80; 95% CI: 0.43 to 1.49, p=0.484) and the treatment effect was generally consistent across the pre-specified subgroups. Subjects in the rivaroxaban group had a statistically significant higher risk of having an ISTH major bleeding event compared with those in the placebo group. This significance was primarily driven by the ISTH major bleeding criterion of hemoglobin drops. Incidence of any treatment-emergent bleeding events based on AEs reported during the study were numerically higher in the rivaroxaban group compared with the placebo group. No new safety signals were uncovered for rivaroxaban.

The CSR submission to EMA via Type II variation (Procedure no.: EMEA/H/C/00944/II/064) was on 6 FEB 2019; CHMP opinion with agreed label update on 25 JUL 2019.

CASSINI study (SN 18262):

Evidence source and strength of evidence: PH-41518, R-12891 (283), randomized clinical trial

The primary efficacy objective was to demonstrate that rivaroxaban is superior to placebo for reducing the risk of the primary composite outcome as defined by objectively confirmed symptomatic lower extremity proximal deep vein thrombosis (DVT), asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal pulmonary embolism (PE), incidental PE, and venous thromboembolism (VTE)-related death in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who were at high risk of developing a VTE.

Subjects received double-blind treatment (oral rivaroxaban 10 mg or matching placebo BID). Subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups, the rivaroxaban arm with 10 mg orally once daily for 180 days or the placebo arm orally once daily for 180 days.

Incidence of treatment-emergent bleeding events:

Overall, in the rivaroxaban arm 83/405 (20.5%) compared to 52/404 (12.9%) subjects in the placebo arm experienced a bleeding event (excluding lab value events) in the safety analysis set. Only events that were identified as ISTH major bleeding or clinically relevant non-major bleeding by a trigger algorithm were sent to the CEC for adjudication.

The primary safety endpoint, major bleeding as defined by ISTH, occurred in 8 (1.98%) subjects in the rivaroxaban 10 mg group and in 4 (0.99%) subjects in the placebo group. For the primary safety endpoint, time to first occurrence of ISTH major bleeding event, the rivaroxaban 10 mg group was compared with the placebo group which yielded a HR of 1.96 (95% CI: 0.59, 6.49). Clinically relevant non-major bleeding occurred in 11 (2.72%) subjects in the rivaroxaban 10 mg group and 8 (1.98%) subjects in the placebo group, HR 1.34 (CI % 0.54, 3.32).

Most frequent treatment-emergent bleeding events:

In both treatment groups the most frequently reported bleeding events by primary location were nasal, 28 (6.9%) in the rivaroxaban group versus 27 (6.7%) in the placebo group, and gastrointestinal localization, 7 (1.7%) versus 5 (1.2%) in the upper GI tract, 15 (3.7%) versus 9 (2.2%) in the lower GI tract.

Onset of bleeding events – cumulative incidences (Kaplan–Meier)

The Kaplan-Meier estimates of cumulative incidences for the primary safety endpoint of ISTH major bleeding during the on-treatment observation period based on the safety analysis population at day 180 were 2.51 % (95% CI 1.25, 4.99) in the rivaroxaban group, and 1.12 % (95% CI 0.42, 2.97) in the placebo group.

Fatal Bleeding

One fatal bleeding event, n=1 (0.2%), (upper gastrointestinal) occurred in a subject diagnosed with gastric/GE junction TNM Stage IV cancer in the rivaroxaban 10 mg group.

Critical Organ Bleedings and other relevant treatment-emergent bleeding sites

There were 4 subjects who had non-fatal critical organ bleeding events: intraocular retinal bleeding in 1 subject in each treatment group and 2 intracranial (1 hemorrhagic and 1 subarachnoid) bleedings, both reported in subjects in the rivaroxaban 10 mg group.

Post-marketing data

There is no registered indication for treatment in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who were at high risk of developing a VTE.

Overall conclusion

Overall, the number of events and incidence rates for the primary safety endpoint of ISTH major bleeding were numerically low and lower in the placebo group compared with the rivaroxaban 10 mg group for all subgroups.

Only a 1% absolute increase in major bleeding was reported, with an overall incidence of major bleeding of less than 2% in the rivaroxaban group. The overall balance of benefit and risk for the use of rivaroxaban is positive in cancer patients receiving systemic cancer therapy who are at high risk for VTE and supports its use in this patient population.

The overall safety profile of rivaroxaban observed in this population of cancer patients receiving systemic cancer therapy who are at high risk for VTE was favorable both in terms of the risk of bleeding and other AE profile.

The CSR submission to EMA via Typ II variation (Procedure no.: EMEA/H/C/00944/II/079) was on 12 JUN 2020; a Request for Supplementary Information was received on 05 SEP 2020.

GALILEO study (SN 17938):

Evidence source and strength of evidence: PH-41518, PH-40182 (284), randomized clinical trial.

The primary objective was to assess whether a rivaroxaban-based anticoagulation strategy, following successful TAVR, compared to an antiplatelet-based strategy, is superior in reducing death or first thromboembolic events (DTE). This comparison was hierarchically preceded by a non-inferiority test that had to be satisfied (i.e., the null hypothesis had to be rejected).

In the rivaroxaban arm drug, 10 mg OD, was started at the time of randomization. ASA 75 to 100 mg OD was continued unchanged or to be started immediately after randomization. In the antiplatelet arm clopidogrel 75 mg OD and ASA 75 to 100 mg OD were to be continued unchanged.

In either strategy, the selection of the ASA dose (75-100 mg) was left at the discretion of the treating physician. In each strategy, one antiplatelet therapy agent was dropped after 90 days following randomization: In the rivaroxaban arm, ASA was discontinued after 90 days and rivaroxaban continued. While, in the antiplatelet arm, clopidogrel had to be discontinued after 90 days and ASA was to be continued.

Incidence of bleeding events:

In the rivaroxaban arm 201/801 (25.1%) compared to 135/807 (16.7%) in the comparator/control arm experienced a treatment-emergent bleeding event (excluding lab value events) in the safety analysis set.

In the Full analysis set considering the ITT data scope the primary safety outcome "primary bleeding event" (PBE) combined the VARC bleeding categories "life-threatening or disabling bleeding" and "major bleeding". A total of 77 study subjects (4.7%) had experienced a PBE, 46 subjects (5.6%) in the rivaroxaban arm and 31 subjects (3.8%) in the antiplatelet arm. This difference resulted in a HR estimate of 1.50 with an associated 95%-CI of [0.95; 2.37] (p=0.07745). Separated by single components, the incidences of life-threatening or disabling bleeds were similar in the treatment arms (2.2% and 2.1%, respectively), and the HR close to 1 (HR=1.06, 95%-CI: [0.55; 2.06], p=0.85843).

Most frequent bleeding events:

Overall, the 3 most common bleedings sites in either treatment arm were located on the skin (69 subjects [8.4%] in the rivaroxaban arm and 53 subjects [6.5%] in the antiplatelet arm), in the GI tract (63 subjects [7.6%] in the rivaroxaban arm and 29 subjects [3.5%] in the antiplatelet arm), and nose bleeds (51 subjects [6.2%] in the rivaroxaban arm and 32 subjects [3.9%] in the antiplatelet arm). It is to note that, as per the study protocol, mild to moderate bruising or ecchymosis within 7 days after TAVR were regarded as expected events, and therefore, should not be reported as AE.

Onset of bleeding events – cumulative incidences (Kaplan–Meier)

The Kaplan-Meier cumulative risk diverged early post randomization and remained higher in the rivaroxaban arm throughout Day 720 (up to a 2.6% higher cumulative risk for the rivaroxaban arm [observed at Day 360]). The cumulative incidences at Day 720 were 6.9% (95%-CI: [4.7; 9.1]) in the rivaroxaban arm and 5.3% (95%-CI: [3.2; 7.3]) in the antiplatelet arm.

Fatal Bleeding

Fatal bleedings (BARC Type 5) within that category were infrequent and reported only in 2 subjects in the rivaroxaban arm and in 1 subject in the antiplatelet arm.

Post-marketing data

There is no registered indication for treatment in patients having recently undergone transcatheter aortic valve replacement (TAVR). Rivaroxaban is not recommended for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR) based on data from the GALILEO study. The safety and efficacy of rivaroxaban have not been studied in patients with other prosthetic heart valves or other valve procedures. To address the potential risk for off-label use in patients undergoing TAVR, a DHPC was disseminated in the EU.

Overall conclusion

The pre-specified primary bleeding events occurred more frequently in the rivaroxaban arm than in the antiplatelet arm (46 subjects [5.6%]) vs. 31 subjects [3.8%]; FAS, ITT data scope). The estimated HR was 1.50 (95%-CI: [0.95; 2.37], p=0.07745). Comprehensive subgroup analyses of the PBE were not indicative of clinically meaningful treatment differences across the analyzed subgroups. Bleeding incidences pertaining to the more severe bleeding categories within the various classification systems tended to be low in either treatment group, fatal and life-threatening or disabling bleeds were similarly infrequent in either treatment arm. No new safety signals were uncovered for rivaroxaban.

The CSR included in response to PRAC on 09 APR 2019 (no separate CSR submission to EMA required as agreed with EMA); final PRAC AR received on 28 Jun 2019 with recommendation for label update, which was implemented.

VOYAGER PAD study (SN 17454)

Evidence source and strength of evidence: PH-41518, PH-40164 (285), randomized clinical trial.

The primary objective was to evaluate whether rivaroxaban added to acetylsalicylic acid (ASA) is superior to ASA alone in reducing the risk of major thrombotic vascular events (defined as myocardial infarction (MI), ischemic stroke, cardiovascular (CV) death, acute limb ischemia (ALI), and major amputation of a vascular etiology) in symptomatic PAD patients undergoing lower extremity revascularization procedure.

Study treatment assignment was double-blind. Study treatment consisted of study medication (rivaroxaban or matching placebo) in addition to study ASA, which was also dispensed by the study.

Incidence of treatment-emergent bleeding events:

In the rivaroxaban arm 546/3256 (16.8%) compared to 354/3248 (10.9%) in the placebo arm experienced a bleeding event (excluding lab value events) in the safety analysis set.

62 (1.9%) subjects in the rivaroxaban + ASA group and 44 (1.4%) subjects in the placebo + ASA group had TIMI major bleeding events.

There was a 1.43-fold increase in TIMI major bleeding events with rivaroxaban + ASA in comparison with placebo + ASA (hazard ratio; 95% CI 0.97 – 2.10). There was no increase in fatal or intracranial bleeding events compared with placebo + ASA.

Most frequent treatment-emergent bleeding events:

The three most frequent sites of bleeding overall were gastrointestinal tract bleeding- gastric in 17 subjects overall (0.3%); i.e. in 10 (0.3%) of the subjects in the rivaroxaban + ASA group and 7 (0.2%) of the subjects in the placebo group, blood vessel/ vascular procedure site in 16 subjects overall (0.2%); i.e. in 8 subjects (0.2%) of the subjects in each of the treatment groups, and intracranial bleeding – intraparenchymal hemorrhage in overall 12 subjects (0.2%); i.e. in 5 subjects (0.2%) of the subjects in the rivaroxaban + ASA group and 7 (0.2%) of the subjects in the placebo group). Gastrointestinal tract – other bleeding was more frequent in the rivaroxaban + ASA group with 8 subjects (0.2%) compared to none in the placebo group, gastrointestinal tract bleeding- large intestine / colon was reported of 6 (0.2%) subjects in the rivaroxaban + ASA group and none of the placebo group.

Onset of bleeding events – cumulative incidence risk (Kaplan–Meier)

The cumulative incidence risk of treatment-emergent TIMI major bleedings is higher in the rivaroxaban + ASA group compared with the placebo + ASA group. Kaplan-Meier rates at 1 year (365 days post-randomization) were 1.23% (95% CI 0.89-1.70) and 0.75% (95% CI 0.50-1.14), respectively; and at 3 years (1095 days post-randomization) 2.65% (95% CI 2.00-3.50) and 1.87% (95% CI 1.35-2.59), respectively.

Fatal Bleeding

The number of treatment-emergent fatal bleeding events (all non-CABG) were the same for the rivaroxaban + ASA and placebo + ASA groups with comparable HRs for all subgroups. Overall, 6 (0.2%) fatal events in each treatment group; HR 1.02 (95% CI 0.33 -3.15) occurred.

Critical Organ Bleedings and other relevant treatment-emergent bleeding sites

There was more bleeding in the rivaroxaban + ASA group compared to placebo + ASA for ISTH non-fatal non critical organ bleeding (fall in Hb ≥2g/dl or hematocrit ≥6% and/or transfusion ≥2 units), and ISTH fatal/non-fatal gastrointestinal bleeding. ISTH non-fatal critical organ bleeding was not different in the treatment groups, but HRs for ISTH fatal and ISTH fatal intracranial bleeding were again numerically in favor of rivaroxaban + ASA.

Post-marketing data

There is no registered indication for treatment in symptomatic PAD patients having undergone recent lower extremity revascularization procedure.

Overall conclusion

There was a 1.43-fold increase in TIMI major bleeding events with rivaroxaban + ASA in comparison with placebo + ASA (95% CI 0.97 – 2.10). There was no increase in fatal or intracranial bleeding events compared with placebo + ASA in the on-treatment data scope.

The CSR submission to EMA via Type II variation (Procedure no.: EMEA/H/C/00944/II/081) was on 26 AUG 2020.

SVII.3.1.2 Important Potential risk: Embryo-fetal toxicity

General information:

According to the American College of Chest Physicians (ACCP) guidelines, anticoagulant therapy is indicated during pregnancy for the prevention and treatment of VTE, for the prevention and treatment of systemic embolism in patients with mechanical heart valves and, in combination with aspirin, for the prevention of recurrent pregnancy loss in women with antiphospholipid antibodies (286). In the recent VTE treatment guidelines of the ACCP, LMWH is listed as the preferred anticoagulant for use in patients who are pregnant or likely to become pregnant, because of the potential for other agents to cross the placenta (58). European Society of Cardiology guidelines for the treatment of PE recommend a weight-adjusted dose of LMWH during pregnancy in patients without shock or hypotension (287).

Potential mechanism:

The inclusion of embryo-fetal toxicity as important potential risk was only based on pre-clinical data. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-fetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations.

As intra-uterine bleeding is considered the primary cause of maternal and fetal effects in animal studies, and this effect is related to the mode of action of rivaroxaban, relevance for humans has to be expected. Pathomechanism of embryo-fetal toxicity for rivaroxaban are not known.

Evidence source and strength of evidence:

Pregnant women were excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC, due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta. Therefore, the overall experience is limited.

On a cumulative basis and across all sources, there were 609 valid case reports of maternal drug exposure during pregnancy (PSUR No.23.1). The duration of exposure during pregnancy in these cases ranged from 1 day to ≥ 36.5 weeks. In one case, exposure occurred throughout pregnancy (trimesters 1–3 until the day of delivery) but the duration of the pregnancy was not reported. Outcomes are summarized in the following Table.

XARELTO®
(Rivaroxaban)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII-5: Cumulative overview of outcomes of cases of maternal rivaroxaban exposure during pregnancy

Outcome	Number of cases	Duration of exposure
Live birth	**176**	**1 d to 36.5 GW or throughout pregnancy**
Healthy	96	~5 d to ≥ 25 GW or throughout pregnancy
Relevant findings[a]	12	2 + 2 GW to 21 GW
IUGR without relevant findings	5	1 GW to 3.5 months
Transient findings/premature birth only[b]	14	6 d to 36.5 GW
Findings unclassified if relevant	1	5 GW
Outcome not further specified[c]	48	1 d to 25 + 1 GW
Abortion	**113**	**2 d to 18 GW**
Spontaneous[d]	63	2 d to 18 GW
Therapeutic[e]	5	1 + 3 GW to 4 + 6 GW
Elective[f]	45	3 d to 12 GW
Stillbirth	**2**	**Not reported**
Unknown[g]	**312**	**1 d to 22 GW**
Other[h]	**6**	**3 + 6 GW[i]**

[a]Confirmed (n = 11) or suspected (n = 1) relevant findings; includes 2 cases of implied live birth (one with ventricular septal defect and birth weight of 3 kg, and one with congenital pyelocaliectasis, congenital central nervous system anomaly and cleft lip).
[b]Premature birth, n = 5 (including 1 case of implied live birth [child born 6 weeks early by Cesarean section]); low birth weight, n = 3; other transient findings, n = 9. Some neonates had more than one transient finding.
[c]Includes 5 cases of implied live birth.
[d]Of the 63 cases of spontaneous abortion, 3 reported relevant findings and 2 reported IUGR.
[e]The reason for therapeutic abortion was maternal health problems in 1 case (the mother had recurrent DVT), relevant findings in the fetus in 3 cases and unclear in 1 case.
[f]Of the 45 cases of elective abortion, 1 reported findings related to the fetus and 1 reported heavy post-procedural uterine bleeding in the mother.
[g]Pregnancies with unknown outcomes included an ongoing pregnancy, 1 report of antiplacental syndrome, 1 report of possible subchorionic hemorrhage, and 1 case in which the mother had cramping/bleeding at the time of the positive pregnancy test but a normal subsequent ultrasound scan.
[h]Other outcomes were as follows: death of the mother from breast cancer 42 days after becoming pregnant (n = 1); left ventricular hypoplasia and oligohydramnios in one of a pair of biamniotic non-identical twins at 20 weeks (final outcome of pregnancy not yet known); 3 ectopic pregnancies; and 1 case of twin pregnancy with rivaroxaban having been stopped ~2 months before conception; the outcomes were fetal death of 1 twin at 28 GW and live birth of the other at 32 GW followed by sudden death at 4 weeks of age.
[i]Duration of exposure was only reported in one case.
GW, gestational weeks; IUGR, intrauterine growth restriction
(Table taken from PSUR No. 23.1)

Characterization of risk:

As pregnant women were excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC no incidence rates can be provided.

Risk factors and risk groups:

The majority of patients receiving rivaroxaban are elderly patients. Only in patients with ACS, and those undergoing treatment for VTE, there may be a higher possibility of women with child-bearing potential receiving rivaroxaban.

A large population-based study concluded that a history of DVT is an independent risk factor for spontaneous preterm delivery (288). This study compared all pregnancies of patients with and without a history of DVT: there were 212,086 deliveries, of which 122 (0.06%) occurred in patients with a history of DVT. No significant differences were noted between the groups regarding perinatal outcomes such as low Apgar scores, congenital malformations or perinatal mortality.

Ben-Joseph et al. determined that patients with a history of DVT were more likely to have caesarean deliveries (OR, 2.6; 95% CI, 1.8–3.8; $p < 0.001$) than non-DVT patients, and DVT was an independent risk factor for preterm birth (OR, 1.8; 95% CI, 1.1–2.9; $p = 0.033$) (288). In a study of 395 patients with a history of VTE and 313 control women stillbirth was slightly more frequent in patients (4.3%) than in controls (3.2%); the difference was not statistically significant. Miscarriage was equally frequent between groups (289).

A population-based study in the USA showed that pregnant women with AF (n = 157) were more likely to have babies that needed to be admitted to the neonatal intensive care unit (NICU) than pregnant women without AF (n = 264 573) (NICU admissions: 10.8% vs 5.1%; $p = 0.003$) (290).

Preventability:

No studies have been performed to assess whether the reproductive toxicity related to the pharmacological mode of action of rivaroxaban can be prevented in pregnant patients receiving rivaroxaban. Women in the reproductive age should avoid becoming pregnant when taking rivaroxaban and rivaroxaban is contraindicated in pregnancy according to the SmPC.

Impact on the benefit-risk balance:

The impact on the benefit-risk balance is considered low, as pregnant women are excluded from clinical trials and contraceptive measures need to be applied in clinical studies, and rivaroxaban is contraindicated in pregnancy.

Public health impact:

A study of pregnancy outcome in patients exposed to direct oral anticoagulants did not indicate that DOAC exposure in pregnancy carries a high risk of embryopathy or that DOAC exposure per se should be used to direct patient counselling towards pregnancy termination. Due to the fact that the current label contraindicates pregnancy and that the vast majority of patients exposed to Xarelto are not of child-bearing age, the public health impact is therefore considered to be low. From the currently available human study data and post-marketing reporting, there is no evidence of embryo-fetal toxicity after inadvertent use of rivaroxaban in therapeutic doses during the first trimester of pregnancy [PBRER/PSUR No. 16.0].

Based on the review of information from PBRER/PSUR No. 23.0; DLP 15 SEP 2022, there are no well documented reports to indicate that rivaroxaban is associated with embryo-fetal toxicity) [PBRER/PSUR No. 23.1, 16.3.1.1 and 16.4.2 on the potential risk of Embryo-fetal toxicity.

Conclusion

From the currently available human study data and cumulative post-marketing reporting, there is no evidence of embryo-fetal toxicity after inadvertent use of rivaroxaban in therapeutic doses during the first trimester of pregnancy. Exposure beyond the first trimester occurs infrequently, but available data do not indicate a safety concern. In particular, no case of relevant bleeding complications that would be attributable to rivaroxaban exposure was received.

SVII.3.1.3 Important Potential risk: Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension

General information:

For children too young or unable to swallow rivaroxaban tablets, the drug will be administered orally as a suspension. This suspension needs to be prepared by the child's caregiver using the drug-device combination kit. Errors in the preparation of the suspension, as well as its subsequent application, may result in over- or underdosing. This has carefully been assessed during the development. The evaluation showed that the results match acceptance criteria for dosing accuracy of the granules for oral suspension. Nevertheless, it has to be considered that this still can carry a certain risk for overdosing and underdosing in the market.

Evidence source and strength of evidence:

Very few events of accidental over- or underdosing of study drug were recorded in the pivotal phase III study EINSTEIN Junior; this does not allow deriving a pattern or trend leading to either sporadic or systematic overdosing or underdosing of study drug with either the liquid or the tablet formulation of rivaroxaban.

The drug-device combination product together with clear instructions to caregivers ensured acceptable accuracy in dosing and resulted in few events of over- or underdosing in the pivotal phase III study EINSTEIN Junior.

Impact on the benefit-risk balance:

The impact on the benefit-risk balance is considered low, as none of the reported events of accidental overdosing or underdosing of study drug were reported as directly associated with other adverse events in the pivotal phase III study EINSTEIN Junior.

SVII.3.2 Presentation of the missing information

Missing information: Remedial pro-coagulant therapy for excessive haemorrhage

Evidence source: Clinical life scenarios, requests

Population in need of further characterisation: Health care professionals, patients

Anticipated risk/consequence of the missing information: Increased risk of bleeding, limited treatment options

Missing information: **Patients with atrial fibrillation (AF) and a prosthetic heart valve**

Evidence source: Patients with prosthetic heart valves not studied

Population in need of further characterization: respective patients, health care professionals

Anticipated risk/consequence: Inadequate anticoagulation therapy

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Part II: Module SVIII - Summary of the safety concerns

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity • Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and prosthetic heart valve

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance was and will be conducted for rivaroxaban as detailed in corresponding pharmacovigilance procedures that are in place at Bayer. These routine activities include the collection, follow-up, evaluation and expedited reporting of individual case reports from all respective sources, ongoing monitoring and signal detection activities, preparation of PBRERs/PSURs, and initiation of label changes as required, and are described in applicable Standard Operating Procedures.

III.1.1 Specific adverse reaction follow-up questionnaires

The internal User Guidance in its updated version, valid from 25 MAR 2021, mentioned the following Specific Questionnaires:

i. LIVER-RELATED ADVERSE EVENTS

ii. RENAL IMPAIRMENT/RENAL FAILURE

iii. RECONSTITUTION OF SUSPENSION AND DOSING WITH RIVAROXABAN GRANULES FOR ORAL SUSPENSION

Upon recommendation in the final Assessemnet Report on PSUR No. 19.0. on 25 MAR 2021 (Procedure no.: EMEA/H/C/PSUSA/00002653/202009) the Follow-up Questionnaires for Severe Hypersensitivity and Severe Skin Reactions were suspended.

III.1.2 Other forms of routine pharmacovigilance activities

None.

III.2 Additional pharmacovigilance activities

An integrated PASS programme was created for the use of rivaroxaban in the long-term indications (DVT, PE, SPAF and ACS). This programme consists of the following Category 1 PASS studies:

- Four healthcare database studies in the UK, Germany, Sweden and the Netherlands comprise cohort studies for the description of drug utilisation as well as analyses to evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (deep vein thrombosis [DVT] and pulmonary embolism [PE], ischaemic stroke, myocardial infarction and death). The study protocols are analogous to each other. All of these studies have been finalized now.
- Three active surveillance studies with a two-component prescription monitoring event (PEM) design in the UK. In this active surveillance design, follow-up questionnaires were sent to each prescribing physician at pre-specified intervals to obtain outcome information. These studies were initiated to proactively monitor the short-term safety

and drug utilization of rivaroxaban with the focus on bleeding events. The three protocols are complementary to each other. All of these studies have been finalized now.

- In addition, one Category 3 PASS study to assess the effectiveness of additional risk minimization activities in place for rivaroxaban (i.e. Patient Alert Card and Prescriber Guide) has been completed and the final study report was submitted to EMA in JUN 2020 (EMEA/H/C/000944/II/0080).
- In the paediatric indication "Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence" a Category 3 PASS observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS) is conducted (EMEA/H/C/000944/MEA/049.3).

The Tabulated Summary of On-going and Completed Pharmacovigilance Study Programme is provided in Annex 2.

The integrated study programme is summarized as follows:

Category 1 PASS Studies

1) Study short name and title: **SN 16647 - Drug Utilization and Outcome Studies in the UK**

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the United Kingdom (EUPAS11299)

Rationale and study objectives:

This study aims to provide a detailed description of patients who are prescribed oral rivaroxaban for the first time and those who are prescribed standard of care (warfarin) for the first time, to describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment), and to determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it evaluates safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban and patients receiving current standard of care. The study was conducted in collaboration with the Fundación Centro Español de Investigación Farmacoepidemiológica (CEIFE), Spain.

Study design:

This study has a cohort design.

Study population:

The study population includes all patients aged two years and above who have been enrolled in The Health Improvement Network (THIN) database for at least 1 year and had their first prescription recorded in the database at least 1 year before study entry. First time users of rivaroxaban or standard of care are identified by the first prescription of the respective drug during the study period.

Milestones:

Data collection started from 01 JAN 2012 and ended on 31 DEC 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017. The final study report was submitted to the European Medicines Agency in DEC 2020 (EMEA/H/C/PSR/S/0027).

2) Study short name and title: **SN 16159 - Drug Utilization and Outcome Studies in Germany**

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EUPAS11145)

Rationale and study objectives:

This study aims to provide a detailed description of patients who are prescribed oral rivaroxaban for the first time and those who are prescribed standard of care (phenprocoumon) for the first time, to describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment) and to determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it evaluates safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban and patients receiving current standard of care. The study was conducted in collaboration with the Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Germany.

Study design:

This study has a cohort design.

Study population:

The study population includes all patients aged 2 years and above who have been enrolled in the claims-based German Pharmacoepidemiological Research Database (GePaRD) for at least one year and had their first prescription recorded in the database at least 1 year before study entry. First time users of rivaroxaban or standard of care are identified by the first prescription of the respective drug during the study period.

Milestones:

Data collection started from 09 DEC 2011 (following marketing authorization in Germany) and ended on 31 DEC, 2017. Interim reports were submitted to EMA Q4 2015 and Q4 2017.

The final study report was submitted to the European Medicines Agency in DEC 2020 (EMEA/H/C/PSR/S/0027).

3) Study short name and title: **SN 16646 - Drug Utilization and Outcome Studies in The Netherlands**

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in The Netherlands (EUPAS11141)

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Rationale and study objectives:

This study aims to provide a detailed description of patients who are prescribed oral rivaroxaban for the first time and those who are prescribed standard of care (acenocoumarol or phenprocoumon) for the first time, to describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment) and to determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it evaluates safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban and patients receiving current standard of care. The study was conducted in collaboration with the PHARMO Institute for Drug Outcomes Research, The Netherlands.

Study design:

This study has a cohort design.

Study population:

Study drug users are selected form the outpatient pharmacy database in the PHARMO Database Network. All patients aged 2 years and above who have been registered in the database for at least 1 year before the index date are included. For part of this population, data from general practice is available, which is crucial for the assignment of the indication of use. First time users of rivaroxaban or standard of care are identified by the first dispensing of the respective drug during the study period.

Milestones:

Data collection started from 10 DEC 2011 (following market authorization in The Netherlands) and ended on 31 DEC 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017.The final study report was submitted to the European Medicines Agency in DEC 2020 (EMEA/H/C/PSR/S/0027).

4) Study short name and title: **SN 17543 - Drug Utilization and Outcome Studies in Sweden**

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Sweden (EUPAS9895)

Rationale and study objectives:

This study aims to provide a detailed description of patients who are prescribed oral rivaroxaban for the first time and those who are prescribed standard of care (warfarin) for the first time, to describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment) and to determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it evaluates safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban and patients receiving current standard of care. The study was conducted in collaboration with Leif Friberg, MD, PhD, Friberg Research AB, Sweden.

Study design:

This study has a cohort design.

Study population:

The study population includes all patients included in the Swedish national health registers (The Drug, Patient and Cause of Death Registers). First time users of rivaroxaban or warfarin are identified by the first prescription of the respective drug during the study period.

Milestones:

Data collection started from 09 DEC 2011 (when rivaroxaban received marketing authorization in Sweden) and ended on 31 DEC 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017.

The final study report was submitted to the European Medicines Agency in DEC 2020 (EMEA/H/C/PSR/S/0027).

5) Study short name and title: **SN 16164 – Modified Prescription Event Monitoring (M-PEM)**

An observational post-authorization Modified Prescription-Event Monitoring safety study to monitor the safety and utilisation of rivaroxaban (XARELTO®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England, extended to include Acute Coronary Syndrome patients (EUPAS15961).

Rationale and study objectives:

This study aims to evaluate the utilisation and long-term safety of rivaroxaban in new-user patients in primary care. Prescriptions of rivaroxaban are identified from dispensed National Health Service (NHS) prescription data. Prescribing doctors are sent M-PEM questionnaires at 3 and 12 months after prescription to gather information on treatment prescribing patterns, acute adverse events and baseline patient characteristics. The primary objective is to quantify the cumulative incidence of major haemorrhage (gastrointestinal, urogenital and intracranial sites). Secondary and exploratory objectives aim to explore the prevalence of non-clinical reasons for prescribing, prognostic and clinical risk factors for haemorrhage, changes in patient health profile and the risk of non-major bleeding events. This is being conducted in collaboration with Drug Safety Research Unit (DSRU), Southampton, UK.

Study design:

This study has a cohort design and uses a prescription-event monitoring technique for cohort accrual.

Study population:

Prescriptions of rivaroxaban issued by GPs in England from JAN 2012- JUN 2016 are identified from dispensed National Health Service (NHS) prescription data, sent to the DSRU by the NHS Prescription Services (NHSRxS) in England. Patients, for whom a study

questionnaire containing useful information has been returned, are included in the study cohort.

Milestones:

Data collection started in JAN 2012 and ended in JUN 2016. Interim reports were submitted to EMA Q1 2014 and Q4 2015. The final study report was submitted in Q4 2017 (EMEA/H/C/PSR/S/0012).

6) Study short name and title: **SN 17542 – SCEM ACS Study**

An Observational Post-authorisation Safety Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilisation of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome (ACS) in England and Wales (EUPAS9977)

Rationale and study objectives:

This study monitors the short-term safety and drug utilisation of rivaroxaban after an ACS episode in the secondary care hospital setting. It aims to quantify the cumulative incidence (risk and rate) of haemorrhage (major bleeding within intracranial, gastrointestinal and urogenital organ sites) occurring during the 12-week observation period. Secondary and exploratory objectives aimed at exploring differences in the prevalence of non-clinical reasons for prescribing; identifying prognostic and clinical risk factors for the safety events of interest between rivaroxaban and a contextual cohort (patients on current standard oral antiplatelet combination therapy (at least dual therapy, but not monotherapy)); describing changes in the health profile of patients over the course of the study and investigating the risk of non-major bleeding events. This was conducted in collaboration with Drug Safety Research Unit (DSRU), Southampton, UK.

Study design:

This study has a cohort design using secondary data (medical chart review) collected at start of treatment (index date) and 12 weeks post-index date.

Study population:

Prescribers and patients in the secondary care setting in England and Wales.

Milestones:

Data collection started Q3 2015 and ended in Q1 2019 for the patients recruited during September 2015 and May 2017. Interim report was submitted to EMA Q4 2017. Final study report was submitted in Q4 2019 (EMEA/H/C/PSR/S/0024).

Category 3 PASS Studies

7) Study short name and title: **SN 16167 - Risk Minimisation Survey Study**

Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages (EUPAS3911)

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Rationale and study objectives:

This study served to evaluate the effectiveness of the additional risk minimisation tools developed for rivaroxaban, which include a Prescriber's Guide (PG) and Patient Alert Card (PAC) that aim increase awareness and understanding among physicians and patients about the potential bleeding risk during treatment with rivaroxaban. The primary objectives of the study are to measure whether physicians and patients received and used the PG and PAC, respectively, and to evaluate their awareness and understanding of the key safety messages concerning two indications: SPAF and DVT treatment and prevention of recurrent DVT and PE. Evaluation surveys were planned in 3 waves at 18 months, 3 years, and 7 years post launch. Some delays have occurred due to unplanned circumstances; the actual dates are reflected in the current version of the RMP. The patient surveys were discontinued after wave 1. This study was conducted in collaboration with RTI Health Solutions, with assistance of Kantar Health for field operations.

The PRAC concluded the current additional risk minimisation tools developed for rivaroxaban appear to aid prescribers by increasing the awareness and understanding of risks associated with rivaroxaban. No amendments regarding the educational material were proposed.

Study design:

This study has a cross-sectional design.

Study population:

Eligible physicians and patients with recent rivaroxaban experience were invited to complete a questionnaire regarding their knowledge of key safety in the rivaroxaban educational materials concerning two indications mentioned above.

Milestones:

Data collection for wave 1 took place between Q3 2014 and Q2 2015. The wave 1 interim report was submitted to EMA Q4 2015. Data collection for wave 2 started in Q1 2017 and ended in Q2 2017; the wave 2 interim report was submitted in Q2 2018. Data collection for wave 3 took place in Q1 2020 and final study report was submitted in Q2 2020 (EMEA/H/C/000944/II/0080). The PRAC concluded the current additional risk minimisation tools developed for rivaroxaban appear to aid prescribers by increasing the awareness and understanding of risks associated with rivaroxaban. No amendments regarding the educational material were proposed.

8) Study short name and title: **Paediatric Investigation Plan (PIP)**

Paediatric Investigation Plan (PIP) for 'Treatment of thromboembolic events'

Rationale and study objectives:

The Paediatric Investigation Plan for rivaroxaban encompasses nine studies, including quality related, non-clinical, and clinical studies. The study programme will evaluate the safety and efficacy of rivaroxaban in patients who are less than 18 years of age. The programme will also evaluate tolerability, pharmacokinetics and pharmacodynamics of rivaroxaban administered

as either an oral suspension or film-coated tablets in children from birth (term neonates) to less than 18 years of age who have been treated for venous thromboembolism following initiation of standard anticoagulation treatment either with subcutaneous low molecular weight heparin (LMWH), subcutaneous fondaparinux, intravenous unfractionated heparin (UFH) and/or vitamin K antagonist (VKA).

Study design:

This study programme encompasses nine studies, including quality related, non-clinical, and clinical studies, with various study designs, including active-controlled, randomized clinical trials.

Study population:

Patients younger than 18 years of age, who have acute venous thromboembolism.

Milestones:

The paediatric investigation plan programme was completed on 20 SEP 2019.

9) Study short name and title: **SN 22195 - Xarelto Paediatric VTE PASS Drug Utilization Study**

Rationale and study objectives:

An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS).

Study design:

This will be an observational, retrospective, descriptive, multi-national cohort study of children initiating anticoagulation therapy. The study will be conducted using secondary data derived from multiple data sources including electronic health records and administrative health insurance claims data in four European countries (France, Sweden, Denmark, Spain).

Study population:

The source population will consist of children aged under two years who initiate an anticoagulation therapy with rivaroxaban oral suspension or any other anticoagulation drug following a VTE diagnosis. The study population will be drawn from population-based data sources in four countries and include all patients who fulfil all inclusion and exclusion criteria during the study period. The inclusion period will start on the market launch date of rivaroxaban granules for oral suspension 1 mg/mL in the respective countries. At this stage it is assumed that the study will last at least seven years to provide enough time to ensure the achievement of the sample size. The study period would end 31 DEC 2027, with the inclusion period ending 31 DEC 2026 to allow a minimum potential follow-up of 12 months.

Milestones:

Start of data collection (date from which data extraction starts) 12 months from the PRAC endorsement of the full study protocol (Assessment Report for the Post-Authorisation

Measure MEA 049.3: CHMP adoption of conclusions: 10 Nov 2022). Five annual study progress reports (Q4 2023 – estimated Q4 2027). End of data collection (estimated Q2 2029). Final report of study results 6 months after end of data collection (estimated Q4 2029) with intention to finalise the study earlier than Q4 2029 depending on follow-up of the overall uptake of rivaroxaban oral suspension reported in annual progress reports.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban. **Xarelto Pediatric VTE PASS Drug Utilization Study:** An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (SN 22195)				
Category 3 - Required additional pharmacovigilance activities				
Xarelto Pediatric VTE PASS Drug Utilization Study (SN: 22195)	An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban granules for oral suspension in children under two years with venous thromboembolism.	**Important identified risk:** •Haemorrhage	Feasibility report	07 APR 2021
			Protocol submission	Q1 2022 (completed)
			Start of data collection: 12 months from the PRAC endorsement of the study protocol[2]	Q4 2023

[2] The number of patients for the study population actually accrued in the data sources will be monitored over time to inform the decision as to when to launch the analyses with intention to finalise the study earlier than Q4 2029 depending on follow-up of the overall uptake of rivaroxaban oral suspension reported in annual progress reports.

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Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			(10 NOV 2022)	
			Interim reports (study progress reports)[3]	Annually 1. Q4 2023 2. Q4 2024 3. Q4 2025 4.Q4 2026 5. Q4 2027
			End of data collection	Q2 2029 (estimated)
			Final report of study results (6 months after end of data collection)	Q4 2029 (estimated)

Please see Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

[3] To monitor the uptake of rivaroxaban oral suspension and follow-up the number of patients for the study population.

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

No new important risk, identified or potential, has been identified since last submission of a RMP update. Therefore, no new risk minimisation activities are lined out in this section. The routine risk minimisation measures already in place are presented in the next section.

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk	
Haemorrhage	**Routine risk communication:** SmPCs: Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interactions) Section 4.8 (Undesirable effects) Section 4.9 (Overdose) & subsection (Management of bleeding) Indication specific differences are listed in the respective SmPCs. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 (Special warnings and precautions for use), and subsections: Information on patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors is provided - monitoring for signs of bleeding complications. Information on groups of patients with an increased bleeding risk is provided. Information for surgery and interventions is provided - information on drug discontinuation. Information on patients with neuraxial (epidural/spinal) anesthesia is provided - information on monitoring of epidural or spinal hematoma Section 4.5 (Interaction with other medicinal products and other forms of interaction) Information on Pharmacokinetic interactions and Pharmacodynamic interactions, food and dairy products Section 4.9 (Overdose) Information on the management of overdose and management of bleeding complications is communicated.

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.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: Pack size limited Prescription medicine
Important potential risk	
Embryo-fetal toxicity	**Routine risk communication:** SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding): Section 5.3 (Preclinical safety data) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Section 4.6 (Pregnancy and lactation) Information: Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban; A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy **Other routine risk minimisation measures beyond the Product Information:** None
Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	**Routine risk communication:** SmPC (Xarelto 1 mg/mL granules for oral suspension) Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.5 (Nature and contents of container) Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 6.6 (Special precautions for disposal and other handling) **Other routine risk minimisation measures beyond the Product Information:** None
Missing information	
Remedial pro-coagulant therapy for excessive haemorrhage	**Routine risk communication:** SmPCs: Section 4.9 (Overdose) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Additional information provided for Management of bleeding

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.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: Prescription-only medicine Limited pack sizes
Patients with atrial fibrillation (AF) and a prosthetic heart valve	**Routine risk communication:** SmPCs: Section 4.4 (Special warnings and precaution for use) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription-only medicine Limited pack sizes

V.2 Additional risk minimisation measures

Description of additional risk minimisation measures by safety concern **important identified risk**	
Important identified risk	**Additional risk minimisation activities**
Haemorrhage	**Objectives:** The aim of the introduction of additional educational materials is to increase the awareness and reduction of the bleeding risk. The objectives of the label text are to prevent physicians from prescribing rivaroxaban to certain patient groups at high risk of bleeding, and to ensure that use of rivaroxaban in other patients with conditions or receiving treatments that can increase the risk of bleeding will be carefully monitored to minimise the risk of bleeding complications. Addionally, **educational material for prescribers** and **patient alert card** were introduced to increase awareness about the risk of bleeding during treatment with rivaroxaban. Rationale for the additional risk minimisation assessment activity: •To assess level of physicians' knowledge and understanding of key safety information as addressed in Prescriber guide •To assess level of patients' knowledge and understanding of the key safety information in Patient alert card •Continuous monitoring of bleeding events, overdose cases or cases with medication errors in drug utilisation studies with outcomes (DUS), modified prescription event monitoring studies, post-marketing non-interventional studies and detailed analyses of these

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Description of additional risk minimisation measures by safety concern **important identified risk**	
Important identified risk	**Additional risk minimisation activities**
	case reports in periodic safety update reports (PSURs)/periodic benefit-risk evaluation reports (PBRERs). Target audience and planned distribution path: Prescibing physicians and patients receiving rivaroxaban are provided with the educational material as agreed in the individual country with the NCA. **Plans to evaluate the effectiveness of the interventions and criteria for success:** The level of knowledge achieved by the educational materials was assessed through periodic surveys in subsets of physicians and patients receiving rivaroxaban for stroke prevention or DVT treatment (see Part III.2 as well as Annex 6). These two indications are considered to reflect the full breadth of the population treated with rivaroxaban regarding demographic and cognitive characteristics. Surveys regarding educational materials for prescriber and patients receiving rivaroxaban for stroke prevention or DVT treatment initially planned to run approximately at 18 months, 3 years and 7 years post-launch, respectively waves 1, 2 and 3. Some delays have occurred. Following wave 1, patient surveys had been discontinued. Progress, interim and final reports on drug utilisation studies with outcome and prescription event monitoring studies will be included in PSURs/PBRERs. The first wave of survey regarding educational materials for prescriber and patients receiving rivaroxaban for stroke prevention or DVT treatment has been completed. The survey involved 1224 physicians and 432 patients in 4 European countries. The survey demonstrated overall adequate levels of knowledge by patients and physicians denoting a success of introduced educational material (i.e. Prescriber guide and Patient alert card) (detailed results are presented in the PSUR/PBER No 14; DLP 15 SEP 2015). On 21 Jul 2016, EMA endorsed a study protocol amendment omitting patients from the following surveys (waves 2 and 3) in light of wave 1 results and of changes in the distribution chain of patient alert cards, which are now included into each medication pack. The wave 2 and 3 assessments evaluated physicians' knowledge of the key messages in the Prescriber guide only. Wave 2 data for physician assessment were collected between 30 March 2017 and 12 June 2017. In total, responses from 1,226 physicians were included in the analysis (detailed results are presented in the PSUR/PBER No 14; DLP 15 SEP 2015). Wave 3 data for physician assessment were collected between 13 January 2020 and 21 February 2020. In total, responses from 1,297 physicians were included in the analysis. The results of all three surveys were similar and adequate, with, as expected, the proportion of correct responses modestly increasing for

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Description of additional risk minimisation measures by safety concern **important identified risk**	
Important identified risk	**Additional risk minimisation activities**
	many questions across the waves. This suggests that the knowledge patterns have been maintained and even slightly improved. The knowledge retention suggests that the existing channels of educational communication are effective. Based on data from conducted post-marketing studies it can be assumed that the impact of the risk minimisation tools is overall positive. Educational materials developed by MAH are valuable sources of information and the MAH will continue its efforts in making them available to all prescribers and patients.

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Desription of additional risk minimisation measures by safety concern **important potential risk**	
Important potential risk	**Additional risk minimisation activities**
Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	**Objectives:** The aim of the introduction of these additional educational materials is to increase the awareness and reduction of the bleeding risk (overdose) and the risk of VTE recurrence (underdose, lack of drug effect). The objectives of the label text are to inform physicians prescribing rivaroxaban granules for oral suspension to children about the correct preparation/reconstitution and administration of the oral suspension and to ensure appropriate risk communication with parents/caregivers of patients and patients in whom the pharmaceutical form 1 mg/mL granules for oral suspension is prescribed. Addionally, **educational material for prescribers** and **patient alert card** and **video** will be introduced to increase awareness about both the risk of bleeding and the risk of medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension during treatment with rivaroxaban. **Rationale for the additional risk minimisation activity:** •Level of physicians' knowledge and understanding of key safety information as addressed in Prescriber guide •Level of patients' knowledge and understanding of the key safety information in Patient alert card •Continuous monitoring of bleeding events, overdose cases or cases with medication errors in a post-marketing non-interventional study and detailed analyses of these case reports in periodic safety update reports (PSURs)/periodic benefit-risk evaluation reports (PBRERs). **Target audience and planned distribution path:** Prescibing physicians and patients receiving rivaroxaban granules for oral suspension are provided with the educational material as agreed in the individual country with the NCA. **Plans to evaluate the effectiveness of the interventions and criteria for success:** -Detailed analyses of case reports from post-marketing non-interventional study in children from birth to less than 2 years treated with rivaroxaban for VTE in periodic safety update reports (PSURs)/periodic benefit-risk evaluation reports (PBRERs). Tracking of access to the video Electronic survey for measurement of effectiveness of the video in terms of understanding of the reconstitution procedure for the suspension, correct dosing and content appreciation on MAH-hosted websites

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Routine risk minimisation activities as described in Part V.2 are sufficient to manage the safety concerns 'potential risk' and 'missing information' of rivaroxaban. There are no additional risk minimisation measures proposed.

Removal of additional risk minimisation activities

None

V.3 Summary of risk minimisation measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: haemorrhage	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications): Section 4.4 (Special warnings and precautions for use): Section 4.8 (Undesirable effects) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** Educational material for prescribers Patient alert cards	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection Periodic analysis and update on 'haemorrhage', including different subcategories (e.g. critical organ bleeding, fatal bleeding, etc.) in every PBRER/PSUR **Additional PV activities:** Xarelto Pediatric VTE PASS Drug Utilization Study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)
Important potential risk: embryo-fetal toxicity	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data): Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** None	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection Periodic analysis and update on 'embryo-fetal toxicity', including updates of pregnancy reports and maternal exposure and breast-feeding incl. outcome (if available) in every PBRER/PSUR **Additional PV activities:** None.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	**Routine risk minimisation measures:** SmPC (Xarelto 1 mg/mL granules for oral suspension) Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.5 (Nature and contents of container) Section 6.6 (Special precautions for disposal and other handling) **Additional risk minimisation measures:** Educational material for prescribers Patient alert cards Video	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection Periodic analysis and update on cases reporting medication errors in PBRER/PSUR Follow-up Questionnaire (Reconstitution of the oral suspension and dosing with Xarelto® granules for oral suspension) **Additional PV activities:** None
Missing information: remedial procoagulant therapy for excessive haemorrhage	**Routine risk minimisation measures:** SmPCs: Section 4.9 (Overdose) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** None	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection **Additional PV activities:** None

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: patients with atrial fibrillation (AF) and prosthetic heart valve	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precaution for use) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** None	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection **Additional PV activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for for Xarelto (rivaroxaban)

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

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

This summary of the EU RMP for Xarelto 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 Xarelto's RMP.

VI.1 The medicine and what it is used for

Xarelto is authorised for:

- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (See section 4.4 for haemodynamically unstable PE patients)
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack
- Xarelto co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see SmPC for the full indication).
- Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.
- Xarelto is indicated for the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least five days of initial parenteral anticoagulation treatment.

It contains rivaroxaban as the active substance, and it is given by oral administration.

Further information about the evaluation of Xarelto's benefits can be found in Xarelto's EPAR, including in its plain-language summary, available on the EMA website, once this document is approved.

VI.2 Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size—the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status—the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Xarelto, 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. Special activities or measures beyond, e.g. a PASS, can be taken and build additional pharmacovigilance activities.

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

VI.2.1 List of important risks and missing Information

Important risks of Xarelto 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 Xarelto. 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.

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Table Part VI.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity • Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and a prosthetic heart valve

VI.2.2 Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: haemorrhage	
Evidence for linking the risk to the medicine	The increased risk for bleeding under treatment with an anticoagulant compound is contributable to its pharmacodynamic property in preventing blood from clotting (pharmacological mode of action is dose dependent inhibition of factor Xa). Evidence was mainly taken from pivotal studies and PBRERs/PSURs.
Risk factors and risk groups	Patients with certain pre-existing conditions (e.g. active cancer, previous stroke, bronchiectasis, history of bleeding, anaemia, uncontrolled hypertension, renal impairment, known GI ulcerations), those receiving concurrent antithrombotics, or the elderly, may be at higher risk of bleeding. Post-operative patients are generally at high risk of bleeding, especially during treatment with anticoagulants. Pre-menopausal women may be at risk for menorrhagia (hypermenorrhoea).
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications): Section 4.4 (Special warnings and precautions for use): Section 4.8 (Undesirable effects) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** Educational material for prescribers Patient alert cards
Additional pharmacovigilance activities	Xarelto Pediatric VTE PASS Drug Utilization Study An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban

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Important identified risk: haemorrhage	
	oral suspension in children under two years with venous thromboembolism (XAPAEDUS).

Important potential risk: embryo-fetal toxicity	
Evidence for linking the risk to the medicine	Pregnant women were excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC, due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta. Therefore, the overall experience is limited.
Risk factors and risk groups	The majority of patients receiving rivaroxaban are elderly patients. Only in patients with ACS, and those undergoing treatment for VTE, there may be a higher possibility of women with child-bearing potential receiving rivaroxaban. A large population-based study concluded that a history of DVT is an independent risk factor for spontaneous preterm delivery (33). This study compared all pregnancies of patients with and without a history of DVT: there were 212,086 deliveries, of which 122 (0.06%) occurred in patients with a history of DVT. No significant differences were noted between the groups regarding perinatal outcomes such as low Apgar scores, congenital malformations or perinatal mortality. Ben-Joseph et al. determined that patients with a history of DVT were more likely to have caesarean deliveries (OR, 2.6; 95% CI, 1.8–3.8; p < 0.001) than non-DVT patients, and DVT was an independent risk factor for preterm birth (OR, 1.8; 95% CI, 1.1–2.9; p = 0.033) (33). In a study of 395 patients with a history of VTE and 313 control women stillbirth was slightly more frequent in patients (4.3%) than in controls (3.2%); the difference was not statistically significant. Miscarriage was equally frequent between groups (34). A population-based study in the USA showed that pregnant women with AF (n = 157) were more likely to have babies that needed to be admitted to the neonatal intensive care unit (NICU) than pregnant women without AF (n = 264 573) (NICU admissions: 10.8% vs 5.1%; p = 0.003) (35).
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data): Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None

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Important potential risk: embryo-fetal toxicity	
Additional pharmacovigilance activities	None

Important potential risk: Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	
Evidence for linking the risk to the medicine	For children too young or unable to swallow rivaroxaban tablets, the drug will be administered orally as a suspension. The drug-device combination product including the pharmaceutical form 1 mg/mL granules for oral suspension needs to be prepared by the child's caregiver using the drug-device combination kit. Errors in the preparation of the suspension, as well as its subsequent application, may result in over- or underdosing. Overdose The increased risk for bleeding under treatment with an anticoagulant compound is contributable to its pharmacodynamic property in preventing blood from clotting (pharmacological mode of action is dose dependent inhibition of factor Xa). Evidence was mainly taken from pivotal studies, EU RMPs and PBRERs/PSURs. Underdose Lack of drug effect; recurrence of VTE
Risk factors and risk groups	Children diagnosed with VTE and too young or unable to swallow rivaroxaban tablets who are treated with the liquid formulation granules for oral suspension.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC (Xarelto 1 mg/mL granules for oral suspension) Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.5 (Nature and contents of container) Section 6.6 (Special precautions for disposal and other handling) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** Educational material for prescribers Follow-up Questionnaire Patient alert cards Video
Additional pharmacovigilance activities	None

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Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	
Evidence for linking the risk to the medicine	Clinical life scenarios, requests
Risk factors and risk groups	Health care professionals, patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.9 (Overdose) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Missing information: Patients with atrial fibrillation (AF) and a prosthetic heart valve	
Evidence for linking the risk to the medicine	Patients with prosthetic heart valves not studied
Risk factors and risk groups	Respective patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precaution for use) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

None

VI.2.3.2 Other studies in post-authorisation development plan

Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban

Xarelto Pediatric VTE PASS Drug Utilization Study: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (SN 22195)

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Xarelto Pediatric VTE PASS Drug Utilization Study (SN 22195)	An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)	**Important identified risk:** • Haemorrhage	Feasibility report	Submission Q1 2021 (completed)
			Protocol submission	Q1 2022 (completed)
			Start of data collection: 12 months from the PRAC endorsement of the study protocol[4] (10 NOV 2022)	Q4 2023
			Interim reports (study progress reports)[5]	Annually 1. Q4 2023 2. Q4 2024 3. Q4 2025 4.Q4 2026

[4] The number of patients for the study population actually accrued in the data sources will be monitored over time to inform the decision as to when to launch the analyses with intention to finalise the study earlier than Q4 2029 depending on follow-up of the overall uptake of rivaroxaban oral suspension reported in annual progress reports.
[5] To monitor the uptake of rivaroxaban oral suspension and follow-up the number of patients for the study population.

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Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
				5. Q4 2027
			End of data collection	Q2 2029 (estimated)
			Final report of study results (6 months after end of data collection)	Q4 2029 (estimated)

Annex 4 - Specific adverse drug reaction follow-up forms

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Rivaroxaban Follow-up
Liver-related Adverse Events

Annex 4.1 - Questionnaire Liver-Related Adverse Events

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**
SECTION II - REPORTER/PATIENT INFORMATION		
REPORTER: O Physician O Nurse O Patient O Other *(specify)*:		
REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at anset af event)*	**Gender:** O Male O Female	**Weight** [kg]:	**Height** [cm]:
Race: O White O Black or African American O American Indian/Alaska Native O Native Hawaiian/Pacific Islander O Asian O Other *(specify)*:			
Ethnicity: O Hispanic or Latino O Not Hispanic or Latino O Unknown			

SECTION III - PRODUCT INFORMATION (Rivaroxaban)	
INDICATION	
O VTE prevention in Major orthopedic surgery O Total hip replacement O Total knee replacement O Other lower limbs *(specify)*:	
O Stroke prevention in atrial fibrillation	O VTE treatment (and secondary prevention)
O Other *(specify)*:	O Unknown
Therapy started: [hours] after Major orthopedic surgery	**Dose / Frequency:**

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered fallow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see SECTION VII)*:

TREATMENT PROVIDED FOR LIVER EVENT	
O Yes *(specify)*:	O No treatment O Unknown
SUSPECTED CAUSE OF EVENT	
Related to Rivaroxaban treatment? O Yes O No *(specify alternative explanatian/ather contributing factors)*:	

Rivaroxaban Follow-up
Liver-related Adverse Events

Action taken with Rivaroxaban		**Date** *(dd/mm/yyyy)*	
○ Dose increased	○ Dose reduced		New dose:
○ Interrupted		From:	To:
○ Withdrawn			
○ None	○ Unknown		

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*	
Signs or symptoms	**Details** *(e.g. provide volues or frequency if available)*
☐ Asthenia / Fatigue	
☐ Pruritus (itching)	
☐ Jaundice	
☐ Ascites	
☐ Altered level of consciousness encephalopathy) ☐ Confusion ☐ Coma	
☐ Hepatomegaly	
☐ Splenomegaly	
☐ Dark Urine	
☐ Spider nevi	
☐ Other liver-related symptoms and signs *(specify)*:	

Rivaroxaban Follow-up
Liver-related Adverse Events

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS						
Laboratory Data	**Units / reference range**	**Before start of drug**	**While taking the drug**			**Normalized after end of drug?**
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date***(dd/mm/yyyy)*
Alk. phosphatase						☐
Total bilirubin						☐
Conjugated (direct) bilirubin						☐
ALT / SGPT						☐
AST / SGOT						☐
Gamma GT						☐
PT						☐
INR						☐
Albumin						☐
LDH						☐
HbdH						☐
Complete Blood Count Hemoglobin						☐
Eosinophils						☐
Amylase						☐
Lipase						☐
Creatinine Kinase						☐
Choline Esterase						☐
Other *(specify)*:						☐

Rivaroxaban Follow-up
Liver-related Adverse Events

Serology test for virus infection	Test date *(dd/mm/yyyy)*	Results with units	Comments
☐ Anti-Hep. A Virus IgM Antibodies			
☐ Hepatitis B surface Antigen ☐ Hepatitis B PCR (viral copies) ☐ Anti-Hep. B surface Antibodies ☐ Anti-Hep. B core IgM Antibodies ☐ Anti-Hep.s B core IgG Antibodies			
☐ Anti-Hepatitis C Virus Antibodies ☐ Anti-Hep. C Virus IgM Antibodies ☐ Hepatitis C PCR (viral copies)			
☐ Anti-Hep. D Virus IgM Antibodies ☐ Hepatitis D PCR (viral copies)			
☐ Anti-Hep. E virus IgG Antibodies ☐ Anti-Hep. E virus IgM Antibodies ☐ Hepatitis E virus RNA (PCR)			
☐ Anti-Cytomegalovirus (CMV) IgM Antibodies ☐ Cytomegalovirus (CMV) PCR			
☐ Anti-Epstein-Barr Virus (EBV) IgM Antibodies ☐ EBV other *(specify)*:			
☐ Adenovirus IgG ☐ Adenovirus IgM			
☐ Coxsackie IgG ☐ Coxsackie IgM			
☐ Herpes Simplex IgG ☐ Herpes Simplex IgM			
☐ Toxoplasmosis			
☐ Brucella *(specify)*:			
☐ Leptospira *(specify)*:			
☐ Other Serology test *(specify)*:			

Rivaroxaban Follow-up
Liver-related Adverse Events

Autoimmune markers	**Test date** *(dd/mm/yyyy)*	**Results with units**	**Comments**
☐ Antinuclear Ab (ANA)			
☐ Anti-smooth muscle Ab (SMA)			
☐ Anti-mitochondrial Antibodies			
☐ Anti-KLM1 Antibodies			
☐ Anti-SLA / LP			
☐ Atypical p-ANCA			
☐ Other autoimmune test *(specify)*:			

Further investigations	**Test date** *(dd/mm/yyyy)*	**Short summary of the result**
☐ Ultrasound		
☐ CT		
☐ MRI		
☐ ERCP		
☐ Liver biopsy		
☐ Other *(specify)*:		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered *hepatotoxic medications* including any drugs given up to *2 months prior* to the liver event.

Concomitant product name	**Route**	**Indication for use**	**Dose / Frequency**	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Possible cause for the event?**
☐ Other antithrombotic therapy						☐
☐ Paracetamol						☐
☐ Methotrexate						☐
☐ Amiodarone						☐
☐ NSAIDs *(specify)*:						☐
☐ Herbal substances *(specify)*:						☐
☐ Antibiotics *(specify)*:						☐
☐ Cancer therapy *(specify)*:						☐
☐ Halothane						☐
						☐

Rivaroxaban Follow-up
Liver-related Adverse Events

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Active malignancy		☐		*Specify type:*
☐ Liver cancer / metastases		☐		
☐ Liver cirrhosis / fibrosis ☐ Child-Pugh Class:		☐		
☐ Fatty liver		☐		
☐ Viral Hepatitis		☐		*Specify acute or chronic, type.*
☐ Hepatis vaccination		N/A	N/A	*Specify type:*
☐ Biliary disease		☐		
☐ Pancreatitis		☐		
☐ Autoimmune disease *(specify)*:		☐		
☐ Hemochromatosis		☐		
☐ Wilson's disease		☐		
☐ Alpha 1-antitrypsin deficiency		☐		
☐ Diabetes mellitus		☐		
☐ Heart failure		☐		
☐ Renal failure		☐		
☐ Alcohol misuse		☐		
☐ Surgery		N/A	N/A	*Specify type af surgery and type af anesthesia:*
☐ Other *(specify)*:		☐		

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*

This section can also be used to provide information on any of the sections above. Please note the relevant sectian number below.

Cause of death *(If selected autcame was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *Continue with SECTION IV*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Rivaroxaban Follow-up
Renal Failure

Annex 4.2 - Questionnaire Renal Failure

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION		
REPORTER: O Physician O Nurse O Patient O Other *(specify)*:		
REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(at onset af event)*	**Gender:** O Male O Female	**Weight** [kg]:	**Height** [cm]:
Race: O White O Black or African American O American Indian/Alaska Native O Native Hawaiian/Pacific Islander O Asian O Other *(specify)*:			
Ethnicity: O Hispanic or Latino O Not Hispanic or Latino O Unknown			

SECTION III - PRODUCT INFORMATION (Rivaroxaban)	
INDICATION	
O VTE prevention in Major orthopedic surgery O Total hip replacement O Total knee replacement O Other lower limbs *(specify)*:	
O Stroke prevention in atrial fibrillation	O VTE treatment (and secondary prevention)
O Other *(specify)*:	O Unknown
Therapy started: [days] after Major orthopedic surgery	**Dose / Frequency:**

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see SECTION VII)*:

TREATMENT PROVIDED FOR RENAL EVENT	
O Yes *(specify)*:	O No treatment O Unknown

SUSPECTED CAUSE OF EVENT
Related to Rivaroxaban treatment? O Yes O No *(specify alternative explanation/ather contributing factors)*:

Rivaroxaban Follow-up
Renal Failure

Action taken with Rivaroxaban		**Date** *(dd/mm/yyyy)*	
○ Dose increased	○ Dose reduced		New dose:
○ Interrupted		From:	To:
○ Withdrawn			
○ None	○ Unknown		

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*

Signs or symptoms	**Details** *(e.g. provide values or frequency if availoble)*
☐ Oliguria	
☐ Hematuria	
☐ Fever	
☐ Anuria	
☐ Dysuria	
☐ Polyuria	
☐ Back pain	
☐ Hypertension	
☐ Other *(specify)*:	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	**Units / reference range**	**Before start of drug**	**While taking the drug**			**Normalized after end of drug?**
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*
Blood test						
Serum creatinine (Scr)						☐
Creatinine Kinase (CK)						☐
GFR						☐
Urea						☐
Potassium (K)						☐
Sodium (Na)						☐
Phosphate						☐
Calcium						☐
Albumin						☐

Rivaroxaban Follow-up
Renal Failure

Laboratory Data	Units / reference range	Before start of drug	While taking the drug			Normalized after end of drug?
		Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*	Date *(dd/mm/yyyy)*
Blood test						
CRP						☐
Leukocytes						☐
LDH						☐
HbdH						☐
Blood Gas Analysis						
pH						☐
Bicarbonate						☐
Oxygen						☐
Urinalysis / Sediment						
Proteinuria						☐
Hematuria						☐
Leukocyturia						☐
Dysmorphic erythrocytes						☐
Casts						☐
Other *(e.g. antibadies, urinary or serum eosinophils, specify)*:						☐
						☐
						☐

Further investigations	Test date *(dd/mm/yyyy)*	Short summary of the result
☐ Ultrasound		
☐ CT		
☐ MRI		
☐ Renal biopsy		
☐ Other *(specify)*:		

Rivaroxaban Follow-up
Renal Failure

SECTION V - RELEVANT CONCOMITANT MEDICATION						
Concomitantly administered drugs with known renal side effects given up to *2 months prior* to the reported event.						
Concomitant product name	**Route**	**Indication for use**	**Dose / Frequency**	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Possible cause for the event?**
☐ Other antithrombotic therapy						☐
☐ NSAIDs *(specify)*:						☐
☐ ACE inhibitors *(specify)*:						☐
☐ Contrast agents *(specify)*:						☐
☐ Antibiotics *(specify)*:						☐
☐ Cancer therapy *(specify)*:						☐
☐ Herbal substances *(specify)*:						☐
						☐
						☐
						☐

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concomitant conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
☐ Active malignancy		☐		*Specify type:*
☐ Renal tumor		☐		
☐ Hypertension		☐		
☐ Infection *(specify)*:		☐		
☐ Glomerulonephritis		☐		
☐ Interstitial nephritis		☐		
☐ Autoimmune disease *(specify)*:		☐		
☐ Diabetes mellitus		☐		
☐ Surgery *(specify type of surgery, type of anesthesio, hypotension during surgery)*		N/A	N/A	
☐ Other *(specify)*:		☐		

Rivaroxaban Follow-up
Renal Failure

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *Continue with SECTION IV*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Rivaroxaban Follow-up
Reconstitution of oral suspension and dosing with Xarelto® Granules for oral suspension

Annex 4.3 - Questionnaire Reconstitution and dosing with Xarelto Granules for oral suspension

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**
SECTION II - REPORTER/PATIENT INFORMATION		
REPORTER: O Physician O Nurse O Patient O Parent/Caregiver O Other *(specify)*:		
REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**
PATIENT INFORMATION		
Age [years]: *(at anset af event)*	**Gender:** O Male O Female O Diverse	**Weight** [kg]: / **Height** [cm]:
Race: O White O Black or African American O American Indian/Alaska Native O Native Hawaiian/Pacific Islander O Asian O Other *(specify)*:		
Ethnicity: O Hispanic or Latino O Not Hispanic or Latino O Unknown		
SECTION III - PRODUCT INFORMATION (Rivaroxaban)		
INDICATION		
O Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence		
O Other *(specify)*:	O Unknown	
Therapy started: [dd/mm/yyyy]	**Dose / Frequency:**	

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered fallow-up)*	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see SECTION V)*:
TREATMENT PROVIDED FOR ADVERSE EVENT			
O Yes *(specify)*:			O No treatment O Unknown
SUSPECTED CAUSE OF EVENT			
Related to Rivaroxaban treatment? O Yes O No *(specify alternative explanation/other contributing factors)*:			
Medication Error in relation to the Reconstitution of the oral suspension and dosing with Rivaroxaban Granules for oral suspension related to Adverse Event? O Yes *(specify in section IV A below)* O No *(specify alternative explanation/other contributing factors)*:			

Rivaroxaban Follow-up
Reconstitution of oral suspension and dosing with Xarelto® Granules for oral suspension

Action taken with Rivaroxaban		**Date** *(dd/mm/yyyy)*	
○ Dose increased	○ Dose reduced		New dose / Frequency: Reason for dose change: *(specify, e.g. weight change, other)*
○ Interrupted		From:	To:
○ Dose increased	○ Dose reduced		New dose / Frequency: Reason for dose change: *(specify, e.g. weight change, other)*
○ Interrupted		From:	To:
○ Dose increased	○ Dose reduced		New dose / Frequency: Reason for dose change: *(specify, e.g. weight change, other)*
○ Interrupted		From:	To:
○ Withdrawn			
○ None	○ Unknown		

SECTION IV A – RELEVANT MEDICATION ERROR RELATED TO RECONSTITUTION OF THE ORAL SUSPENSION AND DOSING WITH RIVAROXABAN GRANULES FOR ORAL SUSPENSION *(to AE of interest reported at time of first report)*	
Type of Medication Error	**Details** *(e.g. provide clear and comprehensive explanation if available)*
☐ The parent/caregiver or you (as a parent/ caregiver) missed or skipped a dose	
☐ The parent/caregiver or you (as a parent/ caregiver) got the dosage wrong	
☐ A mistake in water syringe use led to the wrong dosage administration in a period of use	
☐ A mistake in oral dosing syringe use led to the wrong dosage administration of one or more single dose(s).	
☐ A mistake in Xarelto® oral suspension dose change (due to body weight change of the child) led to the wrong dosage administration	
☐ The child spat or vomited most of his/her dose.	
☐ Other: please specify	
☐ Other: please specify	
☐ Other: please specify	

Rivaroxaban Follow-up
Reconstitution of oral suspension and dosing with Xarelto® Granules for oral suspension

SECTION V - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *Continue with SECTION IV*
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable