EU RISK MANAGEMENT PLAN (RMP)

XARELTO®

BAY59-7939
(Rivaroxaban)

No. 12.4

Date of Report:
03 NOV 2020

Confidential

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

Part I – Product(s) Overview

PART I
PRODUCT(s) OVERVIEW

Active substance(s) (INN or common name):	Rivaroxaban
Pharmaco-therapeutic group (ATC Code):	B01AF01
Name of Marketing Authorisation Holder or Applicant:	Bayer AG
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Xarelto
Marketing authorisation procedure	Centralised procedure
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
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.

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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(iii)) (2.5 mg) and iron oxide red (E 172(ii)) (10 mg, 15 mg, 20 mg). Granules for oral suspension Excipients are as follows: citric acid anhydrous, flavor sweet and creamy, hypromellose 5 cP, mannitol, microcrystalline cellulose and carmellose sodium, sodium benzoate, sucralose, xanthan gum.
Hyperlink to the Product Information	Proposed updated Product Information as available in Module 1.3.1
Indication(s) in the EEA	Current (if applicable): 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

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	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.
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 that haemostasis has been established. *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 3 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 6 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.

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	Proposed (if applicable): *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 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
Pharmaceutical form(s) and strengths	Current (if applicable): Film-coated tablet, 2.5 mg Film-coated tablet, 10 mg Film-coated tablet, 15 mg Film-coated tablet, 20 mg
	Proposed (if applicable): Xarelto 1 mg/mL granules for oral suspension
Is/will the product be subject to additional monitoring in the EU?	Yes

Data lock point for this RMP	15 MAY 2020	Version number	12.4
Date of final sign off	01 FEB 2021		

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ADMINISTRATIVE INFORMATION ON THE RMP

PART	MODULE/ANNEX	Date last update / submission (sign off date)	Version number of RMP when last updated / submitted
PART II Safety Specification	**SI** Epidemiology of the indication and target population(s)	01 FEB 2021	12.4
	SII Non-clinical part of the safety specification	12 OCT 2020	12.3
	SIII Clinical trial exposure	18 MAY 2020	12.2
	SIV Populations not studied in clinical trials	11 NOV 2019	12.1
	SV Post-authorisation experience	11 NOV 2019	12.1
	SVI Additional EU requirements for the safety specification	04 OCT 2017	10.3
	SVII Identified and potential risks	12 OCT 2020	12.3
	SVIII Summary of the safety concerns	12 OCT 2020	12.3
PART III Pharmacovigilance Plan		01 FEB 2021	12.4
PART IV Plan for post-authorisation efficacy studies		24 FEB 2017	10.0
PART V Risk Minimisation Measures		01 FEB 2021	12.4
PART VI Summary of RMP		01 FEB 2021	12.4
PART VII Annexes	**ANNEX 1** EudraVigilance Interface	N/A	N/A
	ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	11 NOV 2019	12.1
	ANNEX 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	N/A	N/A

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PART	MODULE/ANNEX	Date last update / submission (sign off date)	Version number of RMP when last updated / submitted
	ANNEX 4 Specific adverse drug reaction follow-up forms Questionnaires **Annex 4.1:** Liver-Related Adverse Events **Annex 4.2:** Renal Impairment/Renal Failure **Annex 4.3**: Severe Hypersensitivity **Annex 4.4**: Severe Skin Reactions	14 MAR 2018	11.2
	ANNEX 5 Protocols for proposed and ongoing studies in RMP Part IV	N/A	N/A
	ANNEX 6 Details of proposed additional risk 7inimization activities (if applicable) **Annex 6.1** Prescriber Guide **Annex 6.1.1** Posology Card **Annex 6.2** Patient Alert Card	12 OCT 2020	12.3
	ANNEX 7 Other supporting data (including referenced material)	11 NOV 2019	12.1
	ANNEX 8 Summary of changes to the risk management plan over time	11 NOV 2019	12.1

EU QPPV name [redacted]

EU QPPV Deputy name Dr [redacted]

Contact person for this RMP [redacted]

E-mail address of contact person

Electronic QPPV signature is attached at the end of the document.

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Overview of Versions

Version number of last agreed RMP:

Version number	11.4
Agreed within	EMEA/H/C/000944/II/0058

Current RMP Versions under Evaluation

RMP:

Version number	12.2
Submitted on:	20 MAY 2020

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Part II – Module SI: Epidemiology of the Indication(s) and Target Population

PART II
Module SI: Epidemiology of the Indication(s) and Target Population

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 MAY 2020

Version number of RMP when this module was last updated	12.4

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Part II – Module SI: Epidemiology of the Indication(s) and Target Population

Abbreviations

ABI	ankle-brachial index
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
ARB	angiotensin receptor blocker
aRR	adjusted rate ratio
ASA	acetylsalicylic acid
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke or transient ischaemic attack, Vascular disease, Age 65–74 years and Sex category
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and prior Stroke or transient ischaemic attack
CI	confidence interval
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
COPD	chronic obstructive pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CVC-VTE	central venous catheter- venous thromboembolism
CVST	cerebral vein and sinus thrombosis
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ESC	European Society of Cardiology
GI	gastrointestinal
GPRD	General Practice Research Database
GRACE	Global Registry of Acute Coronary Events
HFS	hip fracture surgery
HIT	heparin-induced thrombocytopenia

HR	hazard ratio
INR	international normalised ratio
IPCD	intermittent pneumatic compression device
IR	immediate release
IV	intravenous
LDUH	low-dose unfractionated heparin
LEAD	lower extremity artery disease
LMWH	low molecular weight heparin
MI	myocardial infarction
min	minutes(s)
NSAID	non-steroidal anti-inflammatory drug
NSTEMI	non-ST-segment elevation myocardial infarction
OR	odds ratio
PAD	peripheral arterial disease
PE	pulmonary embolism
PO	*per os* = by mouth
PTS	post-thrombotic syndrome
RR	relative risk
SR	sustained release
STEMI	ST-segment elevation myocardial infarction
THR	total hip replacement
TIA	transient ischaemic attack
TKR	total knee replacement
UA	unstable angina
UFH	unfractionated heparin
VTE	venous thromboembolism

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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

1. 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.

1.1 Incidence

Table 1-1 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.

Table 1-1: 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.

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1.2 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).

1.3 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).

1.4 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).

1.5 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 1-2.

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Table 1-2: 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 2-1
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 1-2: 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 (Imberti et al. 2012).
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 9327 and 41,744 patients), TKR (13,846 patients) and HFS (2448 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)

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

2.1 Incidence

VTE 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 1 year and 17.6% at 10 years (44, 45). In a study conducted in Italy, VTE recurrence rates at 1,

3, 5 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 2 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).

2.2 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).

2.3 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).

2.4 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.

2.5 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 2-1.

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

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Table 2-1: Co-morbidities in patients with VTE

Age	See Table 1-2
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 2-1: 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 2-1: 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).

3. 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.

3.1 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).

3.2 Prevalence

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

3.3 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).

3.4 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 $\geq$ 2, it may be reasonable to use oral anticoagulants with clopidogrel, but without aspirin (105).

3.5 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).

3.6 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 3-1.

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 3-1: 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 3-1: 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 renal dysfunction (defined as creatinine clearance < 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).

4. 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.

4.1 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).

4.2 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).

4.3 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).

4.4 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).

4.5 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).

4.6 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 4-1.

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Table 4-1: 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.

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Table 4-1: Co-morbidities in patients with ACS

Diabetes mellitus	In an international registry of patients with ACS, 26% had diabetes (Goodman et al. 2009); in an Italian registry, 35.5% had diabetes (172). In 169 diabetic patients with prior MI, the sex and age-adjusted incidences (per 1000 person-years) of myocardial 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 1000 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 major bleeding occurred in 10.1% of patients without thrombocytopenia, and in 53.3% of patients with moderate/severe thrombocytopenia.

5. Prevention of cardiovascular events in stable 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). 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) (189).

5.1 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) (190). In the Multi-Ethnic Study of Atherosclerosis (META) cohort (n = 5756), the incidence of newly detectable coronary artery calcification, a marker for atherosclerosis, was 6.6% per year in individuals aged 45–84 years old. (191). 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 (192).

5.2 Prevalence

In the British Regional Heart Study cohort (n = 7735) of men aged 40–59 years, 10.3% had evidence of myocardial ischemia (193). 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 (194). In 2010, LEAD was estimated to affect 202 million people globally, following an increase of 23.5% from 164 million affected in 2000 (195). 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 (196). The prevalence of carotid artery stenosis (≥50% narrowing) in the general population ranges from 0.2%–7.5%, depending on age and gender (197).

5.3 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 (194). 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 (198). 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 (197).

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 (199). 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 (200). In Finland, the age-standardized annual incidence of angina was 1.89 per 100 population in women and 2.03 in men (201). 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% (202). There is no consistent sex difference in the risk of LEAD, although severe and symptomatic disease may be more common in men (203). 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 (196).

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 (195, 203-208). Diabetes and smoking are the most significant risk factors for LEAD, specifically (203).

5.4 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) 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 long-term single antiplatelet therapy (aspirin or clopidogrel) in symptomatic patients and in those patients who have undergone revascularization. Revascularization, if required, is achieved by lower-extremity bypass

grafting (189). 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 (189).

5.5 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 (209). Chronic occlusion of lower-limb arteries can cause critical limb ischemia, requiring major amputation in 30% of cases (210). 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 (211).

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 (212). 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 (213). 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) (214). 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 (215). 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) (216).

5.6 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% (217). Patients with CAD and concommitant 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) (218). A meta-analysis of 19 prospective studies found that 25–28% of individuals with LEAD (n = 4573) have carotid artery stenosis (219). As would be expected from their shared pathophysiology, CAD and PAD also share several co-morbidities, shown in **Error! Reference source not found.**.

Table 5-1: 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 (194). In a Canadian cohort (n = 16 440), 18% of individuals with LEAD had history of MI (220). 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 (221).
Stroke and TIA	Prior history of stroke was present in 14% of patients with confirmed angina in a European cohort (n = 117) (194). 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 (222). In a database study (n = 16 440), stroke occurred in 13% and TIA in 14% of LEAD patients (220). 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 (221).
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 (223). In a Canadian cohort of individuals with LEAD (n = 16 440), 5% of individuals had AF (220).
Heart failure	In a large database study (n = 16 440), LEAD and co-morbid HF was present in 25% of individuals (220). In a British cohort of patients with HF (n = 136), 52% of patients had CAD (224).
Hypertension	In a European cohort of patients with confirmed angina (n = 117), 83.5% had a history of hypertension (194). In a cohort of patients with LEAD (n = 16 440), 58% were hypertensive (220).
Renal disease	A cross-sectional US study found CAD was present in 38% of patients with end-stage renal disese (n = 3925) (225). 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) (226). The prevalence of LEAD in patients with end-stage renal disease ranges from 15–46% depending on diagnostic criteria used (n = 37 218) (227).

Table 5-1: Co-morbidities of coronary artery disease and peripheral arterial disease

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 (228). In a database study (n = 16 440), 19% of individuals with LEAD had type 2 diabetes (220). 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) (228).
Hypercholesterolemia	In a cohort of patients with confirmed angina (n = 117), 75.6% of individuals had hypercholesterolemia (194). Hypercholesterolemia was present in 7% of a large cohort of individuals with LEAD (n = 16 440) (220).

6. Proposed: Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years after initial parenteral anticoagulation treatment.

6.1 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 (229-232). 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 (233-237).

Pediatric VTE is an increasingly common complication amongst hospitalized children, occurring in 42–58/10 000 admissions (235, 238). The incidence of VTE in pediatric patients has increased by 70% in under a decade (235). This trend is most dramatic in children who are hospitalized, averaging 5–22 per 10 000 pediatric inpatients (229, 239-241), but community-acquired pediatric VTE is also increasing (0.1–0.5 per 10 000 children) (229, 240).

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 (242). 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 (243).

6.2 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 (237).

Several studies have reported changing rates of VTE with time, for example, from 34 to 58 cases per 10 000 admissions from 2001–2007 (235), or from 0.3 to 28.8 per 10 000 admissions from 1992–2005 (234). 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 (244). 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 (245). Teenage girls have twice the rate of VTE compared with teenage boys; this is associated with the use of oral contraceptives and pregnancy (240).

6.3 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%) (229).

VTE in children is often provoked by a variety of risk factors and rarely is unprovoked in nature (246). 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.

6.4 The main existing treatment options

The most recent American College of Chest Physicians (ACCP) management guidelines of 2012 (247) 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 (248). 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 (249). 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 (250). 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 (251). Despite this, use of anticoagulants in children is widespread

(252). 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 (251, 254).

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 (252). This is compounded in young children due to variability in the plasma concentration of thrombin and antithrombin, resulting in heparin resistance or sensitivity (255). An additional concern with the use of UFH therapy is the rare but serious side effect of heparin-induced thrombocytopenia (HIT)(252). In addition, as UFH is derived from animal tissue, there is a potential risk of contamination with over-sulfated chondroitin sulfate (OSCS) (256).

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 (252).

The low-molecular-weight heparin (LMWH) dalteparin sodium (FRAGMIN) has been approved in the US on May 16, 2019 for treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older (257).

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 (258, 259). 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 (252). 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 (260, 261) and bivalirudin (255, 262) 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 (255). 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 (255, 260-262). In the pediatric population, these drugs are used predominantly in the context of suspected or confirmed HIT (263).

Clinical trials of other non-VKA oral anticoagulants (NOACs) including rivaroxaban are ongoing for the treatment and/or prevention of VTE in children (264).

6.5 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 (265, 266). Pediatric VTE is an increasingly common complication amongst hospitalized children, occurring in 42–58/10 000 admissions (235, 238).

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 (248, 267). 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 (248).

6.6 Important co-morbidities

Approximately 95% of venous thromboembolisms (VTEs) in children are associated with serious disease (244), 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 (229, 230, 268, 269). The incidence of VTE in pediatric patients has increased by 70% in under a decade (235).

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 (247, 270) suggest therapeutic anticoagulation for children without significant intracranial hemorrhage, while the American Heart Association (AHA) guidelines published in 2008 (271) suggest anticoagulants only in case of evidence of thrombus propagation, multiple cerebral or systemic emboli or if a severe prothrombotic state is present.

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Part II – Module SII: Non-Clinical Part of the Safety Specification

PART II
Module SII: Non-Clinical Part of the Safety Specification

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 SEP2019

Version number of RMP when this module was last updated	12.3

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Part II – Module SII: Non-Clinical Part of the Safety Specification

Abbreviations

APCC	activated prothrombin complex concentrate
AUC	area under the curve
FEIBA NF	factor eight inhibitor bypassing activity nanofiltered
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PCC	prothrombin complex concentrate
rFVIIa	recombinant Factor VIIa
RMP	Risk Management Plan

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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	• 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
andexanet alfa).	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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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
- 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

- None

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Part II – Module SIII: Clinical Trial Exposure

PART II
Module SIII: Clinical Trial Exposure

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 MAY 2020

Version number of RMP when this module was last updated	12.2

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Part II – Module SIII: Clinical Trial Exposure

Abbreviations

ACS	acute coronary syndrome
ADR	adverse drug reaction
ASA	acetylsalicylic acid
ATLAS	Anti-FXa Therapy to Lower cardiovascular events in addition to aspirin with/without thienopyridine therapy in patients with Acute coronary Syndromes
BID	*bis in die* = twice daily
CAD	coronary artery disease
CHMP	Committee for Medicinal Products for Human Use
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CrCl	creatinine clearance
CRF	case record form
CYP3A4	cytochrome P450 3A4
DLP	data lock point
DVT	deep vein thrombosis
EC	European Commission
EU	European Union
F	female
J-ROCKET	Japanese Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial
LMWH	low molecular weight heparin
M	male
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
Med Ill	medically ill
MSSO	Maintenance and Support Services Organization
OD	once daily
PAD	peripheral artery disease

PCI	Percutaneous coronary intervention
PE	pulmonary embolism
ROCKET	Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial
SMQ	Standard MedDRA Query
SPAF	stroke prevention in atrial fibrillation
TDD	total daily dose
THR	total hip replacement
TKR	total knee replacement
VKA	Vitamin K antagonist
VTE	venous thromboembolism
VTE-P	venous thromboembolism prophylaxis
VTE-T	venous thromboembolism treatment

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Part II – Module SIII: Clinical Trial Exposure

1. 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 population and at different strengths.

This RMP is being submitted with an application for a new indication. Therefore, the clinical trial data specific to the application are presented separately at the start of this module.

New proposed indicaton: 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 following initiation of standard anticoagulation treatment.

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 1-1 to Table 1-9. 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 SEP 2017).

Table 1-1: 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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Part II – Module SIII: Clinical Trial Exposure

Table 1-2: 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 1-3: 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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Part II – Module SIII: Clinical Trial Exposure

Table 1-4: 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	**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 1-5: 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	**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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Part II – Module SIII: Clinical Trial Exposure

Table 1-6: 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 1-7: 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 1-8: 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 1-9: 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.

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Part II – Module SIII: Clinical Trial Exposure

Table 1-10: 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**

Table 1-11: 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**

Table 1-12: 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**

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Table 1-13: 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

Table 1-14: 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**

Table 1-15: Duration of exposure

Across indications (All completed rivaroxaban phase II and III studies)

Duration of study medication	Patients	Person time (years)
1 day	351	1
>1 to 7 days	2512	37
>1 to 2 weeks	4438	133
>2 to 4 weeks	1310	76
>4 to 8 weeks	8255	821
>8 to 12 weeks	1512	299
>3 to 6 months (180 days)	4727	1809
>6 to 12 months (360 days)	11361	8143
>12 to 18 months (540 days)	9739	11452
>18 to 24 months (720 days)	7594	13073
>24 to 30 months (900 days)	6175	13468
>2.5 to 3 years (1080 days)	3328	8941
>3 years	2176	6947
Missing	32	0
Total person time		**65200**

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Table 1-16: 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 1-17: 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 1-18: 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

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Table 1-18: SPAF/PCI (Pool of SN 11390, 11866, 12024, 11630, 12620, 15572, 15693, 15694, 16320 and 16523)

Duration of study medication	Patients	Person time (years)
>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**

Table 1-19: 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**

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Table 1-20: VTE prevention in Med ill (SN 12839)

Duration of study medication	Patients	Person time (years)
1 day	82	0
>1 to 7 days	362	5
>1 to 2 weeks	327	10
>2 to 4 weeks	217	12
>4 to 8 weeks	3007	289
Missing	2	0
Total person time for indication		**316**

Table 1-21: Age group and gender

Across indications (All completed rivaroxaban phase II and III studies) Age group	Patients		Person time (years)	
	M	F	M	F
Adults				
18–40 years	1036	829	622	424
>40 to <65 years	17100	7406	16592	4964
Elderly people				
65–74 years	15813	7851	21189	7279
75–84 years	7024	5213	8501	4688
≥85 years	621	617	520	421
Total	**41594**	**21916**	**47423**	**17777**

Table 1-22: 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**

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Table 1-23: 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**

Table 1-24: 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 1-25: 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**

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Table 1-26: 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**

Table 1-27: 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	16243	23462
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	175	11
10 mg TDD: 10 mg OD	12413	2132
10 mg TDD: 5 mg BID	15083	22185
15 mg TDD: 15 mg OD	2835	3388
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
Total	**63510**	**65200**

Table 1-28: 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 1-29: 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**

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Table 1-30: 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 1-31: 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 1-32: 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 1-33: Race or ethnic origin

Across indications (All completed rivaroxaban phase II and III studies)		
Race or ethnic origin	**Patients (N)**	**Person time (years)**
White	46169	45811
Black or African American	919	676
Asian	9673	10537
American Indian or Alaska native	38	25
Native Hawaiian or other Pacific Islander	16	9
Other	5249	7439
Multiple	6	2
Not reported	321	241
Missing	1119	461
Total	**63510**	**65200**

Table 1-34: 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**

Table 1-35: 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**

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Table 1-36: 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 1-37: 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 1-38: 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 1-39: Special populations (totals)

Across indications (All completed rivaroxaban phase II and III studies)		
Total population	**Persons**	**Person time**
Lactating women		
Yes	1	0
No	9709	1778
Missing	53800	63422
Renal impairment		
<30 mL/min	368	307
30-<50 mL/min	6373	6617
50-≤80 mL/min	24919	28483
>80 mL/min	31312	29572
Missing	538	221
Hepatic disorder at baseline		
No	1956	1709
Yes	61554	63491
Total	**63510**	**65200**

Table 1-40: 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 1-41: 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 1-42: 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 1-43: 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 1-44: 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**

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Part II – Module SIV: Populations not studied in Clinical Trials

PART II
Module SIV: Populations not studied in Clinical Trials

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 SEP 2019

Version number of RMP when this module was last updated	12.1

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Part II – Module SIV: Populations not studied in Clinical Trials

Abbreviations

ACS	acute coronary syndrome
AE	adverse event
AF	atrial fibrillation
ALT	alanine transaminase = alanine aminotransferase
ASA	acetylsalicylic acid
ATLAS	Anti-FXa therapy to lower cardiovascular events in addition to aspirin with/without thienopyridine therapy in patients with acute coronary syndromes
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
CAD	Coronary artery disease
CCDS	Company Core Data Sheet
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and prior Stroke or transient ischaemic attack
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CrCl	creatinine clearance
CYP	cytochrome P450
DVT	deep vein thrombosis
EMA	European Medicines Agency
HIV	human immunodeficiency virus
LMWH	low molecular weight heparin
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PAD	peripheral arterial disease
PDCO	Paediatric Committee
PE	pulmonary embolism
P-gp	p-glycoprotein
PK	pharmacokinetics
PT	prothrombin time

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Part II – Module SIV: Populations not studied in Clinical Trials

RECORD	REgulation of Coagulation in ORthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism
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
SmPC	Summary of Product Characteristics
SN	study number
SPAF	stroke prevention in atrial fibrillation
TIA	transient ischaemic attack
UFH	unfractionated heparin
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism
XALIA	Xarelto for Long-term and Initial Anticoagulation in Venous Thromboembolism (VTE)
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-embolism in patients with non-valvular atrial fibrillation: A non-interventional study

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Part II – Module SIV: Populations not studied in Clinical Trials

1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion	Reason for exclusion	Included as missing information	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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Part II – Module SIV: Populations not studied in Clinical Trials

Criterion	Reason for exclusion	Included as missing information	Rationale
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 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 is contraindicated.	Yes	Patients were excluded from pivotal studies so population is not adequately characterised.
7 Pregnancy and breast-feeding	Pregnancy and breast-feeding are contraindications and women of child-bearing potential	Yes	Pregnant and breast-feeding women were not included in the clinical development

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Part II – Module SIV: Populations not studied in Clinical Trials

Criterion	Reason for exclusion	Included as missing information	Rationale
	should avoid becoming pregnant during treatment with rivaroxaban.		program. The contraindication will remain unless any potential risk can clearly be excluded.
8 CrCl < 30 mL/min (in children younger than 1 year, serum creatinine results above 97.5th percentile)	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.	Yes	Addressed in the SmPCs (Section 4.4 Special warnings and precautions for use)
9 Patients younger than 6 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)
11 CYP3A4 and P-gp inhibitors	Concomitant use of rivaroxaban with strong inhibitors of	Yes	Addressed in the SmPCs (Section 4.4 Special warnings

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Part II – Module SIV: Populations not studied in Clinical Trials

Criterion	Reason for exclusion	Included as missing information	Rationale
	both CYP3A4 and P-gp may increase blood plasma concentrations of rivaroxaban which may lead to an increased bleeding risk.		and precautions for use)
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)
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	No	Addressed in the SmPC for 10 mg/15 mg/ 20 mg (VTE-T, SPAF) (Section 4.4 Special warnings and precautions for use)

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Part II – Module SIV: Populations not studied in Clinical Trials

Criterion	Reason for exclusion	Included as missing information	Rationale
	data in this population are not available, therefore these patients have been excluded from the EINSTEIN clinical trial programme.		

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.

3. Limitations in Respect to Populations Typically under-represented in Clinical Trial Development Programmes

Table 3-1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Pregnant women were not included in the clinical development program, incl. the pre-authorisation program; no relevant data on exposure can be presented
Patients with relevant comorbidities: Patients with hepatic impairment	Across all completed rivaroxaban phase II and III studies [n=63,932 (100%)]: Exposure in patients with hepatic impairment under treatment with rivaroxaban was: 1,969 with hepatic disorder at baseline.
Patients with renal impairment	Exposure in patients with renal impairment under treatment with rivaroxaban was: 24,949 patients with eGFR 50 - <=80 ml/min 6,376 patients with eGFR 30 - <50 ml/min 368 patients with eGFR <30 ml/min
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

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Part II – Module SIV: Populations not studied in Clinical Trials

Immunocompromised patients	Not applicable/included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable/included in the clinical development program
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	Not included in the clinical development program
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.	

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Part II – Module SV: Post-authorisation Experience

PART II
Module SV: Post-authorisation Experience

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 SEP 2019

Version number of RMP when this module was last updated	12.1

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Part II – Module SV: Post-authorisation Experience

Abbreviations

ACS	acute coronary syndrome
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
DVT	deep vein thrombosis
DVT-T	Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults
EMA	European Medicines Agency
PBRER	Periodic Benefit-Risk Evaluation Report
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
SmPC	Summary of Product Characteristics
SPAF	stroke prevention in atrial fibrillation
VTE-P	venous thromboembolism prophylaxis

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Part II – Module SV: Post-authorisation Experience

1. Post-authorisation 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 2019[1] (this DLP is taken from the recent PSUR/PBRER No 18.0) is approx. 29.7 million patient-years.

All exposure estimates (2.5 mg, 10 mg, 15 mg and 20 mg) exclude use in clinical trials and observational studies.

Table 1-1: Cumulative Worldwide Post marketing Exposure Estimate for Xarelto (covering period from 15 SEP 2008 to 31 AUG 2019)

Strength	Tablets	Patients-Months	Patient -Years
2,5 mg[b]	51 546 819	884 524	73 710
10 mg	1 120 317 927	37 343 931	3 111 994
15 mg	3 152 855 045	105 095 168	8 757 931
20 mg	6 426 773 206	214 225 774	17 852 148
Total	**10 751 492 997**	**357 549 396**	**29 795 783**

[b] Used at a daily dose of 5 mg (2.5 mg BID)

Rivaroxaban has been evaluated in randomized controlled trials involving more than 113 000 rivaroxaban-exposed patients since start of development.

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

[1] The date range of the sales period is slightly earlier than the reporting period (01 Sep 2008 to 31 Aug 2019 versus 15 Sep 2008 to 15 Sep 2019), 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.

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.

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Part II – Module SVI: Additional EU Requirements for the Safety Specification

PART II
Module SVI: Additional EU Requirements for the Safety Specification

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	31 DEC 2016

Version number of RMP when this module was last updated	10.3

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Part II – Module SVI: Additional EU Requirements for the Safety Specification

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.

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Part II – Modules SVII: Identified and Potential Risks

PART II
Module SVII: Identified and Potential Risks

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 MAY 2020

Version number of RMP when this module was last updated	12.3

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Part II – Modules SVII: Identified and Potential Risks

Abbreviations

ACS	acute coronary syndrome
ADR	adverse drug reaction
AE	adverse event
AF	atrial fibrillation
aPTT	activated partial thromboplastin time
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
CABG	coronary artery bypass graft
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CEAC	Clinical Event Adjudication Committee
CEC	Clinical Endpoint Committee
CI	confidence interval
CIAC	central independent adjudication committee
CLARITY	Clopidogrel as Adjunctive Reperfusion Therapy
C_{max}	maximum plasma concentration of drug
C_{max}/D	dose-normalised maximum plasma concentration of drug
C_{min}	minimum plasma concentration achieved by drug
CrCl	creatinine clearance
COMMIT	ClOpidogrel and Metoprolol in Myocardial Infarction Trial
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events trial
CYP	cytochrome P450
DVT	deep vein thrombosis

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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
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 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
EMA	European Medicines Agency
ETP	endogenous thrombin potential
EU	European Union
GI	gastrointestinal
GUSTO	Global Use of Strategies to Open Occluded Arteries
HFS	hip fracture surgery
HIV	human immunodeficiency virus
INR	international normalised ratio
ISTH	International Society on Thrombosis and Haemostasis
LFT	liver function test
LLT	low level term
LMWH	low molecular weight heparin
MAA	Marketing Authorisation Application
MAGELLAN	Multicenter, rAndomized, parallel Group Efficacy and safety study in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities

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Med ill	medically ill
NSAID	non-steroidal anti-inflammatory drug
NSTE-ACS	non-ST segment elevation acute coronary syndrome
Op	operative
OR	odds ratio
PAD	Peripheral artery disease
PBRER	Periodic Benefit-Risk Evaluation Report
PE	pulmonary embolism
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
PK	pharmacokinetics
PLATO	Study of Platelet Inhibition and Patient Outcomes
PSUR	Periodic Safety Update Report
PT	preferred term
PV	Pharmacovigilance
QoL	quality of life
RECORD	REgulation of Coagulation in ORthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism
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
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SN	study number
SOC	system organ class
SPAF	stroke prevention in atrial fibrillation
TDD	total daily dose
THR	total hip replacement

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TIMI	Thrombolysis In Myocardial Infarction
TKR	total knee replacement
UFH	unfractionated heparin
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
VTE	venous thromboembolism
VTE-P	venous thromboembolism prophylaxis
XALIA	Xarelto for Long-term and Initial Anticoagulation in Venous Thromboembolism (VTE)
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
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

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Part II – Modules SVII: Identified and Potential Risks

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

2. 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 thoroughful evaluation have not been included in the list of safety concern cannot be recapitulated.

2.1 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:

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

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

- 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),
- very common in children from birth to < 18 years: vomiting
- 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:

- 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
- common in children from birth to < 18 years: thrombocytosis (incl.platelet count increased), tachycardia, increase in bilirubin, thrombocytopenia
- rare: bilirubin conjugated increased (with or without concomitant increase of ALT), jaundice, vascular pseudoaneurysm (postprocedural)
- uncommon in children from birth to < 18 years: bilirubin conjugated increased (with or without concomitant increase of ALT)

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)

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%

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Part II – Modules SVII: Identified and Potential Risks

3. Risks considered important for Inclusion in the List of Safety Concerns in the RMP

3.1 Important Identified Risks

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 definitely 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. Overall, in pivotal studies performed the majority of treatment-emergent bleeding events were mild to moderate.
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% in children from birth to less than 18 years as assessed by adjudication committees based on predefined adjudication criteria (see section 5, Table 5-1)
Severity	Overall, in pivotal studies performed the majority of treatment-emergent bleeding events were mild to moderate in severity [Source EU RMP v 9.1].

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3.2 Important Potential Risks

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 incapacity, may lead to (imminent) abortion what may be life-threatening or result in death (see section 5, Table 5-2).
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.

Safety Concern: Important potential risks	
1. 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

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	EINSTEIN Junior were reported as directly associated with other adverse events.

3.3 Missing information

Safety Concern: Missing information	
1. Patients with severe renal impairment (CrCl <30ml/min)	
Reasons for classification	Patients with severe renal impairment may be at risk of both haemorrhage and thrombosis. Clinical trial data suggest that the increased risk of thrombosis is greater with increasing kidney damage than the increased risk of bleeding. However, limited data suggest that levels of rivaroxaban in the bloodstream are increased in patients with severe renal impairment. Therefore, Xarelto is to be used withcaution in these patients. Use is not recommended in patients with creatinine clearance less than 15 mL/min.
Data required	Impact of severe renal impairment on risk of haemorrhage and thrombosis and adequate recommendation on treatment.
2. 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)	
Reasons for classification	The use of rivaroxaban in combination with strong inhibitors of both CYP3A4 and P-gp (such as ketoconazole [for fungal infections] or ritonavir [for HIV treatment]) results in increased levels of rivaroxaban and is therefore not recommended. However, weak/moderate inhibitors of CYP3A4 and P-gp, or inhibitors of only one of these two enzymes, are expected to increase rivaroxaban levels in the bloodstream to a lesser extent. Rivaroxaban should be used with caution in patients with impaired kidney function who are taking potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin).
Data required	Impact of using strong inhibitors of both CYP3A4 and P-gp on risk of haemorrhage and adequate recommendation on treatment.
3. 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.
4. Pregnant or breast-feeding women	
Reasons for classification	The safety and efficacy of rivaroxaban have not been established in pregnant or breast-feeding women. Animal studies have suggested reproductive toxicity and secretion of rivaroxaban in milk. Therefore, it is contraindicated during pregnancy and breast-feeding. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto.
Data required	Impact on pregnant or breast-feeding women on the unborn or newborn infant, or the pregnant women (bleeding).

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Safety Concern: Missing information	
5. 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.
6. Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	
Reasons for classification	Based on post-marketing exposure for more than 16.9 million patient years, and the information received from the extensive clinical program (exposure of over 18 months: 7398 patients, 14,918 patient-years), and long-term data from clinical practice (e.g. XANTUS and XALIA), limitations appear to minimal.
Data required	Reassuring data for all different dosages, indications, treatment durations and populations.
7. Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	
Reasons for classification	The risks of Xarelto use in patients with severe liver impairment are unknown, as these patients were excluded from clinical trials. In patients with liver disease that is associated with blood clotting disorders (including patients with Child-Pugh B or C with cirrhosis), the use of Xarelto is contraindicated.
Data required	Impact on patients with significant liver diseases

4. New Safety Concerns and Reclassification with a Submission of an Updated RMP

None.

Missing information on Patients < 18 years removed with the submission of pediatric program.

5. Details of Important Identified Risks, Important Potential Risks, and Missing Information

General information

In the current EU RMP version 12.3 vs. the previous version 11.4, data of the completed pediatric study program including the recently completed phase III study EINSTEIN Junior have been added:

Phase III study EINSTEIN Junior (SN 14372): Multicenter, open-label, active-controlled, randomized 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

Regarding spontaneous post marketing ADR reports, the DLP for the data presented in this section was 15 SEP 2019 (note: this DLP is taken from the PSUR/PBRER No 18) unless stated otherwise.

In the following, important identified risks are defined as the most important identified adverse events / adverse reactions that are 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.

5.1 Details of Important Identified Risks: Haemorrhage

Potential mechanism:

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.

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Evidence source 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; EU RMP version 6.5; PH39589; EU RMP version 10.3.; COMPASS, PH-39342, PBRER/PSUR No. 16.0.

Characterization:

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 also in patients receiving comparator (e.g. enoxaparin/VKAs.

The variability in the rate of bleeding across the rivaroxaban programme may be due to differences in baseline characteristics, 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 study of rivaroxaban for VTE prevention in medically ill patients (VTE P in Med ill). 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 5-1 the incidence of treatment-emergent bleeding events in Phase III studies is presented under treatment with rivaroxaban:

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Table 5-1: Incidence of treatment-emergent bleeding events in Phase III studies (as assessed by respective CIAC based on pre-defined adjudication criteria; EINSTEIN Choice investigator reported)

	Any bleeding				Major			
	Rivaroxaban		Comparator		Rivaroxaban		Comparator	
RECORD	6.30%	(384/6097)	5.81%	(355/6109)[A]	0.36%	(22/6097)	0.16%	(10/6109)[A]
Surgical site	3.40%	(207/6097)	3.04%	(186/6109)	0.21%	(13/6097)	0.10%	(6/6109)
Extra-surgical site	3.20%	(195/6097)	2.96%	(181/6109)	0.15%	(9/6097)	0.07%	(4/6109)
Pooled EINSTEIN-DVT and -PE	28.30%	(1169/4130)	28.00%	(1153/4116)[B]	1.0%	(40/4130)	1.7%	(72/4116)[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%	(360/2234)	13.62%	(154/1131)[D]	0.49%	(11/2234)	0.27%	(3/1131)[D]
Pooled ROCKET and J-ROCKET	22.68%	(1758/7750)	22.00%	(1708/7764)[E]	5.43%	(421/7750)	5.36%	(1708/7764)[E]
PIONEER AF-PCI	31.95%	448/1402	40.03%	279/697[FG]	1.85%	(26/1402)[E]	2.87%	(20/697)[FG]
MAGELLAN (up to day 35)	12.5%	(501/3997)	8.5%	(341/4001)[A]	1.1%	(43/3997)	0.4%	(15/4001)[A]
ATLAS ACS 2–TIMI 51	22%	(2252/10225)	12.5%	(643/5125)[C]	1.5%	(153/10225)[E]	0.5%	(27/5125)[CF]
COMPASS	10.7%	(1953/18244)	6.7%	(613/9107)	2.7%	(488/18244)	1.6%	(144/9107)
EINSTEIN Junior Phase III	39.5%	(130/329)	30.2%	(49/162)[H]	0%	0/329	1.2%	(2/162)

[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)

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]

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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 5 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 (50/10225 [0.5%]) and haematuria (28/10225 [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 (680/18244) [3.7%], from the respiratory tract (464/18244) [2.5%], and epistaxis, (403/18244) [2.2%]).n In Table 5-2 the incidence of treatment-emergent adverse events and bleeding events as reported by investigator from the COMPASS study is presented:

Table 5-2: 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=9134 (100%)	Rivaroxaban 5mg bid N=9110 (100%)	ASA 100mg od N=9107 (100%)
Any Event	1149 (12.6%)	1027 (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%)

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)

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[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 5–3: Study 14372: Principal safety outcome during the main treatment period; Safety Analysis Set

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 rates (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].

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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 modied 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 5mg 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, 2 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 5–4 Study 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 period	Age group (years)	Rivaroxaban		Comparator	
		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

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 = 8778; standard of care, N = 8635) 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].

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 benefit-risk balance:

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 ISTH guidelines) 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 ($\geq$ 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].

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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 5mg 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 10.3].

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% (3/4130) in the rivaroxaban (2 intracranial, 1 gastrointestinal bleeding) and 0.2 % (8/4116) 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% [22/7750]) than the warfarin group (0.58% [45/7764]). 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] and [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).

5.2 Details of Important Potential Risks: 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 (1). 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 (2). 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 (3).

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 are 489 case reports of maternal drug exposure during pregnancy (17 of which are from company-sponsored clinical trials). The duration of exposure during pregnancy in these cases ranged from 1 day to ≥ 25 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 **Error! Reference source not found.**.

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

Outcome	Number of cases			Duration of exposure
	Post-marketing	Clinical trial	Total	
Live birth	**136[a]**	**2**	**138[a]**	**1 d to ≥ 25 wks or throughout pregnancy**
Healthy	80	2	82	~5 d to ≥ 25 wks or throughout pregnancy
Relevant findings[b]	9[a]	0	9[a]	2 wks 2 d to 21 wks
Transient findings/IUGR/premature birth only[c]	11	0	11	6 d to 19 wks
Unknown outcome	36[a]	0	36[a]	1 d to 25 wks 1 d
Abortion	**93**	**14**	**107**	**2 d to 18 wks**
Spontaneous[d]	49	4	53	2 d to 18 wks
Therapeutic[e]	4	1	5	1 wk 3 d
Elective[f]	40	9	49	3 d to 12 wks
Stillbirth	**4**	**0**	**4**	**11 wks[g]**
Unknown[h]	**234**	**1**	**235**	**1 d to 22 wks**
Other[i]	**5**	**0**	**5**	**Not reported**

[a]Number includes 1 case with implied live birth (child born with ventricular septal defect and birth weight of 3 kg).
[b]Confirmed (n = 8) or suspected (n = 1) relevant findings; incudes the case of cleft palate and jaundice/weight loss; see PBRER/PSUR No. 18.0 section 16.4.2 for details.
[c]Transient findings included methadone in a neonate whose mother had received methadone substitution therapy (n = 1), clinical icterus (n = 1), mild hip dysplasia and flu-like symptoms (n = 1), mild hypoglycemia and episodes of apnea-bradycardia (n = 1), and transient hypoglycemia and transient hypocalcemia (n = 1) as well as IUGR (n = 6) (see PBRER/PSUR No. 18.0 section 16.4.2 for details of IUGR cases) and premature birth (n = 2). Some neonates had more than one transient findings.
[d]Of the 53 cases of spontaneous abortion, 5 reported findings related to the fetus (IUGR [n = 2], findings consistent with chromosomal abnormalities [n = 1], crumpled limbs [n = 1] and anhydramnios [n = 1]); no other relevent findings related to the fetus were reported.
[e]The reason for therapeutic abortion was reported as absence of cerebellum and vertebral column in the fetus in 1 case, recurrent DVT in the mother in 1 case, and persistent anhydramnios and premature rupture of membranes in 1 case; in the remaining 2 cases of therapeutic abortion, the reason was unclear.
[f]Of the 46 cases of elective abortion, 1 reported findings related to the fetus (ventricular septal defect and truncus arteriosus persistent).
[g]Duration of exposure was only reported in one case.
[h]Pregnancies with unknown outcomes included ongoing pregnancies, 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.
[i]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); and 3 ectopic pregnancies
IUGR, intrauterine growth restriction.

Characterization:

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 (4). 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; $p = 0.033$) (4). 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 (5).

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%; $p = 0.003$) (6).

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 (36). 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].

5.3 Details of Important Potential Risks: 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.

5.4 Details of Missing information: Patients with severe renal impairment (CrCl < 30 mL/min)

Evidence source: Patient population has not been studied

Population in need of further characterization: Respective patients with severe renal impairment

Anticipated risk/consequence: Increased risk of bleeding

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

Evidence source: Pharmacokinetc data

Population in need of further characterization: Respective patients

Anticipated risk/consequence: Increased risk of bleeding.

5.6 Details of Missing information: Remedial pro-coagulant therapy for excessive haemorrhage

Evidence source: Clinical life scenarios, requests

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

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

5.7 Details of Missing information: Pregnant or breast-feeding women

Evidence source: Pharmacokinetic data, pregnancy/nursing mother reports

Population in need of further characterization: respective population

Anticipated risk/consequence: Increased risk of bleeding.

5.8 Details of 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

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

Evidence source: Limitation of respective data

Population in need of further characterization: Patients under long-term therapy, health care professionals

Anticipated risk/consequence: Inadequate anticoagulation therapy, increased risk of bleeding, adverse drug reactions

5.10 Details of Missing information: Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

Evidence source: Patient subpopulation has not been studied

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

Anticipated risk/consequence: Increased risk of bleeding.

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Part II – Modules SVIII: Summary of the Safety Concerns

PART II
Module SVIII: Summary of the Safety Concerns

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 SEP 2019

Version number of RMP when this module was last updated	12.3

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Part II – Modules SVIII: Summary of the Safety Concerns

Abbreviations

ACS	Acute Coronary Syndrome
AF	atrial fibrillation
CAD	Coronary Artery Disease
CrCl	Creatinine Clearance
CYP	Cytochrome P 450 (enzyme)
DVT	Deep Venous Thrombosis
HIV	Human Immuno-deficiency Virus
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PAD	Peripheral Artery Disease
PE	Pulmonary Embolism
P-gp	P-glycoprotein (Multidrug-resistance-protein)
RMP	Risk Management Plan
SPAF	Stroke prevention in atrial fibrillation (indication)

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Part II – Modules SVIII: Summary of the Safety Concerns

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	• Patients with severe renal impairment (CrCl < 30 mL/min) • 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) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

PART III

Pharmacovigilance Plan

Active substance:	Rivaroxaban
Product(s) concerned	Xarelto
MAH/MAA name	Bayer AG

Data lock point for this module	15 SEP 2019
Version number of RMP when this module was last updated	12.3

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Part III – Pharmacovigilance Plan

Abbreviations

ACS	acute coronary syndrome
AE	adverse event
AF	atrial fibrillation
CAD	Coronary artery disease
CI	confidence interval
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CrCl	creatinine clearance
CYP	cytochrome P450
DLP	data lock point
DVT	deep vein thrombosis
DVT-T	Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults
EMA	European Medicines Agency
EU	European Union
FPFV	first patient, first visit
GePaRD	German Pharmacoepidemiological Research Database
HIV	human immunodeficiency virus
LPLV	last patient, last visit
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
M-PEM	modified prescription event monitoring
OR	odds ratio
PAD	Peripheral artery disease
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamic
PE	pulmonary embolism
PEM	prescription event monitoring

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Part III – Pharmacovigilance Plan

PE-T	Treatment of pulmonary embolism (PE) and prevention of recurrent deep vein (DVT) thrombosis and PE in adults
P-gp	p-glycoprotein
PhV	Pharmacovigilance
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RECORD	REgulation of Coagulation in ORthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism
RMP	Risk Management Plan
SAE	serious adverse event
SCEM	Specialist Cohort Event Monitoring
SmPC	Summary of Product Characteristics
SoC	standard of care
SPAF	stroke prevention in atrial fibrillation
TBD	to be decided
THIN	The Health Improvement Network
THR	total hip replacement
TKR	total knee replacement
VTE	venous thromboembolism
VTE-P	venous thromboembolism prophylaxis
XALIA	Xarelto for long-term and initial anticoagulation in venous thromboembolism (VTE)
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-embolism in patients with non-valvular atrial fibrillation: a non-interventional study

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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.

1.1 Specific Adverse Reaction Follow-up Questionnaires

The internal User Guidance in its updated version, valid from 13-MAR-2017, mentioned the following Specific Questionnaires:

i. LIVER-RELATED ADVERSE EVENTS

ii. RENAL IMPAIRMENT/RENAL FAILURE

iii. SEVERE HYPERSENSITIVITY

iv. SEVERE SKIN REACTIONS

1.2 Other forms of Routine Pharmacovigilance Activities

None.

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. Studies finalization is estimated for Q4 2020.Three active surveillance studies with a two-component prescription monitoring event (PEM) design in the UK. In this active surveillance design, follow-up questionnaires are 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. Two of these studies have been finalized; one is currently ongoing and will be finalised December 2019.

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Progress reports for all Category 1 PASS studies, are provided annually in the PSURs/PBRERs. Interim reports are provided as agreed with the regulatory authorities.

In the paediatric indication "Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence" one Category 3 PASS study is planned to investigate the use of rivaroxaban in children from birth to less than 2 years of age to gather more data on the safety profile of rivaroxaban in paediatric use, particularly regarding the bleeding pattern in the youngest children.

In addition, one Category 3 PASS study is ongoing to assess the effectiveness of additional risk minimization activities in place for rivaroxaban (i.e. Patient Alert Card and Prescriber Guide). The integrated study programme is summarized as follows:

Category 1 PASS Studies

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 will provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care (warfarin) for the first time, describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment), and determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it will evaluate safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban in comparison with individuals receiving current standard of care. This is being 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 2 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 January, 2012 and will end on 31 December, 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017. Final study report will be submitted in Q4 2020.

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

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

Rationale and study objectives:

This study will provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care (phenprocoumon) for the first time, describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment) and determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it will evaluate safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban in comparison with individuals receiving current standard of care. This is being 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 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 09 December, 2011 (following marketing authorization in Germany) and will end on 31 December, 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017. Final study report will be submitted in Q4 2020.

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)

Rationale and study objectives:

This study will provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care (acenocoumarol or phenprocoumon) for the first time, describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment) and determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it will evaluate safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban in comparison with individuals receiving current standard of care. This is being

conducted in collaboration with the PHARMO Institute for Drug Outcomes Research, The Netherlands.

Study design:

This study has a cohort design.

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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 December, 2011 (following market authorization in The Netherlands) and will end on 31 December, 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017. Final study report will be submitted in Q4 2020.

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 will provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care (warfarin) for the first time, describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment) and determine time-trends in the characteristics of first-time use of rivaroxaban. In addition, it will evaluate safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; non-infective liver disease) and effectiveness outcomes among users of rivaroxaban in comparison with individuals receiving current standard of care. This is being 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 December, 2011 (when rivaroxaban received marketing authorization in Sweden) and will end on 31 December, 2018. Interim reports were submitted to EMA Q4 2015 and Q4 2017. Final study report will be submitted in Q4 2020.

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 January 2012- June 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 January, 2012 and ended in June, 2016. Interim reports were submitted to EMA Q1 2014 and Q4 2015. Final study report was submitted in Q4 2017.

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 will monitor 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 are 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 is being conducted in collaboration with Drug Safety Research Unit (DSRU), Southampton, UK.

Study design:

This study had 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 will end in Q1 2019 for the patients recruited during September 2015 and May 2017. Interim report will be submitted to EMA Q4 2017. Final study report will be submitted in Q4 2019.

Category 3 PASS Studies

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)

Rationale and study objectives:

This study serves 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), with the aim of increasing 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 prescriber guide and PAC, respectively, and to evaluate their awareness and understanding of the key safety messages. Evaluation surveys were planned for administration in 3 waves at 18 months, 3 years, and 7 years post launch. The patient surveys have been discontinued after wave 1. This study is being conducted by RTI Health Solutions, with assistance of Kantar Health for field operations.

Study design:

This study has a cross-sectional design.

Study population:

Eligible physicians and patients with recent rivaroxaban experience are invited to complete a questionnaire regarding their knowledge of key safety in the rivaroxaban educational materials.

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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 Q1 2018. Wave 3 and final study report submission are planned for Q4 2019 – Q1/Q2 2020 and Q3 2020, respectively.

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 September 2019.

Study short name and title: **SN XXXXX – Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban or other anticoagulants**

Rationale and study objectives

This study will investigate the safety of rivaroxaban granules for oral suspension in at least 50 very young (< 2 years of age) VTE patients from start of rivaroxaban treatment until 1 month (30 days) after stop of treatment and children with VTE treated with other anticoagulants.

In addition to the routine collection of AEs, processes (or measures) will be implemented in this study aiming to collect relevant information which may detect safety events indicative of

medication errors related to the use of the granules for oral suspension formulation (e.g. use of treatment/dosing diaries, additional follow-up calls by site personnel where legally permitted).

Study design:

Non-interventional, multi-centre cohort study evaluating the safety and tolerability of rivaroxaban granules for oral suspension in children from birth to less than 2 years diagnosed with VTE and children with VTE treated with other anticoagulants.

Study population:

Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban and children diagnosed with VTE and treated with other anticoagulants.

Milestones:

Feasibility report to be submitted to EMA within Q1 2021. Data collection starts with commercial availability (product listed in pharmacy formulary and available for prescription by the treating physician) of the liquid formulation in the market in one major EU country (France, Germany, Italy, Spain) (estimated Q3-Q4 2021) and will end three years after enrolment of first patient (estimated Q3-Q4 2024). Interim report (study progress report) report will be submitted to EMA within one year after start of data collection (estimated Q3-Q4 2022). Final study report of study results will be submitted to EMA within six months after end of data collection of last patient (LP) treated with rivaroxaban (estimated Q1-Q2 2025).

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3. Summary Table of additional Pharmacovigilance Activities

Table 3-1: On-going and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
THIN (UK) (SN 16647)				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **THIN (UK) (SN 16647)** **(EUPAS11299)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years	Start of data collection Interim report 1 Interim report 2 End of data collection Final data available Final report of study results	Q4 2011 Q4 2015 submitted on 21 Dec 2015 Q4 2017 submitted on 15 Nov 2017 Q4 2018 Q4 2019 Q4 2020
GePaRD (Germany) (SN 16159)				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings;	**Important identified risk:** • Haemorrhage **Important potential risk:**	Start of data collection Interim report 1	Q1 2012 Q4 2015 submitted on

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033]): **GePaRD (Germany) (SN 16159)** **(EUPAS11145)** Ongoing	other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	• Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years		21 Dec 2015 Interim report 2 Q4 2017 submitted on 15 Nov 2017 End of data collection Q4 2018 Final data available Q4 2020 Final report of study results Q4 2020
PHARMO (the Netherlands) (SN 16646)				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **PHARMO (the Netherlands) (SN 16646)** **(EUPAS11141)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in	Start of data collection Q1 2012 Interim report 1 Q4 2015 submitted on 21 Dec 2015 Interim report 2 Q4 2017 submitted on 15 Nov 2017 End of data collection Q4 2018 Final data available Q4 2019 Final report of study results Q4 2020	

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		treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years		

Swedish National Registers (Sweden) (SN 17543)

Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation

Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **Swedish National Registers (Sweden) (SN 17543)** **(EUPAS9895)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years	Start of data collection End of data collection Interim report 1 Interim report 2 Final data available Final report of study results	Q4 2011 Q4 2018 Q4 2015 submitted on 21 Dec 2015 Q4 2017 submitted on 15 Nov 2017 Q4 2019 Q4 2020

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SCEM ACS (SN 17542)

Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation

Specialist Cohort Event Monitoring Study for ACS **(SCEM ACS) (PAM [ANX 034])** **(EUPAS9977)** Ongoing	To proactively monitor the short-term safety and drug utilisation of rivaroxaban for the secondary prevention of major cardiovascular events in patients with ACS with elevated biomarkers as prescribed to patients by specialists	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years	Start of data collection Interim report 1 End of data collection Final report of study results	Q3 2015 Q4 2017 submitted on 15 Nov 2017 Q1 2019 (estimated) Q4 2019 (estimated)

Risk Minimisation Survey Study (SN 16167)

Category 3 - Required additional pharmacovigilance activities

Survey on Prescribers' Guide/Patient Alert Card (for DVT-T and SPAF) PAM [MEA 23]	To measure physician and patient awareness and understanding of the key messages in the prescriber guide and patient card	**Important identified risk:** • Haemorrhage	Questionnaires finalized following cognitive testing Regulatory and ethical approval Start of data	Q2 2013 Q2 2014 Q3 2014

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(SN 16167) Ongoing			collection (Wave 1) End of data collection (Wave 1) Report of study results (Wave 1) Start of data collection (Wave 2) End of data collection (Wave 2) Report of study results (Wave 2) Start of data collection (Wave 3) End of data collection (Wave 3) Final report of study results (Wave 3)	 Q2 2015 Submitted 11 Dec 2015 Q1 2017 Q3 2017 Q1/Q2 2018 submitted on 13 Jun 2018 Q3 2019 – Q1 2020 (estimated) Q1/Q2 2020 (estimated) Q1/Q2 2020 (estimated)

Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban in comparison to children with VTE treated with other anticoagulants (SN XXXXX)				
Category 3 - Required additional pharmacovigilance activities				
Non-interventional cohort study In planning	To investigate the safety of rivaroxaban granules for oral suspension in at least 50 very young (< 2 years of age) VTE	**Important identified risk:** • Haemorrhage **Important potential**	Feasibility report Start of data collection	Submission Q1 2021 Estimated Q3-Q4 2021

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	patients in comparison to children with VTE treated with other anti-coagulants.	**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	Interim report (study progress report) End of data collection Final report of study results (6 months after end of data collection LP treated with Xarelto)	One year after start of data collection Estimated Q3-Q4 2022 Estimated Q3-Q4 2024 Estimated Q1-Q2 2025

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Part IV – Plans for post-authorisation efficacy studies

PART IV

Plans for post-authorisation efficacy studies

Active substance:	Rivaroxaban
Product(s) concerned	Xarelto
MAH/MAA name	Bayer AG

Data lock point for this module	31 DEC 2016
Version number of RMP when this module was last updated	10.0

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Part IV – Plans for post-authorisation efficacy studies

1. List of the Planned and Ongoing Imposed Post-authorization Efficacy Studies

Table 1-1: 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 circumstance				
None				

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Part V – Risk Minimisation Measures

PART V
Risk Minimisation Measures

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 SEP 2019

Version number of RMP when this module was last updated	12.4

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Part V – Risk Minimisation Measures

Abbreviations

ACS	acute coronary syndrome
APCC	activated prothrombin complex concentrate
AUC	area under the curve
CAD	Coronary artery disease
C_{max}	maximum observed plasma concentration
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CrCl	creatinine clearance
CYP	cytochrome P450
DUS	drug utilisation study
DVT	deep vein thrombosis
HIV	human immunodeficiency virus
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
NSAID	non-steroidal anti-inflammatory drug
PAD	peripheral arterial disease
PBRER	Periodic Benefit-Risk Evaluation Report
PCC	prothrombin complex concentrate
PD	pharmacodynamic
PE	pulmonary embolism
P-gp	p-glycoprotein
PK	pharmacokinetics
PSUR	Periodic Safety Update Report
PT	prothrombin time
rFVIIa	recombinant Factor VIIa
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPAF	stroke prevention in atrial fibrillation
UFH	unfractionated heparin
VKA	vitamin K antagonist

VTE	venous thromboembolism
VTE-P	venous thromboembolism prophylaxis
VTE-T	venous thromboembolism treatment

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Part V – Risk Minimisation Measures

1. Risk Minimisation Plan

One 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) has been identified since last submission of a RMP update. Therefore, new risk minimisation activities are lined out in this section. The routine risk minimisation measures already in place are presented in the next section.

2. Routine Risk Minimisation Measures

Desription of routine risk minimisation measures by safety concern **important identified risk**	
Important identified risk	**Routine risk minimisation activities**
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) 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 4.4.2 (Special warnings and precautions for use) Pat. with severe renal impairment or increased bleeding risk: monitoring for signs of bleeding, regular physical examination, close observation of the surgical wound drainage, periodic measurements of haemoglobin • Section 4.4.5 (Special warnings and precautions for use) Information on groups of patients with an increased bleeding risk is provided, as well as procedre for neuraxial (epidural/spinal) anesthesia and for surgery and interventions • Section 4.4.6 (Special warnings and precautions for use) Patients with prosthetic heart valves • Section 4.5 (Interaction with other medicinal products and other forms of interaction)

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Desription of routine risk minimisation measures by safety concern **important identified risk**	
Important identified risk	**Routine risk minimisation activities**
	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 is communicated. **Other routine risk minimisation measures beyond the Product Information:** Pack size limited Prescription medicine

Desription of routine risk minimisation measures by safety concern **important potential risk**	
Important potential risk	**Routine risk minimisation activities**
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 4.4.7 (Women of childbearing potential) Use of effective contraception. • Section 4.6 (Pregnancy and lactation) Information: contraception should be used in women of childbearing potential; nursing to be stopped as rivaroxaban is secreted into breast milk **Other routine risk minimisation measures beyond the Product Information:** None
Desription of routine risk minimisation measures by safety concern **important potential risk**	

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Important potential risk	Routine 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	**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

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Desription of routine risk minimisation measures by safety concern **missing information**	
Missing information	**Routine risk minimisation activities**
Patients with severe renal impairment (CrCl < 30 mL/min)	**Routine risk communication:** SmPCs: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Comment (e.g. on any differences between SmPCs) Indication specific differences are listed in the respective SmPCs **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Section 4.4.2 (Renal impairment) • Patients with severe renal impairment to be carefully monitored for signs of bleeding complications • Regular physical examination of patients, periodic measurements of haemoglobin • Awareness that patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min) have increased rivaroxaban exposure, to prevent physicians prescribing rivaroxaban to patients with CrCl < 15 mL/min **Other routine risk minimisation measures beyond the Product Information:** Prescription-only medicine Limited pack sizes
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)	**Routine risk communication:** SmPCs: Section 4.4 (Special warnings and precautions for use): Section 4.5 (Interaction with other medicinal products and other forms of interaction): Indication specific differences are listed in the respective SmPCs. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Patients with azole-antimycotics or HIV protease inhibitors are to be carefully monitored for signs of bleeding complications • Regular physical examination of patients, periodic measurements of haemoglobin

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Desription of routine risk minimisation measures by safety concern **missing information**	
Missing information	**Routine risk minimisation activities**
	Other routine risk minimisation measures beyond the Product Information: Prescription-only medicine Limited pack sizes
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:** • Section 4.9.1 (Management of bleeding) additional information is provided **Other routine risk minimisation measures beyond the Product Information:** Prescription-only medicine Limited pack sizes
Pregnant or breast-feeding women	**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:** None **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

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Desription of routine risk minimisation measures by safety concern **missing information**	
Missing information	**Routine risk minimisation activities**
	Other routine risk minimisation measures beyond the Product Information: Prescription-only medicine Limited pack sizes
Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	**Routine risk communication:** None **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
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	**Routine risk communication:** SmPCs: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 5.2 (Pharmacokinetic properties) **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

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3. Additional Risk Minimisation Measures

Desription 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 these 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 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 drug utilisation studies with outcomes (DUS), modified prescription event monitoring studies, post-marketing non-interventional studies 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 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 will be 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 Part VII Annex 6). These two

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Desription of additional risk minimisation measures by safety concern **important identified risk**	
Important identified risk	**Additional risk minimisation activities**
	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. Following wave 1, patient surveys have been discontinued. Status of these surveys will be presented regularly in PSURs/PBRERs. Progress, interim and final reports on drug utilisation studies with outcome and prescription event monitoring studies will be included in PSURs/PBRERs. Study status updates as well as demography, therapy and safety data of the post-marketing non-interventional studies including a summary 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 will evaluate physicians' knowledge of the key messages in the Prescriber guide only. Based on data from conducted post-marketing studies it can be assumed that the impact of the risk minimisation tools is overall positive.

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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-

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Desription of additional risk minimisation measures by safety concern **important potential risk**	
Important potential risk	**Additional risk minimisation activities**
	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

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

3.1 Removal of additional risk minimisation measures

None

4. Summary of Risk Minimisation Measures

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**	**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:** • Drug utilisation and

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Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	measures: Educational material for prescribers Patient alert cards	specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
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:** • Drug utilisation and specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
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:**	**Additional PV activities:** Non-interventional study in children from birth to less than 2 years

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Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	Educational material for prescribers Patient alert cards Video	
Missing information: patients with severe renal impairment (CrCl < 30 mL/min)	**Routine risk minimisation measures:** SmPCs: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions 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 Periodic and ad hoc analysis and update on 'renal impairment', in PBRER/PSUR **Additional PV activities:** • Drug utilisation and specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
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
Missing information: patients receiving	**Routine risk minimisation measures:** SmPCs:	**Routine PV activities:** AE/ADR collection,

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Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** None	evaluation and reporting, Signal detection **Additional PV activities:** • Drug utilisation and specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: pregnant or breast-feeding women	**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 'pregnancy' reports, maternal exposure and 'breast-feeding' incl. outcome (if available) in every PBRER/PSUR **Additional PV activities:** • Drug utilisation and specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: patients with	**Routine risk minimisation measures:** SmPCs:	**Routine PV activities:** AE/ADR collection,

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Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
prosthetic valves	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	evaluation and reporting, Signal detection **Additional PV activities:** None
Missing information: long-term therapy for treatment of DVT, PE, SPAF and ACS in real-life setting	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection **Additional PV activities:** • Drug utilisation and specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: patients with significant liver diseases (severe hepatic impairment/ Child Pugh C)	**Routine risk minimisation measures:** SmPCs: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 5.2 (Pharmacokinetic properties) Prescription-only medicine Limited pack sizes Exclusion from clinical development	**Routine PV activities:** AE/ADR collection, evaluation and reporting, Signal detection **Additional PV activities:** • Drug utilisation and specific outcome studies • Modified Prescription Event Monitoring Study (M-PEM) • Specialist Cohort

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Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	program **Additional risk minimisation measures:** None	Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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Part VI – Summary of Activities in the Risk Management Plan by Product

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Summary of Activities in the Risk Management Plan by Product

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 MAY 2020

Version number of RMP when this module was last updated	12.3

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Abbreviations

ACS	acute coronary syndrome
AF	atrial fibrillation
APCC	activated prothrombin complex concentrate
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
CAD	Coronary artery disease
C_{max}	maximum observed plasma concentration
CrCl	creatinine clearance
CYP	cytochrome P450
DVT	deep vein thrombosis
DVT-T	Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GePaRD	German Pharmacoepidemiological Research Database
HIV	human immunodeficiency virus
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MI	myocardial infarction
NSAID	non-steroidal anti-inflammatory drug
PAD	Peripheral artery disease
PASS	Post-authorization safety study
PCC	prothrombin complex concentrate
PD	pharmacodynamic
PE	pulmonary embolism
PE-T	Treatment of pulmonary embolism (PE) and prevention of recurrent deep vein (DVT) thrombosis and PE in adults
P-gp	p-glycoprotein

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PhV	Pharmacovigilance
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PL	package leaflet
PT	prothrombin time
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
SmPC	Summary of Product Characteristics
SPAF	stroke prevention in atrial fibrillation
THIN	The Health Improvement Network
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE-T	venous thromboembolism treatment
XALIA	Xarelto for Long-term and Initial Anticoagulation in Venous Thromboembolism (VTE)
XANTUS	Xarelto in prevention of stroke and non-embolism in patients with non-valvular atrial fibrillation: A non-interventional study

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Summary of Risk Management Plan 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 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.

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.
- Proposed: Xarelto is indicated for the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years after initial parenteral anticoagulation treatment.

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

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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.

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*.

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

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. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

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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	• Patients with severe renal impairment (CrCl < 30 mL/min) • 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) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

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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, EU RMPs 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.
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	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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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

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Important potential risk: embryo-fetal toxicity	
	Additional risk minimisation measures: None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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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 Patient alert cards Video

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Additional pharmacovigilance activities	Non-interventional study in children from birth to less than 2 years of age

Missing information: Patients with severe renal impairment (CrCl < 30 mL/min)	
Evidence for linking the risk to the medicine	Patient population has not been studied
Risk factors and risk groups	Respective patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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Missing information: 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)	
Evidence for linking the risk to the medicine	Pharmacokinetc data
Risk factors and risk groups	Respective patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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

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Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	
Additional pharmacovigilance activities	None

Missing information: Pregnant or breast-feeding women	
Evidence for linking the risk to the medicine	Pharmacokinetic data, pregnancy/nursing mother reports
Risk factors and risk groups	Respective population
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
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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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

Missing information: Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	
Evidence for linking the risk to the medicine	Limitation of respective data
Risk factors and risk groups	Patients under long-term therapy, health care professionals
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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Missing information: Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	
Evidence for linking the risk to the medicine	Patient subpopulation has not been studied
Risk factors and risk groups	Respective patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 5.2 (Pharmacokinetic properties) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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2.3 Post-authorisation Development Plan

2.3.1 Studies which are conditions of the Marketing Authorisation

THIN (UK) (SN 16647)

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

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **THIN (UK) (SN 16647)** **(EUPAS11299)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years	Start of data collection Interim report 1 Interim report 2 End of data collection Final data available Final report of study results	Q4 2011 Q4 2015 submitted on 21 Dec 2015 Q4 2017 Q4 2018 Q4 2019 Q4 2020

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GePaRD (Germany) (SN 16159)

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

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **GePaRD (Germany) (SN 16159)** **(EUPAS11145)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years	Start of data collection Interim report 1 Interim report 2 End of data collection Final data available Final report of study results	Q1 2012 Q4 2015 submitted on 21 Dec 2015 Q4 2017 Q4 2018 Q4 2020 Q4 2020

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PHARMO (the Netherlands) (SN 16646)

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

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **PHARMO (the Netherlands) (SN 16646)** **(EUPAS11141)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years	Start of data collection Interim report 1 Interim report 2 End of data collection Final data available Final report of study results	Q1 2012 Q4 2015 submitted on 21 Dec 2015) Q4 2017 Q4 2018 Q4 2019 Q4 2020

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Swedish National Registers (Sweden) (SN 17543)

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

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug utilisation and specific outcome studies for DVT-T, PE-T, SPAF and ACS (PAM [ANX 033]): **Swedish National Registers (Sweden) (SN 17543)** **(EUPAS9895)** Ongoing	To evaluate specific safety outcomes (intracranial, gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) • Patients < 18 years	Start of data collection End of data collection Interim report 1 Interim report 2 Final data available Final report of study results	Q4 2011 Q4 2018 Q4 2015 Submitted on 21 Dec 2015 Q4 2017 Submitted on 15 Nov 2017 Q4 2019 Q4 2020

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M-PEM (SN 16164)

Purpose of the study: 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 Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
M-PEM (SN16164) Modified Prescription Event Monitoring Study (M-PEM) for DVT-T, PE-T, SPAF and ACS **(EUPAS15961)** Ongoing	To proactively capture safety and drug utilisation data for rivaroxaban as prescribed to patients by general practitioners in primary care	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant/ breast-feeding women • Long-term therapy with rivaroxaban for DVT, PE, SPAF and ACS treatment in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years	Start of data collection	Q4 2011
			Start of extended data collection	Q4 2014 (continued from original M-PEM study)
			End of data collection	Q4 2016
			Interim report 1	Q1 2014 (presented in PSUR/PBRER No 11)
			Interim report 2	Submitted 21 Dec 2015
			Final study report	Q4 2017 Submitted on 15 Nov 2017

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SCEM ACS (SN 17542)

Purpose of study: This study will monitor 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 are 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 is being conducted in collaboration with Drug Safety Research Unit (DSRU), Southampton, UK.

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Specialist Cohort Event Monitoring Study for ACS **(SCEM ACS)** **(PAM [ANX 034])** **(EUPAS9977)** Ongoing	To proactively monitor the short-term safety and drug utilisation of rivaroxaban for the secondary prevention of major cardiovascular events in patients with ACS with elevated biomarkers as prescribed to patients by specialists	**Important identified risk:** • Haemorrhage **Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years	Start of data collection Interim report 1 End of data collection Final report of study results	Q3 2015 Q4 2017 Submitted on 15 Nov 2017 Q1 2019 (estimated) Q4 2019 (estimated)

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2.3.2 Other Studies in Post-authorisation Development Plan

Risk Minimisation Survey Study (SN 16167)

Purpose of the study: This study serves 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), with the aim of increasing 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 prescriber guide and PAC, respectively, and to evaluate their awareness and understanding of the key safety messages. Evaluation surveys were planned for administration in 3 waves at 18 months, 3 years, and 7 years post launch. The patient surveys have been discontinued after wave 1. This study is being conducted by RTI Health Solutions, with assistance of Kantar Health for field operations.

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Survey on Prescribers' Guide/Patient Alert Card (for DVT-T and SPAF) PAM [MEA 23]) (SN 16167) Ongoing	To measure physician and patient awareness and understanding of the key messages in the prescriber guide and patient card	**Important identified risk:** • Haemorrhage	Questionnaires finalized following cognitive testing	Q2 2013
			Regulatory and ethical approval	Q2 2014
			Start of data collection (Wave 1)	Q3 2014
			End of data collection (Wave 1)	Q2 2015 (completed)
			Report of study results (Wave 1)	Q4 2015 submitted on 11 Dec 2015
			Start of data collection (Wave 2)	Q4 2016/Q1 2017 (estimated)
			End of data collection (Wave 2)	Q3/Q4 2017 (estimated)
			Report of study results (Wave 2)	Q1/Q2 2018 (estimated)
			Start of data collection (Wave 3)	Q1/Q2 2019 (estimated)
			End of data collection (Wave 3)	Q3/Q4 2019 (estimated)
			Final report of study results (Wave 3)	Q1/Q2 2020 (estimated)

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Paediatric Investigational Programme (PIP)

Purpose of the study: This study will monitor the short-term safety and drug utilisation of rivaroxaban in patients who are less than 18 years of age. This will include clinical evaluation of the safety, tolerability, pharmacokinetics and pharmacodynamics of rivaroxaban administered as either an oral suspension or film-coated tablets in children from term birth to less than 18 years of age who have been treated for venous thromboembolism following initiation of standard anticoagulation treatment either with low molecular weight heparin (LMWH), subcutaneous fondaparinux, intravenous unfractionated heparin (UFH) and/or vitamin K antagonist (VKA).

Category 3 - Required additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Paediatric Investigation Plan (PIP) for 'Treatment of thromboembolic events' EMA/PDCO/415136/2019 Completed	To assess rivaroxaban exposure and safety in patients < 18 years	**Missing information:** • Patients < 18 years	Paediatric programme PIP PIP programme completion: Positive Opinion of the Paediatric Committee on compliance with a Paediatric Investigation Plan EMEA-C-000430-PIP01-08-M11	Completed Q3 2019 20 SEP 2019

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Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban (SN XXXXX)

Purpose of study: This study will investigate the safety and tolerability of rivaroxaban granules for oral suspension in at least 50 very young (< 2 years of age) VTE patients from start of rivaroxaban treatment until at least 1 month (30 days) after stop of treatment and in children with VTE treated with other anticoagulants.

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Non-interventional, multicentre cohort study In planning	To investigate the safety and tolerability of rivaroxaban granules for oral suspension in at least 50 very young (< 2 years of age) VTE patients and in children with VTE treated with other anticoagulants.	**Important identified risk:** • Haemorrhage **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	Feasibility report Start of data collection Interim report (study progress report) End of data collection Final report of study results (6 months after end of data collection LP treated with Xarelto)	Submission Q1 2021 Q3-Q4 2021 (estimated) One year after start of data collection Q3-Q4 2022 (estimated) Q3-Q4 2024 (estimated) Q1-Q2 2025 (estimated)

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Part VII - Annexes

PART VII
Annexes

Active substance(s) (INN or common name):	Rivaroxaban

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	15 SEP 2019

Version number of RMP when this module was last updated	12.3

ELECTRONIC SIGNATURES

Signed by	Meaning Of Signature	Date
[redacted]	QPPV Approval	01-Feb-2021 1:23:39 PM UTC